NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia [ID779]

The following documents are made available to the consultees and commentators:

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - **Sanofi**
   - **HEART UK**

   'No comment' response received from the Department of Health and Pfizer

3. **Comments on the Appraisal Consultation Document received through the NICE website**

4. **Appendix of new evidence** prepared by Sanofi

5. **Evidence Review Group critique of the company new evidence**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

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

Definitions:

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 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 determination (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, 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.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Sanofi	Sanofi welcomes the opportunity to comment upon this preliminary decision and seeks to address the concerns and questions raised by the Appraisal Committee. Our response to the consultation is in three parts; 1) this covering letter setting our response in overview; 2) a summary of technical comments/corrections on the ACD (Appendix 1); and 3) new cost-effectiveness results based on a revised simple Patient Access Scheme (Appendix 2). The ACD provides a thorough overview of the information submitted, concluding that alirocumab is clinically effective in reducing LDL-c levels (paragraph 4.6) and recognising that this effect may reduce cardiovascular events in the future (paragraph 4.7). We consider the ACD also reflects positively on our approach to two key aspects essential to the Committee's decision-making; namely identifying the population for which alirocumab offers greatest clinical benefit (paragraph 4.2), and the robust approach to cost-effectiveness modelling (paragraph 4.8).	Thank you for your comment. Please see Section 4 of the FAD for further details and responses to comments on each issue below.
Sanofi	***Focussing on the right populations; those with the highest residual risk and unmet need*** The Appraisal Committee recognised in paragraph 4.2 of the ACD that *"the company submission focussed on those patients who have the greatest unmet need despite current treatment and that this was in line with where clinicians and patients would use alirocumab"*. Sanofi took a responsible approach to focus on patients in whom treatment with alirocumab would offer the greatest value. We believe alirocumab is most valuable for those patients in whom significant risk of future CV events remains high, despite the use of best available treatments. In its recent draft guidance on evolocumab, the Appraisal Committee indicated that certain high-risk patients with persistent LDL-c levels above 4mmol/L might represent a 'cost-effective' use of evolocumab, particularly among patients who are statin-intolerant. While an LDL-c treatment threshold above 4 mmol/L may be an appropriate cut-off for some patients at high risk of future CV events, this threshold level may unnecessarily leave patients considered at 'very high risk' of future CV events without an effective option to reduce that risk. These very high-risk patients not only include those unable to tolerate treatments (i.e. statin intolerant), but also heterozygous familial hypercholesterolaemia patients with a past history of CV events, and those non-familial patients with multiple manifestations of CVD (i.e. those with a history of	Thank you for your comment. The committee considered that the ERG's revised exploratory analysis could be used to more accurately identify the LDL-C level at which the ICER would be within the range normally considered to be a cost-effective use of NHS resources. The committee was persuaded by this comment and other comments received during consultation, that an LDL-c level of 4 mmol/L to

Consultee	Comment [sic]	Response
	multiple CV events in a single vascular bed or patients with >1 affected vascular bed). These patients have demonstrated a significantly higher risk for future CV events compared to other high-risk groups. Using the Appraisal Committee's preferred economic modelling approach (outlined in the ACD) and adjusting our patient access scheme, Sanofi can demonstrate, to the Committee's satisfaction, that alirocumab is cost-effective in these very high risk patients at an LDL-c cut-off >=3.0 mmol/L. Allowing access to this treatment will allow these very high CV risk patients the opportunity to reduce their risk significantly. One patient subgroup that caused the Appraisal Committee to question the uncertainties in the economic modelling more than any other was the familial hypercholesterolaemia patients with no prior CVD (paragraph 4.13). The Appraisal Committee heard that the lifetime risk should be high in the familial hypercholesterolemia population irrespective of whether there is a history of previous events. Notwithstanding the differences in the ICERs between these primary and secondary prevention populations – which is examined later in this response – we support the view that the primary prevention familial hypercholesterolaemia group should be considered at high risk, and recommend that alirocumab should be used in this group when LDL-c persists despite treatment at levels above 4 mmol/L.	start treatment would prevent people with primary hypercholesterolaemia (non-familial and heterozygous-familial) at very high risk of cardiovascular disease from accessing this treatment option. It considered that alirocumab is cost effective in these groups where LDL-C concentration is persistently above 3.5 mmol/L. The committee's full considerations for each population are outlined in FAD (see sections 4.14–4.18).
Sanofi	***Economic evaluations of populations at the highest levels of residual CV risk*** In our original submission, the rationale for using the relationship derived from the Navarese meta-analysis was that this represented estimates from PCSK9 inhibitor studies rather than statin studies. The Appraisal Committee, however, concluded that currently the best available evidence to inform this relationship was from the CTTC meta-analysis which is consistent with the approach taken by the Committee in its previous appraisals of both ezetimibe (ID 627) and evolocumab (ID 765). By applying the CTTC relationship and those other adjustments to the model outlined in the ACD as the Appraisal Committee's preferred approach, we present below new analyses – including the new patient access scheme price and using LDL-c cut-offs – measured in the units of mmol/L – that are pragmatic and aligned to UK clinical practice. These new analyses demonstrate that alirocumab, as an adjunct to maximally tolerated LMTs, can be considered to be cost-effective – in the range of £20,000 to £30,000 per QALY – at LDL-c cut-off levels considered far from goal. Table 1 shows that the LDL-c levels at which alirocumab is cost-effective varies according to patient phenotype and their associated risk of experiencing a CV event as a consequence of elevated LDL-c despite treatment.	The committee discussed the company's new evidence submitted in response to the appraisal consultation document, which used the CTTC meta-analysis. It concluded that the most appropriate evidence to assess this relationship was from the most recent update of the CTTC meta-analysis. (see section 4.9 of the FAD).

Consultee	Comment [sic]	Response

Table 1 Revised ICERs (£/QALY) for key patient populations and background comparators

Population / Intervention threshold	>= 2.5 mmol/L	>= 3.0 mmol/L	>= 3.5 mmol/L	>= 4.0 mmol/L
Primary prevention heterozygous-familial population				
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	£49,682	£45,004	£40,880	£37,228
Secondary prevention heterozygous-familial population				
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	£24,091	£22,600	£21,233	£19,973
Secondary prevention High-risk cardiovascular (non-familial) population				
Alirocumab + Statin vs. Statin	£43,880	£35,471	£29,220	£24,408
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	£44,308	£35,899	£29,647	£24,835
Secondary prevention Recurrent events / polyvascular (non-familial) population				
Alirocumab + Statin vs. Statin	£33,527	£27,184	£22,469	£18,831
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	£33,987	£27,644	£22,929	£19,291

The primary prevention heterozygous-familial population remains above the upper limit of £30,000/QALY even at an LDL-c cut-off of >=4 mmol/L, but we believe there is good reason to expect that the ICER estimates for this group are at the very conservative end of the spectrum.

To understand why the primary prevention population produces higher ICERs than the secondary prevention population one must recognise some key dynamics at play within the economic model, which together come to affect the ICER.

In the first instance, patients in the primary prevention population start in the model 10 years earlier than their

Consultee	Comment [sic]	Response

secondary prevention counterparts (age 50 vs age 60). This affords them more time in the model – to accrue more costs – and whilst they live longer (average 18 years vs. 12 years) they die on average 4 years earlier (age 68 vs. 72). This may not be unrealistic when considering that although those in the secondary prevention group may be at greater risk of second/third events in any one year, they are themselves event-survivors; in the real world, unfortunately some primary prevention patients will not survive their first event.

The fact that some primary prevention patients may not survive their first event could be one reason for their under-representation (along with under-diagnosis) in the real-world data sources used to estimate base-line risks in the model and may therefore be a further source of risk under-estimation affecting the ICERs. In Appendix 2, we undertake a sensitivity analysis for baseline risk factors to establish how far the risk must be adjusted upwards before the primary prevention population achieves more cost-effective ICERs. We consider that it requires only modest upward adjustment of risk for this population, with an LDL-c cut-off >=4 mmol/L, to become cost-effective.

Finally, the Appraisal Committee may take comfort from the knowledge that the ICERs derived – not just for the primary prevention heterozygous-familial population – but all populations in the alirocumab submission are on the more conservative end of the spectrum. A comparison of CTTC-derived risk reductions per 1 mmol/L reduction in LDL-c for major coronary events and death employed in recent appraisals suggests that modelling of CTTC in the original alirocumab submission,[1] is more conservative than the use of CTTC accepted for other recent appraisals (Table 2).[2] Employing the CTTC-derived values used in the other appraisals has the effect of reducing all the ICERs for alirocumab (on average by £1600/QALY compared to the ezetimibe appraisal and £5900/QALY, compared to the evolocumab appraisal).

Table 2 Comparison of the use of CTTC rate ratios in different appraisals

	ID627 - review TA132 (ezetimibe)	ID 765 (evolocumab)	ID 779 (alirocumab)
Non-Fatal MI (ACS)	0.74 (0.69, 0.78)	0.71 (0.58, 0.87)	0.74 (0.71, 0.77)
Coronary Revascularisation	-	0.66 (0.60, 0.73)	0.76 (0.73, 0.78)
Ischaemic Stroke	-	0.69 (0.50, 0.95)	0.79 (0.74, 0.85)
Any Stroke	0.85 (0.80, 0.90)	-	-
CHD Death	-	0.80 (0.74, 0.87)	-
Stroke Death	-	1.00*	-
Any Vascular Death	0.86 (0.82, 0.90)	-	0.88 (0.84, 0.91)
* A rate ratio value of 1.00 was used as opposed to the reported value of 1.04 (0.77, 1.44)			

Consultee	Comment [sic]	Response
	Finally, with regard to the statements in paragraph 4.14 of the ACD on the need for analyses of alirocumab against different comparators, we hope the revised analyses presented above provide the Appraisal Committee with the information they require with respect to *ezetimibe plus a statin* as a comparator. These complement the results already reported in the ACD in which *alirocumab plus statin* was compared with *ezetimibe and a statin*. We have not provided a comparison with evolocumab within this consultation response for two reasons. Firstly, at the time of writing this response evolocumab cannot be considered to be established NHS practice; indeed, until recently, the position of the Institute was not to recommend this medicine. Whilst the Institute is still consulting on the second draft guidance document for evolocumab, which we understand is significantly narrower than its marketing authorisation, the draft recommendation for a highly restricted population arguably precludes evolocumab from being considered as a 'standard of care'. Secondly, but perhaps more importantly, Sanofi does not have access to the confidential PAS price for evolocumab, so any ICERs that we might produce would not inform the Appraisal Committee's decision.	
Sanofi	***Supporting the Committee's decision-making*** We recognise overly complex treatment paradigms based on cost-effectiveness results that vary depending on the combination of patient phenotypes and LDL-c cut-off levels may be difficult to implement in clinical practice, and could lead to confusion with patients and clinicians alike. In light of the evidence, we consider an appropriate approach for the introduction of alirocumab could be for the following patients and LDL-c levels: Patients in the following groups who are at very high risk because their LDL-c remains >=3.0 mmol/L despite maximally tolerated statins +/- ezetimibe - Secondary prevention heterozygous-familial population - Secondary prevention recurrent events / polyvascular (non-familial) population Patients in the following groups who are at high residual risk because their LDL-c remains >=4.0 mmol/L despite maximally tolerated statins +/- ezetimibe - Primary prevention heterozygous-familial population - Secondary prevention High-risk cardiovascular (non-familial) population Patients with statin-intolerance are generally at highest risk within each of these populations due to their	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the Committee recommended alirocumab as specified in section 1 of the FAD. The committee also emphasised that its recommendations for alirocumab should only apply when maximal tolerated lipid-lowering therapy has failed (see section 4.7 of the FAD). The committee's considerations for each population are summarised in

Consultee	Comment [sic]	Response
	higher average LDL-c levels. We consider that alirocumab is cost-effective in these groups under the same phenotype/LDL-c proposals and so they might also be specifically accommodated using the same proposals. The availability of two PCSK9 inhibitors will offer these high and very high risk patients and their attending clinicians a real opportunity to affect their long-term prognosis for the better. Alirocumab further complements this new treatment choice through its two-dose presentation that will allow up- or down-titration in response to the patient's on-treatment LDL-c levels. This will help clinicians individualise their patient's treatment as appropriate, whilst tackling their patient's residual CV risk through very effective lowering of their raised LDL-c. We trust that we have addressed the key concerns of the Appraisal Committee through this consultation response and believe that the Committee can now be confident that alirocumab represents a cost-effective use of NHS resources in high and very high risk patient populations who have the greatest unmet need.	responses above, and outlined in full in FAD (see sections 4.14–4.18). The committee concluded that it was not necessary to make separate recommendations for people who cannot take statins (see section 4.5 of the FAD).
Sanofi	Appendices and References *The consultee submitted several appendices and references in its response to consultation and have not been reproduced here. Please see Committee papers for the full response.*	Comment noted. The FAD has been amended accordingly in response to the summary of technical comments/corrections on the ACD.
HEART UK	HEART UK consulted on this submission and has additional support of 84 individuals, including 56 health care professionals. The authors and some of the listed supporters of this submission are leading experts in the UK and Worldwide. HEART UK are very disappointed that NICE has chosen not to recommend alirocumab (Praluent®) for low density lipoprotein cholesterol (LDL-C) reduction for high cardiovascular risk patients at this time. We have previously commented on NICE's evaluation of evolocumab and it is our view that these 2 PCSK9 inhibitors should be compared by their effectiveness in lowering LDL cholesterol (LDL-C). This appears to be the same and head to head comparison would be futile. Both drugs are likely to be reserved for people who are at particularly high risk of CVD, including people with HeFH, and those who cannot tolerate statins and in whom ezetimibe does not adequately control LDL-C. There are several groups of patients with unmet clinical need for additional lipid lowering therapy, including:	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the Committee recommended alirocumab as specified in section 1 of the FAD. The recommendations also apply to people with familial hypercholesterolemia, people with cardiovascular disease, and people with high LDL-c despite maximal tolerated lipid-lowering

Consultee	Comment [sic]	Response
	1. Patients with HeFH have high LDL-C from birth due to an inherited defect in LDL-C catabolism and accelerated atheroma formation. Such patients may fail to reach achieve adequate LDL-C lowering either due to a high starting level or intolerance to statins resulting in increased mortality. A particularly high priority group are those with progression of CAD requiring interventions 2. Patients with cardiovascular disease but high LDL-C level despite maximum existing medical therapy 3. Alirocumab is a potential alternative treatment for patients, who meet the criteria for lipoprotein apheresis. It may allow discontinuation or less frequent apheresis 4. Patients with diabetes and metabolic syndrome with high LDL-C despite maximum statin therapy and reasonable glycaemic control. Section 3.44 in the ERG statement supports this view. Subgroup analysis by baseline LDL-C shows marked decreases in ICER comparing baseline 2.56 mmol/L with.4.13 mmol/L. In the secondary prevention familial hypercholesterolaemia group comparing alirocumab with statin plus ezetimibe and in the high risk non-familial population comparing alirocumab with statin alone the costs per QALY were £14,242 and £16,043. This must also be true if the comparator is without statin. We believe that alirocumab should be recommended to these high-risk patients with cardiovascular disease who fail to attain an LDL-C lower than 3.0 mmol/L despite maximum tolerated medical therapy. We accept that as for evolocumab, this might be set as high as 4.0 mmol/L for primary prevention pending outcome studies. We agree there is no robust evidence to support lowering LDL-C below 1 mmol/l and this is largely because there are no sufficiently potent second line medications to be used with statins to achieve such low levels. On-going studies should clarify this point. However, this is not relevant to high risk patient groups with high LDL-C despite maximum medical therapy because they are not expected to achieve LDL-C levels below 1mmol/L due to high LDL-C levels prior to deploying PCSK9 inhibitors (as proposed in evolocumab application). There is a powerful rational for adopting a target based approach to management of patients at very high cardiovascular risk associated with high LDL-C. LDL- C is a principal driver of atherogenesis and is the key target for intervention. The lowering of LDL-C is critically related to decreased atheroma volume and improved plaque stability. Mendelian randomisation studies and studies lowering cholesterol by diverse means, have clearly shown that the magnitude of clinical benefit in preventing cardiovascular disease	therapy. The committee was persuaded by this comment and other comments received during consultation, that an LDL-c level of 4 mmol/L to start treatment would prevent people with primary hypercholesterolaemia (non-familial and heterozygous-familial) at very high risk of cardiovascular disease from accessing this treatment option. It considered that alirocumab is cost effective in these groups where LDL-C concentration is persistently above 3.5 mmol/L. For people with non-familial hypercholesterolemia with a high risk of cardiovascular disease, It considered that alirocumab is cost effective for people with an LDL-c concentration persistently above 4.0 mmol/L. For people with heterozygous-familial-hypercholesterolemia with no history of cardiovascular disease, the committee considered that treatments that avoid the need for apheresis would be welcomed and therefore alirocumab could plausibly b

Consultee	Comment [sic]	Response
	(CVD) events relates to the extent of LDL-C lowering rather than the mechanism itself. Nevertheless, PCSK9 inhibitors work in the same way as statins by up-regulating the LDL receptor. The bulk of data underpinning the relationship between LDL-C lowering has been established from statin trials. We agree with NICE that LDL-C lowering is an acceptable surrogate for effectiveness in preventing CVD. Against a background of LDL-C lowering with statin and ezetimibe patients treated with PCSK9 inhibitors more often achieve acceptable LDL-C lowering targets. It should be recalled that regulatory approval has been given to alirocumab in the absence of data on outcomes. Nevertheless, meta-analysis of 24 PCSK9 inhibitor trials including 10,000 patients has shown 55% reduction in all-cause mortality, a 50% reduction in cardiovascular mortality and 51% reduction in myocardial infarction; all statistically significant. There have been no signals of harm in clinical trials although extended surveillance is needed as with all new drugs. It should be remembered that the use of monoclonal antibody medicines is a generic therapy with the nature of the monoclonal determining its site of action and that about 50 of such treatments are in use. HEART UK believes that in their appraisal of alirocumab (Praluent®) NICE has significantly underestimated its clinical utility and the unmet clinical need. **This has disadvantaged patients with heterozygous familial hypercholesterolaemia as a group and many patients at increased cardiovascular risk who cannot adequately lower their LDL-C by existing treatments**. Such patients may be offered apheresis, which is invasive and inconvenient. PCSK9 treatment may substitute for this treatment and/or make it more effective. **Patients currently treated by apheresis have therefore been disadvantaged**. We believe that the cost effectiveness of treating patients with raised LDL-C has been based on a low baseline LDL-C and insufficient account has been taken of the data provided by Sanofi on the cost effectiveness in groups with high LDL-C. Additionally, for consideration by NICE, ought to be the impact of recommendations and decisions it makes on this class of medicines and the following comments were received when HEART UK consulted widely on the ACD: "*There are not many patients like myself that despite taking all medications at maximum doses ie rosuvastatin and estimibe, ldl-aphersis. I still don't reach those allusive target figures especially those for lipoprotein a.*	considered cost-effective for people with an LDL-c concentration persistently above 5.0 mmol/L. The committee's considerations for each population are in responses above, and outlined in full in FAD (see sections 4.14–4.18). The committee considered the potential equality issue that the incidence of familial hypercholesterolaemia could be higher in people of Ashkenazi Jewish origin. It concluded that its recommendations for alirocumab would apply to all patients and that the recommendations would not have a different impact on people protected by the equality legislation compared with the wider population (see section 4.22 of the FAD).

Consultee	Comment [sic]	Response
	I have read the NICE guidance and it is so unfair that it is staggering. *All I can think is that FH patients with high LDL 4mmols on maximum treatment have been forgotten.* *We will not appear on any drug trials as often we are deemed to high risk to be allowed on a blind study and not get the medications we need to live.* *These studies therefore do not represent the effect a drug like this can have on a population like myself.* *Currently LDL aphersis is the only way to remove most lipoprotein out of my blood my levels despite dual tablet therapy come in at over 3000 and I leave with them around 1000 this in combination with a high ldl level make for an aggressive form of vascular insult.* *In last 18 months I have had several events and I was hoping for the last piece in the jigsaw to fall in to place to control the factors me and my doctors can't control.* *I have been told all my life I was born a generation too early and have not only had to fight disease but also for treatment after the event.* *They need to be made aware that people with severe FH don't have a choice about whether a drug as side effects like statins because a side effect is a small price to pay for a active life.* *The same with apheresis it is not a choice; it has extended my life by 16 years and counting."* **Patient** "*My parents both died of heart disease. Had they been born a generation later, their lives may have been saved and transformed with today's generation of drugs. I believe everyone with high cholesterol should have equitable access to drugs, for their personal quality of life, in turn for their family's quality of life and, additionally, for the potential cost savings to the health service for heart disease averted or mitigated.* *My parents were German Jewish refugees - Ashkenazi Jews. Despite best attempts with diet and lifestyle, my cholesterol level remains stubbornly higher than it should be. I have never sought diagnosis of cholesterol-familial hypercholesterolemia, but there must be many descendants of Ashkenazi Jews like me who may need life-enhancing and life-saving drugs for this inherited condition.* *I applaud your energy and efforts into campaigning on behalf of us all.* *Thank you.*" **Patient**	

Consultee	Comment [sic]	Response
	1 "*I support this campaign due to my mother has to have regular dialysis treatments due to FH this would thoroughly improve her condition of life and I believe that every Human being should have a right to this.* *2 She cannot move away or to other parts of the country as lack of these machines are available and if these inhibitor medicines will help her either to reduce treatment or not at all then I believe this to be more cost effective solution to treating her condition.*" **Patient** "*This is ridiculous that NICE plays a role of inhibitor as opposed to facilitator. I believe a campaign should be put in place to revisit the mission of NICE as we are fed up of medicine being denied to people who need it. This is valid for cancer, heart or any other life threatening conditions.* *Enough is enough!*" **Patient** "*As a sufferer of homozygous FH with pre-existing atherosclerosis at only 36 I am doing EVERYTHING I can to keep myself as healthy as possible. Having just had a child through surrogacy I want to do everything I can to see him grow up. Denying persons like myself access to these potentially vital new medications is tantamount to telling me to accept that NICE feels it's ok to limit my life expectancy due to a malignant atherosclerosis, a hard pill to swallow when I know there are options like this I'm being denied access to.* *I urge NICE to reconsider this.*" **Patient** "*As heart attacks are one of the biggest killers, anything that can prevent them should be supported*" **Patient** I have an inherited form of hyperlipidemia/ cholesterolemia which did not respond to the highest doses of statins until it was brought under control with fenofibrates and Omacor. These drugs were prescribed only after extensive investigations, over ten years ago, carried out by consultant lipidologist, Dr Nair, at the Royal Free Hospital. I find it unbelievable that NICE could take a decision on PCSK9 inhibitors without taking the views and opinions of expert lipidologists. I am amazed that decisions are taken without a more rigorous approach to scientific evidence, such as that available from expert lipidologists. **Health care professional and patient** "*I am very concerned about the present NICE view and strongly support that lipidologists should have been represented on the committee*	

Consultee	Comment [sic]	Response
	I had a NSTEMI =+ one stent 2013 (58y - no other risk factors) , I have some arteriosclerosis in my carotid arteries and some small vessel disease) *There is strong FH of polygenic dyslipidaemia* *I have Lipoprotein (a) over 1000 (was over 1400 before I started on Nicotinamide 2 gram per day)* *I am on rosuvastatin 20mgm etc* *I am under the Hammersmith lipid clinic.* *NICE are recommending that I should consider self funding for PCSK9 inhibitor treatment in the light of my high Lp(a) level- this must surely be available on the NHS for patients like myself."* **Health care professional and patient**	
HEART UK	*The consultee submitted the names of the supporters of the comment and have not been reproduced here. Please see Committee papers for the full response.*	Comments noted.

A "no comment" response was received from the Department of Health and Pfizer Ltd

Comments received from members of the public

Role*	Section	Comment [sic]	Response
Health professional (within NHS)	–	I would consider alirocumab (and evolocumab) to be a valuable addition to the treatment options for a small select group of patients attending lipid clinics: those with heterozygous familial hypercholesterolaemia or established CVD, (particularly younger patients) who have ALSO failed to respond or are intolerant of the currently available treatment options, including all five statins, ezetimibe and bile-acid sequestrants. The new agents provide a more acceptable alternative to apheresis in this circumstance	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the Committee recommended alirocumab as specified in section 1 of the FAD. The committee concluded that it was not necessary to make separate recommendations for people who cannot take statins (see section 4.5 of the FAD).

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment [sic]	Response
Health professional (within NHS)	–	Alirocumab should be recommended for high-risk patients who fail to attain an LDL-C lower than 3.0 mmol/L despite maximum tolerated medical therapy. As for evolocumab, this might be set as high as 4 mmol/L pending outcome studies. Section 3.44 in the ERG statement supports this view. Subgroup analysis by baseline LDL-C shows marked decreases in ICER comparing baseline 2.56 mmol/L with.4.13 mmol/L. In the secondary prevention familial hypercholesterolaemia group comparing alirocumab with statin plus ezetimibe and in the high risk non-familial population comparing alirocumab with statin alone the costs per QALY were £14,242 and £16,043. This must be even better if the comparator is without statin. The higher the LDL-C the greater the potential for benefit from cholesterol lowering as this relates to absolute LDL-C reduction. Many factors contribute to cardiovascular risk but few are reversible. The suggestion that there should be a head to head comparison of the effectiveness of alirocumab and evolocumab is misguided. They have very similar effects on LDL-C lowering and a trial would be futile. I am sure that there could be some movement on cost. These drugs should be used in in secondary prevention in patients with an LDL-C somewhere between 3.0 and 4.0 mmol/L at the very least in addition to maximum tolerated lother lipid lowering therapy. Similar patients will qualify for lipoprotein apheresis, which is about 10 times as expensive. I was reminded today in clinic of a group of patients for whom PCSK9 inhibitors are a designer drug. Patients with activating mutations causing increased levels of PCSK9 proteins. Such patients have structurally normal and fully active LDL receptors but have low LDL receptor activity due to PCSK9 catabolism. Unsurprisingly, they respond better than other groups of patient to PCSK9 inhibitors. Clinically, they have a severe phenotype. The patient in question has had a CABG, sequential angioplasties and is just recovering from aortic valve surgery. Aortic arch atheroma is a consequence of poorly controlled familial hypercholesterolaemia. These patients respond relatively poorly to statins because statins increase PCSK9 levels. Although this mutation is a minor cause of familial hypercholesterolaemia they are probably over represented in lipd clinics due to their severe phenotype and poor response to statins. All of this misery is caused by increased PCSK9 levels and it should be inhibited. The category of patient for health economic analysis would be heterozygous familial hypercholesterolaemia with	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the Committee recommended alirocumab as specified in section 1 of the FAD. The committee's considerations for each population are outlined in FAD (see sections 4.14–4.18). The committee concluded that it was not necessary to make separate recommendations for people who cannot take statins (see section 4.5 of the FAD).

Role*	Section	Comment [sic]	Response
		progressive arterial disease and an LDL cholesterol above 4 mmol/L on maximum tolerated standard treatment. In fact this patient is not statin intolerant and is treated with atorvastatin 80mg, ezetimibe 10 mg and colesevelam**.**	
Health professional (within NHS)		There is a considerable unmet clinical need for anti-PCSK9 inhibitors - for example secondary prevention patients who are statin-intolerant and with LDL cholesterol not even close to target despite ezetimibe monotherapy.	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the Committee recommended alirocumab as specified in section 1 of the FAD. The committee concluded that it was not necessary to make separate recommendations for people who cannot take statins (see section 4.5 of the FAD).
Health professional (within NHS)		The Welsh Chemical Pathologists Group (WCPG) is an association of Consultant and Trainee Chemical Pathologists working in Wales, and members of this group provide specialised lipid clinic services for patients with difficult and complex lipid disorders throughout Wales. The WCPG discussed the NICE appraisal consultation document entitled Hypercholesterolaemia (primary) and dyslipidaemia (mixed) - alirocumab [ID779] at its last meeting on 25th February 2016. 1. It is acknowledged that Alirocumab should be reserved primarily for patients established as being at high risk of CVD, which would include patients with genetically confirmed Heterozygous Familial Hypercholesterolaemia and those patients who are unable to tolerate statin therapies and in whom Ezetimibe is ineffective in controlling the LDL-C levels. It is disappointing, therefore that NICE has chosen not to recommend the use of Alirocumab, particularly as we have a significant number of patients in Wales who would fall into this cohort of patients and would therefore, potentially benefit from PCSK9 therapy, especially as this therapeutic product has proven LDL-C lowering capacity. 2. LDL-C Lowering is associated with reducing CVD Risk and the number of CVD Events. It is well established that lowering LDL-C is associated with reducing CVD Risk and events via statin therapies and other lipid modifying approaches. It is noted that some statin therapies and Ezetimibe were approved for therapeutic use prior to confirming clinically	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the Committee recommended alirocumab as specified in section 1 of the FAD. The recommendations also apply to people with familial hypercholesterolemia, people with cardiovascular disease, and people with high LDL-c despite maximal tolerated lipid-lowering therapy. The committee concluded that it was not necessary to make separate recommendations for people who cannot take statins (see section 4.5 of the FAD).

Role*	Section	Comment [sic]	Response
		proven outcome efficacy. The PCSK9 Inhibitors have been shown to have a significant LDL-C lowering capacity via a mechanism that is similar to that of Statin therapies, notably by increasing the number of cell surface LDL receptors. Whilst it is acknowledged that there is currently no completed clinical outcome data re PCSK9 inhibitors there seems little reason to question the use of LDL-C lowering capacity as a surrogate marker for CVD risk and event reduction. 3. Unmet Clinical Need in Wales: (i) We have a well established Genetic Testing service in Wales which is identifying an increasing number of genetically confirmed FH and whilst these patients are initially treated with optimal statin therapy, a significant proportion of these patients are either not reaching satisfactory targets or are intolerant of all available statins and hence remain at increased risk of developing premature CVD and/or exacerbating further CVD events if left unsatisfactorily controlled. (ii) We have a well established Lipid Clinic Service across Wales which is managed by members of the Welsh Chemical Pathologists across each of the Health Boards across the Principality. These clinics as well as being responsible for managing patients with genetically proven FH also see a very large number of patients with CVD and/or Diabetes mellitus with concomitant dyslipidaemia including mixed dyslipidaemia whom also require optimisation of their lipid profiles. As with the FH patients there are a significant number of patients within these groups of patients who are unable to tolerate statin therapies and whose lipid profile is not adequately managed by Ezetimibe alone. (iii) Both these types of patients are therefore, likely to benefit from PCSK9 Inhibition and its proven LDL-C lowering capacity and without adequate treatment remain at sustained risk of CVD and CVD events. 4. Given the evident biochemical efficacy of Alirocumab treatment with a reassuring tolerability profile and given the significant current unmet clinical need in Wales we would strongly urge NICE to reconsider its recommendations in the draft appraisal with a view to recommending using this product in as wide a population as is cost effectively feasible.	

Role*	Section	Comment [sic]	Response
		5. Although this Appraisal concerns Alirocumab our comments given above would apply to any PCSK9 inhibitors that come to market.	
Health professional (within NHS)		Response from Wales FH Professional Advisory Group This response is written on behalf of the Wales FH professional advisory group, which has professional oversight of the All Wales Familial Hypercholesterolaemia (FH) service. This group has extensive clinical experience of assessing and treating patients with inherited hyperlipidaemia, particularly FH. On clinical grounds we consider that PCSK9 inhibitors should have a specific indication for treating Patients with FH who are intolerant of statins Treating patients with FH who have progressive cardiovascular disease with persistently elevated LDL cholesterol concentrations despite optimum treatment by all other approaches. We note that the NICE assessment committee felt that it had insufficient evidence to fully assess these indications. We have summarised our views under 5 headings as below. 1) FH is an inborn error of metabolism We consider that FH is a special case and should be regarded as an inborn error of LDL cholesterol metabolism that requires specific and targeted treatment to lower LDL cholesterol. 2) PCSK9 genetic variants cause/protect from heart disease One of the genetic mutations that cause FH is a gain of function mutation in the PCSK9 gene which leads to increased PCSK9 protein expression. This in turn causes the LDL receptors to be degraded in the cell so that they are available for further clearance of LDL cholesterol from the blood stream. Conversely there is now clear evidence that individuals with genetically	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the Committee recommended alirocumab as specified in section 1 of the FAD. The recommendations also apply to people with familial hypercholesterolemia, people with cardiovascular disease, and people with high LDL-c despite maximal tolerated lipid-lowering therapy. The committee concluded that it was not necessary to make separate recommendations for people who cannot take statins (see section 4.5 of the FAD).

Role*	Section	Comment [sic]	Response
		lower PCSK9 concentrations have lower LDL cholesterol concentrations and significantly lower rates of coronary heart disease. Also some individuals with genetically absent PCSK9 have been described with no adverse clinical features which is very reassuring from a safety perspective. 3) The clinical argument for statin therapy in FH also applies to PCSK9 inhibitors It should be noted that the clinical evidence for statin benefit in FH is not based on randomised clinical trials in FH but rather the pharmacological evidence that it targets LDL cholesterol metabolism, combined with general safety and efficacy data. Randomised placebo controlled trials of statin therapy on cardiovascular events, have not been carried out in FH because it would be regarded as unethical to withhold statin therapy in FH patients. (NICE FH guideline GC 71 2008). Similarly, we would regard it as clinically unethical to withhold treatment with PCSK9 inhibitors from patients with FH in situations where other therapy is not tolerated (ie statins) or is not effective. 4) PCSK9 inhibitors are a form of personalised medicine to be used as a 3rd line agent In the era of personalised medicine, we would regard PCSK9 inhibitors as an agent that specifically targets the metabolic defect that is FH. This should be regarded as genetically targeted 3rd line therapy (after statins and ezetimibe) for patients who are not suitable for these first and second line agents. 5) The number of patients appropriate for PCSK9 inhibitors will be small We estimate that the proportion of FH patients who cannot tolerate statins is less than 5% of the patients with a diagnosis of FH. Therefore we think that the number of patients requiring PCSK9 inhibitors would be relatively small.	

Meindert Boysen
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29th February 2016

Dear Meindert,

Re. NICE Technology appraisal of alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia [ID779]

Sanofi welcomes the opportunity to comment upon this preliminary decision and seeks to address the concerns and questions raised by the Appraisal Committee. Our response to the consultation is in three parts; 1) this covering letter setting our response in overview; 2) a summary of technical comments/corrections on the ACD (Appendix 1); and 3) new cost-effectiveness results based on a revised simple Patient Access Scheme (Appendix 2).

The ACD provides a thorough overview of the information submitted, concluding that alirocumab is clinically effective in reducing LDL-c levels (paragraph 4.6) and recognising that this effect may reduce cardiovascular events in the future (paragraph 4.7). We consider the ACD also reflects positively on our approach to two key aspects essential to the Committee's decision-making; namely identifying the population for which alirocumab offers greatest clinical benefit (paragraph 4.2), and the robust approach to cost-effectiveness modelling (paragraph 4.8).

Focussing on the right populations; those with the highest residual risk and unmet need

The Appraisal Committee recognised in paragraph 4.2 of the ACD that *"the company submission focussed on those patients who have the greatest unmet need despite current treatment and that this was in line with where clinicians and patients would use alirocumab"*.

Sanofi took a responsible approach to focus on patients in whom treatment with alirocumab would offer the greatest value. We believe alirocumab is most valuable for those patients in whom significant risk of future CV events remains high, despite the use of best available treatments.

In its recent draft guidance on evolocumab, the Appraisal Committee indicated that certain high-risk patients with persistent LDL-c levels above 4mmol/L might represent a 'cost-effective' use of evolocumab, particularly among patients who are statin-intolerant. While an LDL-c treatment threshold above 4 mmol/L may be an appropriate cut-off for some patients at high risk of future CV events, this threshold level may unnecessarily leave patients considered at 'very high risk' of future CV events without an effective option to reduce that risk. These very high-risk patients not only include those unable to tolerate treatments (i.e. statin intolerant), but also heterozygous familial hypercholesterolaemia patients with a past history of CV events, and those non-familial patients with multiple manifestations of CVD (i.e. those with a history of multiple CV events in a single vascular bed or patients with >1 affected vascular bed). These patients have demonstrated a significantly higher risk for future CV events compared to other high-risk groups.

Using the Appraisal Committee's preferred economic modelling approach (outlined in the ACD) and adjusting our patient access scheme, Sanofi can demonstrate, to the Committee's satisfaction, that alirocumab is cost-effective in these very high risk patients at an LDL-c cut-off >=3.0 mmol/L. Allowing access to this treatment will allow these very high CV risk patients the opportunity to reduce their risk significantly.

One patient subgroup that caused the Appraisal Committee to question the uncertainties in the economic modelling more than any other was the familial hypercholesterolaemia patients with no prior CVD (paragraph 4.13). The Appraisal Committee heard that the lifetime risk should be high in the familial hypercholesterolemia population irrespective of whether there is a history of previous events. Notwithstanding the differences in the ICERs between these primary and secondary prevention populations – which is examined later in this response – we support the view that the primary prevention familial hypercholesterolaemia group should be considered at high risk, and recommend that alirocumab should be used in this group when LDL-c persists despite treatment at levels above 4 mmol/L.

Economic evaluations of populations at the highest levels of residual CV risk

In our original submission, the rationale for using the relationship derived from the Navarese meta-analysis was that this represented estimates from PCSK9 inhibitor studies rather than statin studies. The Appraisal Committee, however, concluded that currently the best available evidence to inform this relationship was from the CTTC meta-analysis which is consistent with the approach taken by the Committee in its previous appraisals of both ezetimibe (ID 627) and evolocumab (ID 765).

By applying the CTTC relationship and those other adjustments to the model outlined in the ACD as the Appraisal Committee's preferred approach, we present below new analyses – including the new patient access scheme price and using LDL-c cut-offs – measured in the units of mmol/L – that are pragmatic and aligned to UK clinical practice.

These new analyses demonstrate that alirocumab, as an adjunct to maximally tolerated LMTs, can be considered to be cost-effective – in the range of £20,000 to £30,000 per QALY – at LDL-c cut-off levels considered far from goal. Table 1 shows that the LDL-c levels at which alirocumab is cost-effective varies according to patient phenotype and their associated risk of experiencing a CV event as a consequence of elevated LDL-c despite treatment.

Table 1 Revised ICERs (£/QALY) for key patient populations and background comparators

Population / Intervention threshold	>= 2.5 mmol/L	>= 3.0 mmol/L	>= 3.5 mmol/L	>= 4.0 mmol/L
Primary prevention heterozygous-familial population				
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	£49,682	£45,004	£40,880	£37,228
Secondary prevention heterozygous-familial population				
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	£24,091	£22,600	£21,233	£19,973
Secondary prevention High-risk cardiovascular (non-familial) population				
Alirocumab + Statin vs. Statin	£43,880	£35,471	£29,220	£24,408
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	£44,308	£35,899	£29,647	£24,835
Secondary prevention Recurrent events / polyvascular (non-familial) population				
Alirocumab + Statin vs. Statin	£33,527	£27,184	£22,469	£18,831
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	£33,987	£27,644	£22,929	£19,291

The primary prevention heterozygous-familial population remains above the upper limit of £30,000/QALY even at an LDL-c cut-off of >=4 mmol/L, but we believe there is good reason to expect that the ICER estimates for this group are at the very conservative end of the spectrum.

To understand why the primary prevention population produces higher ICERs than the secondary prevention population one must recognise some key dynamics at play within the economic model, which together come to affect the ICER.

In the first instance, patients in the primary prevention population start in the model 10 years earlier than their secondary prevention counterparts (age 50 vs age 60). This affords them more time in the model – to accrue more costs – and whilst they live longer (average 18 years vs. 12 years) they die on average 4 years earlier (age 68 vs. 72). This may not be unrealistic when considering that although those in the secondary prevention group may be at greater risk of second/third events in any one year, they are themselves event-survivors; in the real world, unfortunately some primary prevention patients will not survive their first event.

The fact that some primary prevention patients may not survive their first event could be one reason for their under-representation (along with under-diagnosis) in the real-world data sources used to estimate base-line risks in the model and may therefore be a further source of risk under-estimation affecting the ICERs. In Appendix 2, we undertake a sensitivity analysis for baseline risk factors to establish how far the risk must be adjusted upwards before the primary prevention population achieves more cost-effective ICERs. We consider that it requires only modest upward adjustment of risk for this population, with an LDL-c cut-off >=4 mmol/L, to become cost-effective.

Finally, the Appraisal Committee may take comfort from the knowledge that the ICERs derived – not just for the primary prevention heterozygous-familial population – but all populations in the alirocumab submission are on the more conservative end of the spectrum. A comparison of CTTC-derived risk reductions per 1 mmol/L reduction in LDL-c for major coronary events and death employed in recent appraisals suggests that modelling of CTTC in the original alirocumab submission,[1] is more conservative than the use of CTTC accepted for other recent appraisals (Table 2).[2] Employing the CTTC-derived values used in the other appraisals has the effect of reducing all the ICERs for alirocumab (on average by £1600/QALY compared to the ezetimibe appraisal and £5900/QALY, compared to the evolocumab appraisal).

Table 2 Comparison of the use of CTTC rate ratios in different appraisals

	ID627 - review TA132 (ezetimibe)	ID 765 (evolocumab)	ID 779 (alirocumab)
Non-Fatal MI (ACS)	0.74 (0.69, 0.78)	0.71 (0.58, 0.87)	0.74 (0.71, 0.77)
Coronary Revascularisation	-	0.66 (0.60, 0.73)	0.76 (0.73, 0.78)
Ischaemic Stroke	-	0.69 (0.50, 0.95)	0.79 (0.74, 0.85)
Any Stroke	0.85 (0.80, 0.90)	-	-
CHD Death	-	0.80 (0.74, 0.87)	-
Stroke Death	-	1.00*	-
Any Vascular Death	0.86 (0.82, 0.90)	-	0.88 (0.84, 0.91)
* A rate ratio value of 1.00 was used as opposed to the reported value of 1.04 (0.77, 1.44)			

Finally, with regard to the statements in paragraph 4.14 of the ACD on the need for analyses of alirocumab against different comparators, we hope the revised analyses presented above provide the Appraisal Committee with the information they require with respect to *ezetimibe plus a statin* as a comparator. These complement the results already reported in the ACD in which *alirocumab plus statin* was compared with *ezetimibe and a statin*.

We have not provided a comparison with evolocumab within this consultation response for two reasons. Firstly, at the time of writing this response evolocumab cannot be considered to be established NHS practice; indeed, until recently, the position of the Institute was not to recommend this medicine. Whilst the Institute is still consulting on the second draft guidance document for evolocumab, which we understand is significantly narrower than its marketing authorisation, the draft recommendation for a highly restricted population arguably precludes evolocumab from being considered as a 'standard of care'. Secondly, but perhaps more importantly, Sanofi does not have access to the confidential PAS price for evolocumab, so any ICERs that we might produce would not inform the Appraisal Committee's decision.

Supporting the Committee's decision-making

We recognise overly complex treatment paradigms based on cost-effectiveness results that vary depending on the combination of patient phenotypes and LDL-c cut-off levels may be difficult to implement in clinical practice, and could lead to confusion with patients and clinicians alike.

In light of the evidence, we consider an appropriate approach for the introduction of alirocumab could be for the following patients and LDL-c levels:

Patients in the following groups who are at very high risk because their LDL-c remains >=3.0 mmol/L despite maximally tolerated statins +/- ezetimibe

- Secondary prevention heterozygous-familial population
- Secondary prevention recurrent events / polyvascular (non-familial) population

Patients in the following groups who are at high residual risk because their LDL-c remains >=4.0 mmol/L despite maximally tolerated statins +/- ezetimibe

- Primary prevention heterozygous-familial population
- Secondary prevention High-risk cardiovascular (non-familial) population

Patients with statin-intolerance are generally at highest risk within each of these populations due to their higher average LDL-c levels. We consider that alirocumab is cost-effective in these groups under the same phenotype/LDL-c proposals and so they might also be specifically accommodated using the same proposals.

The availability of two PCSK9 inhibitors will offer these high and very high risk patients and their attending clinicians a real opportunity to affect their long-term prognosis for the better. Alirocumab further complements this new treatment choice through its two-dose presentation that will allow up- or down-titration in response to the patient's on-treatment LDL-c levels. This will help clinicians individualise their patient's treatment as appropriate, whilst tackling their patient's residual CV risk through very effective lowering of their raised LDL-c. We trust that we have addressed the key concerns of the Appraisal Committee through this consultation response and believe that the Committee can now be confident that alirocumab represents a cost-effective use of NHS resources in high and very high risk patient populations who have the greatest unmet need.

Yours sincerely,

[redacted]

Appendix 1

Table 3 Summary of clarifications/corrections

Page	Inaccuracy	Correction	Rationale
Page 4 Paragraph 2.3	'The annual cost of treatment per patient is £4,368 for 75 mg or 150 mg every 2 weeks'	'The annual cost of treatment per patient is £4,383 for 75 mg or 150 mg every 2 weeks'	Typographical correction
Page 4 Paragraph 3.2 Page 5 Paragraph 3.3 Paragraph 3.4 Paragraph 3.5 Page 6 Paragraph 3.7	'…..not adequately controlled with a maximally tolerated, stable, daily dose of statin.'	'……not adequately controlled with a maximally tolerated, stable, daily dose of statin, *with or without other LMT*.'	Clarification that on the use of other lipid lowering/modifying therapies (LMT)
Page 7 Paragraph 3.8	'For patients on atorvastatin 40 mg at baseline, the difference in mean percent change from baseline in LDL-c level at 24 weeks (with possible up-titration) was −39.2% (p<0.0001) with alirocumab with statin (atorvastatin 40 mg) compared with statin (atorvastatin 80 mg) alone.'	'For patients on atorvastatin 40 mg at baseline, the difference in mean percent change from baseline in LDL-c level at 24 weeks (with possible up-titration) was −49.2% (p<0.0001) with alirocumab and statin (atorvastatin 40 mg) compared with statin (atorvastatin 80 mg) alone.'	Typographical correction
Page 12 Paragraph 3.21	'3 types of events: non-fatal acute coronary syndrome including myocardial infarction and unstable angina, non-fatal ischaemic stroke, and elective revascularisation)'	'3 types of events: non-fatal acute coronary syndrome including myocardial infarction and unstable angina requiring hospitalisation, non-fatal ischaemic stroke, and elective revascularisation)'	Clarification regarding unstable angina endpoint
Page 13 Paragraph 3.22	'The baseline LDL-c level was 2.59 mmol/L, 50% of the cohort were men and 7% had diabetes.'	'The baseline LDL-c level was 2.59 mmol/L, 50% of the cohort were men and 7% and 26% had diabetes (primary prevention and secondary prevention HeFH respectively based on the THIN database)'	Inclusion of additional information for completeness
Page 13 Paragraph 3.22	'For recurrent events/polyvascular disease, the starting age was 65 years and the baseline LDL-c level was 2.59 mmol/L/ Around 60% of the cohort were men and 30% had diabetes.'	'For recurrent events/polyvascular disease, the starting age was 65 years and the baseline LDL-c level was 2.59 mmol/L. Around 60% of the cohort were men and 30% had diabetes.'	Typographical correction

Page 19 Paragraph 3.38	'For alirocumab and a statin compared with ezetimibe and a statin, the ICER was £16,896 per QALY gained (incremental costs £39,306; incremental QALYs 2.33).'	'For alirocumab and a statin compared with ezetimibe and a statin, the ICER was £48,193 per QALY gained (incremental costs £45,962; incremental QALYs 0.95).' c.f. Table 2a PAS Submission	Typographical correction Secondary Prevention HeFH base case results incorrectly presented
Page 24 Paragraph 3.47	'In summary, the ERG's exploratory analyses showed only modest changes to the base-case ICERs for all comparisons in all populations using Navarese to estimate the relationship between LDL-c and cardiovascular events. Using CTTC to estimate the relationship between LDL-c and cardiovascular events substantially increased the ICERs for all comparisons in all populations. All these ICERs were in excess of £20,000 per QALY gained.'	'In summary, the ERG's exploratory analyses showed only modest changes to the base-case ICERs for all comparisons in all populations using Navarese to estimate the relationship between LDL-c and cardiovascular events. Using CTTC to estimate the relationship between LDL-c and cardiovascular events substantially increased the ICERs for all comparisons in all populations, in line with the company presented scenario results. All these ICERs were in excess of £20,000 per QALY gained.	Clarification
Page 37 Paragraph 4.13	The Committee considered the ICERs for the non-familial hypercholesterolaemia populations (that is, the high-risk cardiovascular disease and the recurrent events / polyvascular disease [non-familial] populations). For those populations in which a statin is an appropriate treatment, the Committee was concerned that the comparator had been modelled as a statin alone, and not a statin in combination with ezetimibe (see section 4.4). In addition, for all the populations, it was concerned that evolocumab had not been included as a comparator in an incremental analysis (see section 4.5). The Committee noted that all of the ICERs (including those for people who are unable to take statins) were in excess of £30,000 per QALY gained and therefore exceeded the range normally considered to be a cost-effective use of NHS resources (up to £20,000–30,000 per QALY gained). Therefore, the Committee concluded that alirocumab was not a cost-effective use of NHS resources and did not recommend alirocumab for the non-familial hypercholesterolaemia populations.	Recommend deletion of the following statement, or revision: For those populations in which a statin is an appropriate treatment, the Committee was concerned that the comparator had been modelled as a statin alone, and not a statin in combination with ezetimibe (see section 4.4).	This is incorrect. The relevant information is presented in paragraphs 3.40., 3.41., and Tables 3 and 4 within the ACD

Page 38 Paragraph 4.14	In summary, the Committee considered that the ICERs presented for its consideration contained several uncertainties. In particular, the Committee was concerned by the absence of ezetimibe plus a statin as a comparator in the analyses for the non-familial hypercholesterolaemia populations, and evolocumab as a comparator for all the populations. The Committee recalled its earlier conclusion that both alirocumab and evolocumab appeared to have similar efficacy in terms of LDL-c reduction and, therefore, their relative drug acquisition costs would be a likely key driver of their cost-effectiveness. Therefore, the Committee concluded that both the high ICERs and key uncertainties meant that alirocumab was not a cost-effective use of NHS resources and therefore did not recommend alirocumab for treating hypercholesterolaemia (heterozygous-familial and non-familial).	Recommend deletion of the following statement, or revision: ezetimibe plus a statin as a comparator in the analyses for the non-familial hypercholesterolaemia populations, and	This is incorrect. The relevant information is presented in paragraphs 3.40., 3.41., and Tables 3 and 4 within the ACD
Page 42 Uncertainties around and plausibility of assumptions and inputs in the economic model	'Committee preferred the more up-to-date follow-up costs used in the ERG's exploratory analyses because the company's costs for each health state did not reflect the true cost associated with care following a cardiovascular event.'	'Committee preferred the more up-to-date follow-up costs used in the ERG's exploratory analyses because the company's costs for each health state were conservative and did not reflect the true cost associated with care following a cardiovascular event.'	Point of clarification – conservative approach
Page 45 What are the key drivers of cost effectiveness?	For those populations in which a statin is an appropriate treatment, the Committee was concerned that the comparator had been modelled as a statin alone, and not a statin in combination with ezetimibe. In addition, for all the populations, it was concerned that evolocumab had not been included as a comparator in an incremental analysis.	Recommend revision of the following statement: For those populations in which a statin is an appropriate treatment, the Committee was concerned that the comparator had been modelled as a statin alone, and not a statin in combination with ezetimibe.	This is incorrect. The relevant information is presented in paragraphs 3.40., 3.41., and Tables 3 and 4 within the ACD

HEART UK
THE CHOLESTEROL CHARITY

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TO: NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

RE: Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia [ID779]

FROM: [redacted]
HEART UK- The Cholesterol Charity

DATE: 29th February 2016

This submission from HEART UK has been prepared by [redacted] MSc, MD, FRCP [redacted] Medical Scientific & Research Committee, Consultant Physician and Endocrinologist & Clinical Lead Department of Medicine. Honorary Senior Lecturer [redacted] MD FRCP FRCPath [redacted] Medical Scientific & Research Committee, Consultant in Biochemistry& Metabolic Medicine [redacted] and [redacted] MBBS, MSc, FRCPath, Consultant Chemical Pathologist, [redacted].

HEART UK consulted on this submission and has additional support of 84 individuals, including 56 health care professionals. The authors and some of the listed supporters of this submission are leading experts in the UK and Worldwide.

HEART UK are very disappointed that NICE has chosen not to recommend alirocumab (Praluent®) for low density lipoprotein cholesterol (LDL-C) reduction for high cardiovascular risk patients at this time.

We have previously commented on NICE's evaluation of evolocumab and it is our view that these 2 PCSK9 inhibitors should be compared by their effectiveness in lowering LDL cholesterol (LDL-C). This appears to be the same and head to head comparison would be futile. Both drugs are likely to be reserved for people who are at particularly high risk of CVD,

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including people with HeFH, and those who cannot tolerate statins and in whom ezetimibe does not adequately control LDL-C.

There are several groups of patients with unmet clinical need for additional lipid lowering therapy, including:

1. Patients with HeFH have high LDL-C from birth due to an inherited defect in LDL-C catabolism and accelerated atheroma formation. Such patients may fail to reach achieve adequate LDL-C lowering either due to a high starting level or intolerance to statins resulting in increased mortality. A particularly high priority group are those with progression of CAD requiring interventions

2. Patients with cardiovascular disease but high LDL-C level despite maximum existing medical therapy

3. Alirocumab is a potential alternative treatment for patients, who meet the criteria for lipoprotein apheresis. It may allow discontinuation or less frequent apheresis

4. Patients with diabetes and metabolic syndrome with high LDL-C despite maximum statin therapy and reasonable glycaemic control.

Section 3.44 in the ERG statement supports this view. Subgroup analysis by baseline LDL-C shows marked decreases in ICER comparing baseline 2.56 mmol/L with.4.13 mmol/L. In the secondary prevention familial hypercholesterolaemia group comparing alirocumab with statin plus ezetimibe and in the high risk non-familial population comparing alirocumab with statin alone the costs per QALY were £14,242 and £16,043. This must also be true if the comparator is without statin.

We believe that alirocumab should be recommended to these high-risk patients with cardiovascular disease who fail to attain an LDL-C lower than 3.0 mmol/L despite maximum tolerated medical therapy. We accept that as for evolocumab, this might be set as high as

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4.0 mmol/L for primary prevention pending outcome studies. We agree there is no robust evidence to support lowering LDL-C below 1 mmol/l and this is largely because there are no sufficiently potent second line medications to be used with statins to achieve such low levels. On-going studies should clarify this point. However, this is not relevant to high risk patient groups with high LDL-C despite maximum medical therapy because they are not expected to achieve LDL-C levels below 1mmol/L due to high LDL-C levels prior to deploying PCSK9 inhibitors (as proposed in evolocumab application).

There is a powerful rational for adopting a target based approach to management of patients at very high cardiovascular risk associated with high LDL-C. LDL- C is a principal driver of atherogenesis and is the key target for intervention. The lowering of LDL-C is critically related to decreased atheroma volume and improved plaque stability. Mendelian randomisation studies and studies lowering cholesterol by diverse means, have clearly shown that the magnitude of clinical benefit in preventing cardiovascular disease (CVD) events relates to the extent of LDL-C lowering rather than the mechanism itself.

Nevertheless, PCSK9 inhibitors work in the same way as statins by up-regulating the LDL receptor. The bulk of data underpinning the relationship between LDL-C lowering has been established from statin trials.

We agree with NICE that LDL-C lowering is an acceptable surrogate for effectiveness in preventing CVD. Against a background of LDL-C lowering with statin and ezetimibe patients treated with PCSK9 inhibitors more often achieve acceptable LDL-C lowering targets. It should be recalled that regulatory approval has been given to alirocumab in the absence of data on outcomes.

Nevertheless, meta-analysis of 24 PCSK9 inhibitor trials including 10,000 patients has shown 55% reduction in all-cause mortality, a 50% reduction in cardiovascular mortality and 51% reduction in myocardial infarction; all statistically significant. There have been no signals of harm in clinical trials although extended surveillance is needed as with all new drugs. It should be remembered that the use of monoclonal antibody medicines is a generic therapy with the nature of the monoclonal determining its site of action and that about 50 of such treatments are in use.

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HEART UK believes that in their appraisal of alirocumab (Praluent®) NICE has significantly underestimated its clinical utility and the unmet clinical need.

This has disadvantaged patients with heterozygous familial hypercholesterolaemia as a group and many patients at increased cardiovascular risk who cannot adequately lower their LDL-C by existing treatments.

Such patients may be offered apheresis, which is invasive and inconvenient. PCSK9 treatment may substitute for this treatment and/or make it more effective. **Patients currently treated by apheresis have therefore been disadvantaged**. We believe that the cost effectiveness of treating patients with raised LDL-C has been based on a low baseline LDL-C and insufficient account has been taken of the data provided by Sanofi on the cost effectiveness in groups with high LDL-C.

Additionally, for consideration by NICE, ought to be the impact of recommendations and decisions it makes on this class of medicines and the following comments were received when HEART UK consulted widely on the ACD:

"There are not many patients like myself that despite taking all medications at maximum doses ie rosuvastatin and estimibe, ldl-aphersis. I still don't reach those allusive target figures especially those for lipoprotein a.

I have read the NICE guidance and it is so unfair that it is staggering.

All I can think is that FH patients with high LDL 4mmols on maximum treatment have been forgotten.

We will not appear on any drug trials as often we are deemed to high risk to be allowed on a blind study and not get the medications we need to live.

These studies therefore do not represent the effect a drug like this can have on a population like myself.

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Currently LDL aphersis is the only way to remove most lipoprotein out of my blood my levels despite dual tablet therapy come in at over 3000 and I leave with them around 1000 this in combination with a high ldl level make for an aggressive form of vascular insult.

In last 18 months I have had several events and I was hoping for the last piece in the jigsaw to fall in to place to control the factors me and my doctors can't control.

I have been told all my life I was born a generation too early and have not only had to fight disease but also for treatment after the event.

They need to be made aware that people with severe FH don't have a choice about whether a drug as side effects like statins because a side effect is a small price to pay for a active life.

The same with apheresis it is not a choice; it has extended my life by 16 years and counting."
[redacted]- patient

"My parents both died of heart disease. Had they been born a generation later, their lives may have been saved and transformed with today's generation of drugs. I believe everyone with high cholesterol should have equitable access to drugs, for their personal quality of life, in turn for their family's quality of life and, additionally, for the potential cost savings to the health service for heart disease averted or mitigated.

My parents were German Jewish refugees - Ashkenazi Jews. Despite best attempts with diet and lifestyle, my cholesterol level remains stubbornly higher than it should be. I have never sought diagnosis of cholesterol-familial hypercholesterolemia, but there must be many descendants of Ashkenazi Jews like me who may need life-enhancing and life-saving drugs for this inherited condition.

I applaud your energy and efforts into campaigning on behalf of us all.
Thank you."
NAME REDACTED- patient

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"I support this campaign due to my mother has to have regular dialysis treatments due to FH this would thoroughly improve her condition of life and I believe that every Human being should have a right to this.

She cannot move away or to other parts of the country as lack of these machines are available and if these inhibitor medicines will help her either to reduce treatment or not at all then I believe this to be more cost effective solution to treating her condition."
NAME REDACTED – patient

"This is ridiculous that NICE plays a role of inhibitor as opposed to facilitator. I believe a campaign should be put in place to revisit the mission of NICE as we are fed up of medicine being denied to people who need it. This is valid for cancer, heart or any other life threatening conditions.

Enough is enough!"
NAME REDACTED - patient

"As a sufferer of homozygous FH with pre-existing atherosclerosis at only 36 I am doing EVERYTHING I can to keep myself as healthy as possible. Having just had a child through surrogacy I want to do everything I can to see him grow up. Denying persons like myself access to these potentially vital new medications is tantamount to telling me to accept that NICE feels it's ok to limit my life expectancy due to a malignant atherosclerosis, a hard pill to swallow when I know there are options like this I'm being denied access to.

I urge NICE to reconsider this."
NAME REDACTED - patient

"As heart attacks are one of the biggest killers, anything that can prevent them should be supported"
NAME REDACTED - patient

I have an inherited form of hyperlipidemia/ cholesterolemia which did not respond to the highest doses of statins until it was brought under control with fenofibrates and Omacor. These drugs were prescribed only after extensive investigations, over ten years ago, carried

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out by consultant lipidologist, [redacted], at the Royal Free Hospital. I find it unbelievable that NICE could take a decision on PCSK9 inhibitors without taking the views and opinions of expert lipidologists. I am amazed that decisions are taken without a more rigorous approach to scientific evidence, such as that available from expert lipidologists.
NAME REDACTED - health care professional and patient

"I am very concerned about the present NICE view and strongly support that lipidologists should have been represented on the committee

I had a NSTEMI =+ one stent 2013 (58y - no other risk factors) , I have some arteriosclerosis in my carotid arteries and some small vessel disease)

There is strong FH of polygenic dyslipidaemia

I have Lipoprotein (a) over 1000 (was over 1400 before I started on Nicotinamide 2 gram per day)

I am on rosuvastatin 20mgm etc

I am under the Hammersmith lipid clinic.

NICE are recommending that I should consider self funding for PCSK9 inhibitor treatment in the light of my high Lp(a) level- this must surely be available on the NHS for patients like myself."
NAME REDACTED - GP and patient

Supporters for this submission include 56 health care professionals and 28 members of the public and patients. The names of these supporters have been provide to NICE.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Consultant Medical Biochemist
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD: I would consider alirocumab (and evolocumab) to be a valuable addition to the treatment options for a small select group of patients attending lipid clinics: those with heterozygous familial hypercholesterolaemia or established CVD, (particularly younger patients) who have ALSO failed to respond or are intolerant of the currently available treatment options, including all five statins, ezetimibe and bile-acid sequestrants. The new agents provide a more acceptable alternative to apheresis in this circumstance	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Consultant Chemical Pathologist
Other role	
Organisation	
Location	
Conflict	N/A
Notes	
Comments on individual sections of the ACD: Alirocumab should be recommended for high-risk patients who fail to attain an LDL-C lower than 3.0 mmol/L despite maximum tolerated medical therapy. As for evolocumab, this might be set as high as 4 mmol/L pending outcome studies. Section 3.44 in the ERG statement supports this view. Subgroup analysis by baseline LDL-C shows marked decreases in ICER comparing baseline 2.56 mmol/L with.4.13 mmol/L. In the secondary prevention familial hypercholesterolaemia group comparing alirocumab with statin plus ezetimibe and in the high risk non-familial population comparing alirocumab with statin alone the costs per QALY were £14,242 and £16,043. This must be even better if the comparator is without statin. The higher the LDL-C the greater the potential for benefit from cholesterol lowering as this relates to	

absolute LDL-C reduction. Many factors contribute to cardiovascular risk but few are reversible.

The suggestion that there should be a head to head comparison of the effectiveness of alirocumab and evolocumab is misguided. They have very similar effects on LDL-C lowering and a trial would be futile. I am sure that there could be some movement on cost. These drugs should be used in in secondary prevention in patients with an LDL-C somewhere between 3.0 and 4.0 mmol/L at the very least in addition to maximum tolerated lother lipid lowering therapy. Similar patients will qualify for lipoprotein apheresis, which is about 10 times as expensive.

I was reminded today in clinic of a group of patients for whom PCSK9 inhibitors are a designer drug. Patients with activating mutations causing increased levels of PCSK9 proteins. Such patients have structurally normal and fully active LDL receptors but have low LDL receptor activity due to PCSK9 catabolism. Unsurprisingly, they respond better than other groups of patient to PCSK9 inhibitors. Clinically, they have a severe phenotype. The patient in question has had a CABG, sequential angioplasties and is just recovering from aortic valve surgery. Aortic arch atheroma is a consequence of poorly controlled familial hypercholesterolaemia. These patients respond relatively poorly to statins because statins increase PCSK9 levels. Although this mutation is a minor cause of familial hypercholesterolaemia they are probably over represented in lipd clinics due to their severe phenotype and poor response to statins. All of this misery is caused by increased PCSK9 levels and it should be inhibited. The category of patient for health economic analysis would be heterozygous familial hypercholesterolaemia with progressive arterial disease and an LDL cholesterol above 4 mmol/L on maximum tolerated standard treatment. In fact this patient is not statin intolerant and is treated with atorvastatin 80mg, ezetimibe 10 mg and colesevelam**.**

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	Consultant Chemical Pathologist
Other role	
Organisation	
Location	
Conflict	Yes - Currently seeing patients in open label treatment extension of a double blind trial of an anti PCSK9 inhibitor.
Notes	
Comments on individual sections of the ACD:	

There is a considerable unmet clinical need for anti-PCSK9 inhibitors - for example secondary prevention patients who are statin-intolerant and with LDL cholesterol not even close to target despite ezetimibe monotherapy.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
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Name	[redacted]
Role	Consultant Chemical Pathologist
Other role	
Organisation	Welsh Chemical Pathologists Group
Location	Wales
Conflict	The Scientific Adviser Cardiovascular- [redacted], [redacted] presented clinical and safety data on alirocumab to us at the recent Welsh Chemical Pathologists meeting.
Notes	

Comments on individual sections of the ACD:

The Welsh Chemical Pathologists Group (WCPG) is an association of Consultant and Trainee Chemical Pathologists working in Wales, and members of this group provide specialised lipid clinic services for patients with difficult and complex lipid disorders throughout Wales. The WCPG discussed the NICE appraisal consultation document entitled Hypercholesterolaemia (primary) and dyslipidaemia (mixed) - alirocumab [ID779] at its last meeting on 25th February 2016.

1. It is acknowledged that Alirocumab should be reserved primarily for patients established as being at high risk of CVD, which would include patients with genetically confirmed Heterozygous Familial Hypercholesterolaemia and those patients who are unable to tolerate statin therapies and in whom Ezetimibe is ineffective in controlling the LDL-C levels. It is disappointing, therefore that NICE has chosen not to recommend the use of Alirocumab, particularly as we have a significant number of patients in Wales who would fall into this cohort of patients and would therefore, potentially benefit from PCSK9 therapy, especially as this therapeutic product has proven LDL-C lowering capacity.

2. LDL-C Lowering is associated with reducing CVD Risk and the number of CVD Events. It is well established that lowering LDL-C is associated with reducing CVD Risk and events via statin therapies and other lipid modifying approaches. It is noted that some statin therapies and Ezetimibe were approved for therapeutic use prior to confirming clinically proven outcome efficacy. The PCSK9 Inhibitors have been shown to have a significant LDL-C lowering capacity via a mechanism that is similar to that of Statin therapies, notably by increasing the number of cell surface LDL receptors. Whilst it is acknowledged that there is currently no completed clinical outcome data re PCSK9 inhibitors there seems little reason to question the use of LDL-C lowering capacity as a surrogate marker for CVD risk and event reduction.

3. Unmet Clinical Need in Wales:

(i) We have a well established Genetic Testing service in Wales which is identifying an increasing number of genetically confirmed FH and whilst these patients are initially treated with optimal statin therapy, a significant proportion of these patients are either not reaching satisfactory targets or are intolerant of all available statins and hence remain at increased risk of developing premature CVD and/or exacerbating further CVD events if left unsatisfactorily controlled.

(ii) We have a well established Lipid Clinic Service across Wales which is managed by members of the Welsh Chemical Pathologists across each of the Health Boards across the Principality. These clinics as well as being responsible for managing patients with genetically proven FH also see a very large number of patients with CVD and/or Diabetes mellitus with concomitant dyslipidaemia including mixed dyslipidaemia whom also require optimisation of their lipid profiles. As with the FH patients there are a significant number of patients within these groups of patients who are unable to tolerate statin therapies and whose lipid profile is not adequately managed by Ezetimibe alone.

(iii) Both these types of patients are therefore, likely to benefit from PCSK9 Inhibition and its proven LDL-C lowering capacity and without adequate treatment remain at sustained risk of CVD and CVD events.

4. Given the evident biochemical efficacy of Alirocumab treatment with a reassuring tolerability profile and given the significant current unmet clinical need in Wales we would strongly urge NICE to reconsider its recommendations in the draft appraisal with a view to recommending using this product in as wide a population as is cost effectively feasible.

5. Although this Appraisal concerns Alirocumab our comments given above would apply to any PCSK9 inhibitors that come to market.

Section 1 (Appraisal Committee's preliminary	

recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	[redacted]
Other role	
Organisation	Wales Familial Hypercholesterolaemia Professional Advisory Group
Location	Wales
Conflict	
Notes	

Comments on individual sections of the ACD:

[redacted]; All Wales FH Professional Advisory Group

[redacted]

[redacted]

[redacted]

Email [redacted]

[redacted]

Response from Wales FH Professional Advisory Group

This response is written on behalf of the Wales FH professional advisory group, which has professional oversight of the All Wales Familial Hypercholesterolaemia (FH) service. This group has extensive clinical experience of assessing and treating patients with inherited hyperlipidaemia, particularly FH.

On clinical grounds we consider that PCSK9 inhibitors should have a specific indication for treating

Patients with FH who are intolerant of statins

Treating patients with FH who have progressive cardiovascular disease with persistently elevated LDL cholesterol concentrations despite optimum treatment by all other approaches.

We note that the NICE assessment committee felt that it had insufficient evidence to fully assess these indications. We have summarised our views under 5 headings as

below.

1) FH is an inborn error of metabolism

We consider that FH is a special case and should be regarded as an inborn error of LDL cholesterol metabolism that requires specific and targeted treatment to lower LDL cholesterol.

2) PCSK9 genetic variants cause/protect from heart disease

One of the genetic mutations that cause FH is a gain of function mutation in the PCSK9 gene which leads to increased PCSK9 protein expression. This in turn causes the LDL receptors to be degraded in the cell so that they are available for further clearance of LDL cholesterol from the blood stream.

Conversely there is now clear evidence that individuals with genetically lower PCSK9 concentrations have lower LDL cholesterol concentrations and significantly lower rates of coronary heart disease. Also some individuals with genetically absent PCSK9 have been described with no adverse clinical features which is very reassuring from a safety perspective.

3) The clinical argument for statin therapy in FH also applies to PCSK9 inhibitors

It should be noted that the clinical evidence for statin benefit in FH is not based on randomised clinical trials in FH but rather the pharmacological evidence that it targets LDL cholesterol metabolism, combined with general safety and efficacy data. Randomised placebo controlled trials of statin therapy on cardiovascular events, have not been carried out in FH because it would be regarded as unethical to withhold statin therapy in FH patients. (NICE FH guideline GC 71 2008). Similarly, we would regard it as clinically unethical to withhold treatment with PCSK9 inhibitors from patients with FH in situations where other therapy is not tolerated (ie statins) or is not effective.

4) PCSK9 inhibitors are a form of personalised medicine to be used as a 3rd line agent

In the era of personalised medicine, we would regard PCSK9 inhibitors as an agent that specifically targets the metabolic defect that is FH. This should be regarded as genetically targeted 3rd line therapy (after statins and ezetimibe) for patients who are not suitable for these first and second line agents.

5) The number of patients appropriate for PCSK9 inhibitors will be small

We estimate that the proportion of FH patients who cannot tolerate statins is less than 5% of the patients with a diagnosis of FH. Therefore we think that the number of patients requiring PCSK9 inhibitors would be relatively small.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4	

(Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Appendix 2

Summary

- Revised analyses use the Appraisal Committee's preferred modelling approach and a new PAS

- New base-case results indicate alirocumab, as an adjunct to ezetimibe plus statins, is cost-effective in patients who are at high and very high risk because their LDL-c remains far from goal:

  >=3.0 mmol/L despite maximally tolerated LMTs

  - **Secondary prevention heterozygous-familial population**

    (£22,600/QALY vs. ezetimibe + statin; with a probability of being cost-effective at £30,000/QALY of 93%)

  - **Secondary prevention recurrent events / polyvascular (non-familial) population**

    (£27,644/QALY vs. ezetimibe + statin; with a probability of being cost-effective at £30,000/QALY of 67%)

  >=4.0 mmol/L despite maximally tolerated LMTs

  - **Primary prevention heterozygous-familial population**

    (£37,228/QALY vs. ezetimibe + statin; factors related to uncertainties in baseline risk data indicates this figure may be conservatively high)

  - **Secondary prevention High-risk cardiovascular (non-familial) population**

    (£24,835/QALY vs. ezetimibe + statin; with a probability of being cost-effective at £30,000/QALY of 85%)

- Revised scenario analyses for statin intolerant populations indicates that ICERs improve for all groups at all cut-offs, with alirocumab becoming cost-effective in more groups at lower LDL-c cut-offs.

- Scenario analyses indicate that the ICERs would fall further if alternative rate ratios from the CTTC meta-analyses – as accepted in other recent NICE appraisals – were applied to the alirocumab model.

Change to the confidential discount

A new confidential discount to the price of alirocumab has been agreed with the Department of Health. The list price and details of the proposed scheme are provided in Table 1 below.

Table 1. Current list price and new PAS discount.

	List price and discount
Current UK list price(s)	Alirocumab is available at 75mg and 150mg doses as a single use pre-filled pen in either a 1-pen or 2-pen pack 75 MG pack of 1 pen: £168 75 MG pack of 2 pens: £336 150 MG pack of 1 pen: £168 150 MG pack of 2 pens: £336
Updated discount	[redacted]

Model specification for the revised cost-effectiveness analyses incorporating the new PAS

The model adjusted by the ERG for their exploratory analyses, and endorsed by the Appraisal Committee as their preferred specification, has been used to produce these revised analyses. Adjustments listed in paragraph 3.46 of the ACD are applied throughout these results:

- applied annual post-cardiovascular event costs (such as care for stroke) over the entire modelled time horizon (lifetime) instead of 3 years
- applied follow-up costs to the second half of first year costs following a cardiovascular event
- applied an updated cost of £8618 for stroke and an annual care cost for stroke of £1769
- applied a rate ratio of 0.79 per 1 mmol/L reduction in LDL-c for ischaemic stroke based on results from CTTC, instead of assuming the same rate ratio of 0.64 per 1 mmol/L reduction
- applied an annual discontinuation rate of 8% instead of 0% so that it is consistent with discontinuation observed in ODYSSEY and LONG-TERM
- applied the effects of ezetimibe on LDL-c reduction using rate ratios from CTTC.

With the exception of identified sensitivity analyses, the revised results use the CTTC meta-analyses to determine the link between LDL-c reduction and cardiovascular outcomes.

One additional modification has been made, and this has been done to support the Appraisal Committee's decision-making in light of feedback regarding the choice of original intervention thresholds. Alternative baseline mean LDL-c values for each population – important in the calculation of the population's baseline CV risk – have been used in order to report results for the more pragmatic LDL-c intervention thresholds (cut-offs).

a) >=2.0 mmol/L; b) >=2.5 mmol/L; c) >=3.0 mmol/L; d) >=3.5 mmol/L; e) >=4.0 mmol/L

Mean LDL-c values for each population of patients with LDL-c values in excess of the specified thresholds despite maximally tolerated LMTs could not extracted from the original THIN dataset in time for this response, so to derive revised mean LDL-c values, a simple interpolation of the existing means and thresholds was examined for suitability. The relationship between mean LDL-c values and the original cut-off thresholds indicated a simple positive linear relationship was appropriate for all subgroups. As the new thresholds fall within the range defined by the original thresholds, it was considered reasonable to use the 'TREND' function in Excel to generate revised mean LDL-c values for each new cut-off threshold, in each population. Table 2 presents the original and revised mean

LDL-c values, for each population subgroup, for intervention threshold. In each subgroup, the approximated linear relationship is reported.

Table 2 Mean LDL-c values used to calculate baseline risk at different intervention cut-offs

Population	**Intervention thresholds**				
Primary prevention heterozygous-familial population					
Original submission thresholds for intervention	**>= 1.81 mmol/L**	**>= 2.59 mmol/L**	-	**>= 3.36 mmol/L**	**>= 4.13 mmol/L**
Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	4.50 0.125 1.81-7.20	4.82 0.131 2.59-7.05	-	5.28 0.139 3.36-7.20	5.59 0.143 4.13-7.05
Revised thresholds for ACD consultation [Approximated y = 0.4809x + 3.6188]	**>= 2.0 mmol/L**	**>= 2.5 mmol/L**	**>= 3.0 mmol/L**	**>= 3.5 mmol/L**	**>= 4.0 mmol/L**
Revised Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	4.58 0.127 2.00-7.16	4.82 0.131 2.50-7.14	5.06 0.135 3.00-7.12	5.30 0.139 3.50-7.10	5.54 0.143 4.00-7.08
Secondary prevention heterozygous-familial population					
Original submission thresholds for intervention	**>= 1.81 mmol/L**	**>= 2.59 mmol/L**	-	**>= 3.36 mmol/L**	**>= 4.13 mmol/L**
Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	4.40 0.123 1.81-6.98	4.56 0.126 2.59-6.52	-	4.80 0.131 3.36-6.25	5.23 0.138 4.13-6.33
Revised thresholds for ACD consultation [Approximated by = 0.3557x + 3.6893]	**>= 2.0 mmol/L**	**>= 2.5 mmol/L**	**>= 3.0 mmol/L**	**>= 3.5 mmol/L**	**>= 4.0 mmol/L**
Revised Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	4.40 0.123 2.00-6.80	4.58 0.127 2.50-6.66	4.76 0.130 3.00-6.51	4.93 0.133 3.50-6.37	5.11 0.136 4.00-6.22
Secondary prevention High-risk cardiovascular (non-familial) population					
Original submission thresholds for intervention	**>= 1.81 mmol/L**	**>= 2.59 mmol/L**	-	**>= 3.36 mmol/L**	**>= 4.13 mmol/L**
Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	2.68 0.082 1.81-3.54	3.31 0.100 2.59-4.02	-	4.03 0.116 3.36-4.70	4.76 0.130 4.13-5.38
Revised thresholds for ACD consultation [Approximated by y = 0.9012x + 1.0136]	**>= 2.0 mmol/L**	**>= 2.5 mmol/L**	**>= 3.0 mmol/L**	**>= 3.5 mmol/L**	**>= 4.0 mmol/L**
Revised Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	2.82 0.086 2.00-3.63	3.27 0.099 2.50-4.03	3.72 0.109 3.00-4.43	4.17 0.119 3.50-4.84	4.62 0.128 4.00-5.24
Secondary prevention Recurrent events / polyvascular (non-familial) population					
Original submission thresholds for intervention	**>= 1.81 mmol/L**	**>= 2.59 mmol/L**	**-**	**>= 3.36 mmol/L**	**>= 4.13 mmol/L**
Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	2.66 0.082 1.81-3.52	3.31 0.100 2.59-4.03	-	4.05 0.117 3.36-4.73	4.78 0.130 4.13-5.43
Revised thresholds for ACD consultation [Approximated by y = 0.9162x + 0.9766]	**>= 2.0 mmol/L**	**>= 2.5 mmol/L**	**>= 3.0 mmol/L**	**>= 3.5 mmol/L**	**>= 4.0 mmol/L**
Revised Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	2.81 0.086 2.00-3.62	3.27 0.099 2.50-4.04	3.73 0.110 3.00-4.45	4.18 0.119 3.50-4.87	4.64 0.128 4.00-5.28

Data on baseline LDL-c values for statin intolerant patients for each cut-off were obtained from the ALTERNATIVE trial (Table 3). For comparisons of alirocumab plus ezetimibe vs ezetimibe (statin intolerant patients receiving alirocumab as an adjunct) baseline LDL-c data from the ezetimibe-arm were used. For comparisons of alirocumab versus ezetimibe (a direct comparison of alirocumab versus ezetimibe in statin intolerant patients) baseline LDL-c data after the trial wash-out period was used.

Table 3 Mean LDL-c values used to calculate baseline risk at different intervention cut-offs – statin intolerants

Population	**Intervention thresholds**				
Primary & Secondary prevention heterozygous-familial population					
Revised thresholds for ACD consultation	**>= 2.0 mmol/L**	**>= 2.5 mmol/L**	**>= 3.0 mmol/L**	**>= 3.5 mmol/L**	**>= 4.0 mmol/L**
Alirocumab plus ezetimibe vs. ezetimibe					
Revised Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	N/A	5.25 0.138 2.5 – 7.99	5.36 0.140 3.0 – 7.71	5.55 0.143 3.5 – 7.60	5.99 0.149 4.0 – 7.98
Alirocumab vs. ezetimibe					
Revised Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	N/A	7.18 0.164 2.5 – 11.87	7.18 0.164 3.0 – 11.37	7.18 0.164 3.5 – 10.87	7.33 0.166 4.0 – 10.65
Secondary prevention High-risk cardiovascular (non-familial) population & Recurrent events / polyvascular (non-familial) populations					
Revised thresholds for ACD consultation	**>= 2.0 mmol/L**	**>= 2.5 mmol/L**	**>= 3.0 mmol/L**	**>= 3.5 mmol/L**	**>= 4.0 mmol/L**
Alirocumab plus ezetimibe vs. ezetimibe					
Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	N/A	3.98 0.115 2.5 – 5.46	4.20 0.120 3.0 – 5.39	4.60 0.127 3.5 – 5.69	4.91 0.133 4.0 – 5.83
Alirocumab vs. ezetimibe					
Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	N/A	4.60 0.127 2.5 – 6.70	4.72 0.129 3.0 – 6.45	4.94 0.133 3.5 – 6.88	5.31 0.139 4.0 – 6.62

Revised base-case results (including additional comparisons for the non-familial populations)

Table 4 presents the revised base-case ICERs (with incremental costs and QALYs) for each population, at one of four intervention thresholds. The comparators are presented as in the original submission, however *alirocumab plus ezetimibe and a* statin is also compared with *ezetimibe and a statin* for the non-familial populations analyses.

As observed in paragraph 3.44 of the ACD and paragraph 3.48 in relation to the ERG's own analysis, the ICERs for each population decrease as the baseline LDL-c level increases.

At all intervention thresholds, alirocumab as an adjunct is cost-effective in the secondary prevention heterozygous-familial population. At thresholds above >=3 mmol/L, alirocumab as an adjunct is cost-effective in the secondary prevention Recurrent events / polyvascular (non-familial) population, and at thresholds >= 4 mmol/L, alirocumab as an adjunct is cost-effective in the secondary prevention High-risk cardiovascular (non-familial) population.

Table 4 Revised ICERs (£/QALY) for key patient populations and comparators (Deterministic – using ERG/CTTC)

Population		>= 2.5 mmol/L	>= 3.0 mmol/L	>= 3.5 mmol/L	>= 4.0 mmol/L
Primary prevention heterozygous-familial population					
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	16,883 0.34 **49,682**	16,773 0.37 **45,004**	16,656 0.41 **40,880**	16,531 0.44 **37,228**
Secondary prevention heterozygous-familial population					
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	13,500 0.56 **24,091**	13,368 0.59 **22,600**	13,232 0.62 **21,233**	13,092 0.66 **19,973**
Secondary prevention High-risk cardiovascular (non-familial) population					
Alirocumab + Statin vs. Statin	Inc. Cost Inc. QALY ICER	13,659 0.31 **43,880**	13,394 0.38 **35,471**	13,105 0.45 **29,220**	12,789 0.52 **24,408**
Alirocumab + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	11,665 0.17 **69,430**	11,514 0.20 **56,334**	11,352 0.24 **46,787**	11,179 0.28 **39,566**
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	13,792 0.31 **44,308**	13,556 0.38 **35,899**	13,297 0.45 **29,647**	13,012 0.52 **24,835**
Secondary prevention Recurrent events / polyvascular (non-familial) population					
Alirocumab + Statin vs. Statin	Inc. Cost Inc. QALY ICER	12,381 0.37 **33,527**	12,051 0.44 **27,184**	11,696 0.52 **22,469**	11,312 0.60 **18,831**
Alirocumab + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	10,683 0.20 **53,137**	10,491 0.24 **43,276**	10,290 0.28 **36,105**	10,078 0.33 **30,686**
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	12,551 0.37 **33,987**	12,255 0.44 **27,644**	11,935 0.52 **22,929**	11,588 0.60 **19,291**

Cost-effectiveness results improve with increasing intervention threshold in the Primary prevention heterozygous-familial population as well, but the ICERs remain above £30,000/QALY. As described in the covering letter, one of the reasons why the primary prevention population produces higher ICERs than the secondary prevention familial hypercholesterolaemia population is because patients in the primary prevention population start the model 10 years earlier than their secondary prevention counterparts (age 50 vs age 60). This affords them more time in the model – to accrue more costs – and whilst they live longer (average 18 years vs. 12 years) they die on average 4 years earlier (age 68 vs. 72).

The real-world data sources used to estimate base-line risks in the model may be a source of risk under-estimation also affecting the ICERs. To examine the threshold of baseline risk at which the primary prevention population achieves cost-effective ICERs at £30,000/QALY we used the 'goal-seek' function in Excel to adjust factors affecting baseline risk. Each factor was adjusted simultaneously and proportionality to their original values maintained. As can be seen from Table 5 the goal-seek analysis indicates that underlying baseline risks must increase by only 50% for the >=4mmol/L cut-off to achieve this level of cost-effectiveness, representing a change for the composite CV event rate of 2.26% to 3.43%.

It requires a relatively modest adjustment to baseline risk for alirocumab to be considered cost-effective at £30,000/QALY in this primary prevention population. If the baseline risk in this population is indeed underestimated in the real-world evidence, this adjustment may be within a clinically plausible ranges.

Table 5 Sensitivity analysis on baseline CV risk components for primary prevention hypercholesterolaemia population to achieve an ICER of £30,000/QALY

LDL-c threshold	Mean LDL-c	Initial Age	Event risks				
			ACS	Revascularisation	Ischaemic stroke	CV death	Composite CV event
Risk levels derived for base-case model							
>= 4.0	5.54	50	1.49%	0.34%	0.20%	0.23%	**2.26%**
Risk levels derived to goal seek to achieve ICER of £30,000/QALY							
>= 2.5	4.82	50	4.13%	0.96%	0.58%	0.71%	6.38%
>= 3.0	5.06	50	3.09%	0.71%	0.43%	0.51%	4.74%
>= 3.5	5.30	50	2.59%	0.59%	0.35%	0.41%	3.95%
>= 4.0	5.54	50	2.26%	0.51%	0.31%	0.34%	**3.43%**

Probabilistic results

Table 6 and Table 7 present the probabilistic analyses for the original base case populations/comparisons. For simplicity, the results are presented for the two most relevant intervention thresholds; namely LDL-c cut-offs of >= 3.0 mmol/L and >= 4.0 mmol/L. The probabilistic results are similar to the deterministic results.

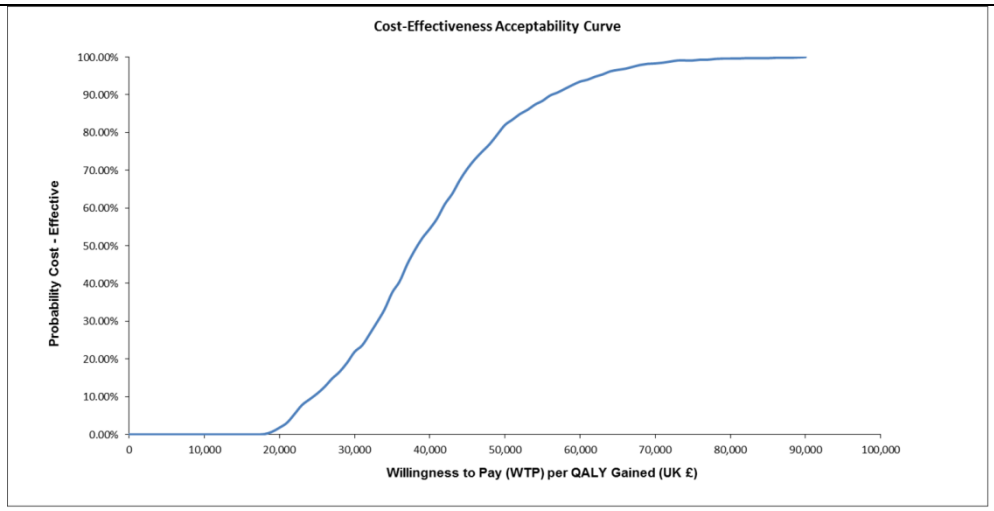
Table 6 Probabilistic results by willingness to pay threshold

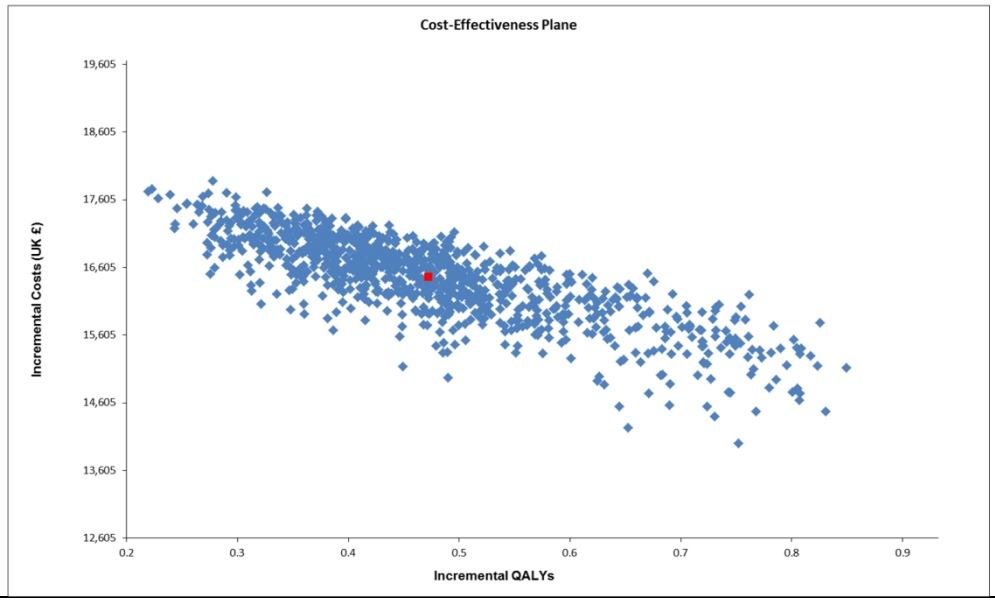
Population/Comparison	**WTP £20,000 / QALY**		**WTP £30,000 / QALY**	
	>= 3.0 mmol/L	**>= 4.0 mmol/L**	**>= 3.0 mmol/L**	**>= 4.0 mmol/L**
Primary prevention heterozygous-familial population				
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	0.2%	1.8%	9.0%	21.9%
Secondary prevention heterozygous-familial population				
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	31.6%	51.8%	88.4%	95.6%
Secondary prevention High-risk cardiovascular (non-familial) population				
Alirocumab + Statin vs. Statin	0.0%	17.8%	22.4%	81.0%
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	0.0%	14.6%	18.8%	78.2%
Secondary prevention Recurrent events / polyvascular (non-familial) population				
Alirocumab + Statin vs. Statin	5.4%	59.0%	67.2%	98.2%
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	5.8%	55.4%	62.6%	98.8%

Table 7 Revised ICERs (£/QALY) for key patient populations and comparators (Probabilistic – using ERG/CTTC)

Population		**>= 3.0 mmol/L**	**>= 4.0 mmol/L**
Primary prevention heterozygous-familial population			
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	16,708 0.38 43,439	16,466 0.45 36,650
Secondary prevention heterozygous-familial population			
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	13,245 0.60 22,192	12,976 0.66 19,662
Secondary prevention High-risk cardiovascular (non-familial) population			
Alirocumab + Statin vs. Statin	Inc. Cost Inc. QALY ICER	13,272 0.37 35,858	12,667 0.52 24,486
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	13,386 0.37 35,748	12,909 0.52 25,048
Secondary prevention Recurrent events / polyvascular (non-familial) population			
Alirocumab Statin vs. Statin	Inc. Cost Inc. QALY ICER	11,878 0.44 27,289	11,225 0.60 18,743
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	12,077 0.44 27,535	11,486 0.59 19,467

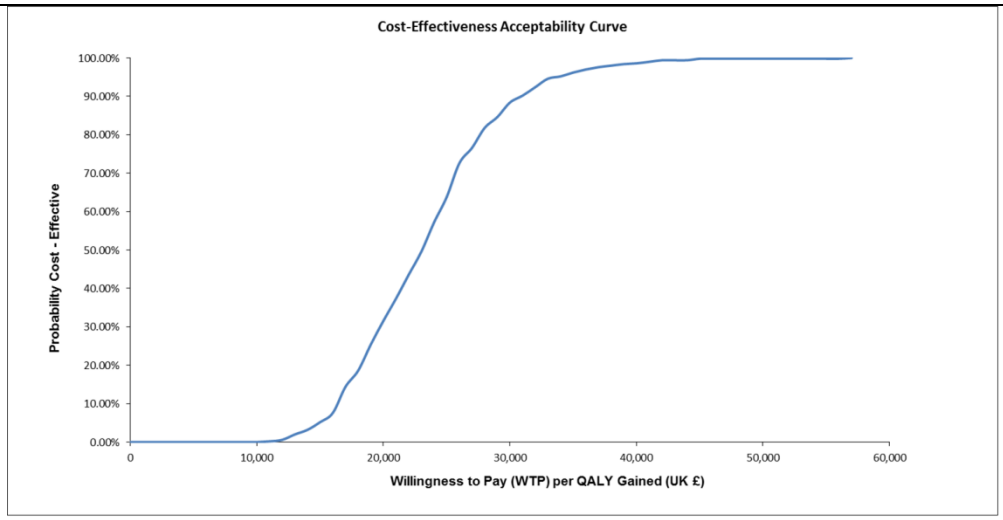
Figure 1 CEAC and C/E plane for Primary prevention heterozygous-familial population LDL-c >=4.0mmol/L

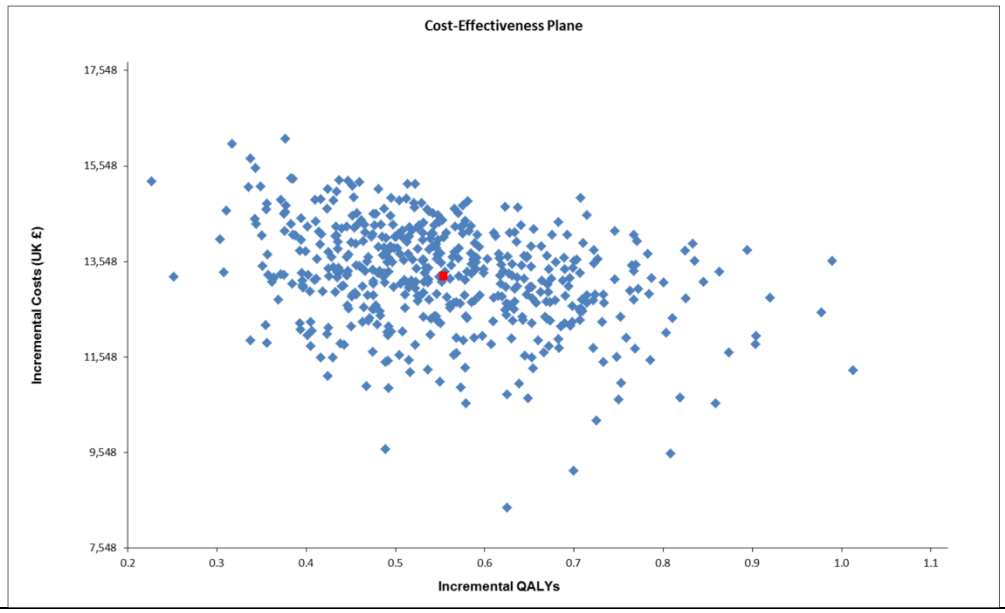




Alirocumab + Ezetimibe + Statin
Vs.
Ezetimibe + Statin

Figure 2 CEAC and /E plane for Secondary prevention heterozygous-familial population LDL-c >=3.0mmol/L





Alirocumab + Ezetimibe + Statin
Vs.
Ezetimibe + Statin

Figure 3 Secondary prevention High-risk cardiovascular (non-familial) population LDL-c >=4.0mmol/L

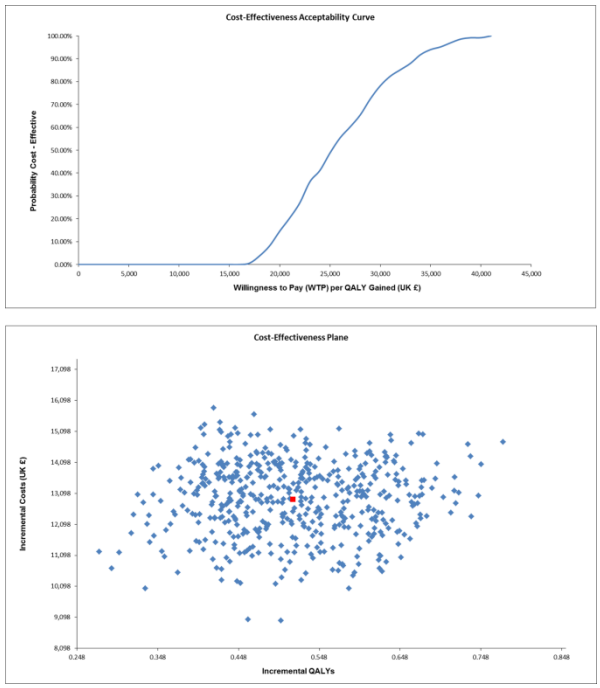
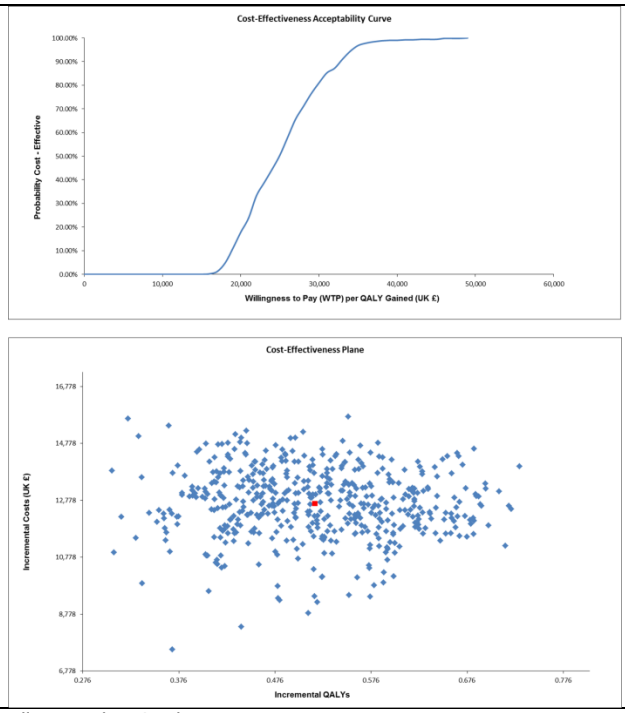
	
Alirocumab + Ezetimibe + Statin Vs. Ezetimibe + Statin	Alirocumab + Statin Vs. Statin

Figure 4 Secondary prevention Recurrent events / polyvascular (non-familial) population LDL-c >=3.0mmol/L

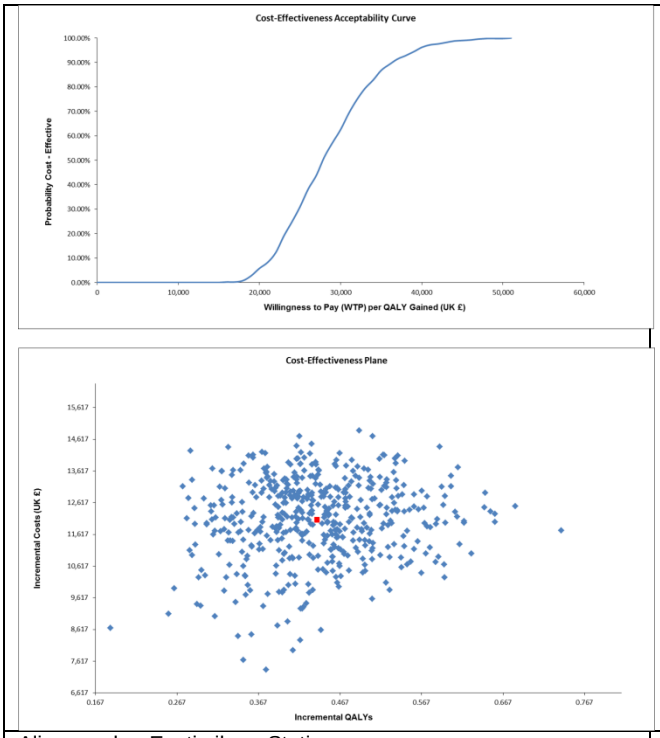
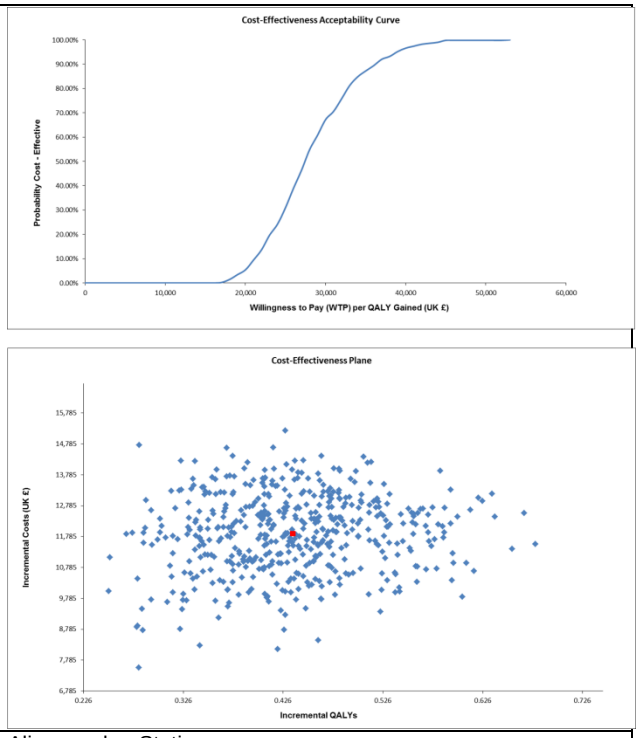
	
Alirocumab + Ezetimibe + Statin Vs. Ezetimibe + Statin	Alirocumab + Statin Vs. Statin

Table 8 presents the deterministic analyses for the original base case populations/comparisons using the Navarese meta-analysis. This is presented for comparison.

Table 8 Revised ICERs (£/QALY) for key patient populations and comparators (Deterministic – using ERG/Navarese)

Population		>= 3.0 mmol/L	>= 4.0 mmol/L
Primary prevention heterozygous-familial population			
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	16,998 0.60 28,171	16,785 0.70 24,134
Secondary prevention heterozygous-familial population			
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	14,790 1.24 11,884	14,625 1.34 10,904
Secondary prevention High-risk cardiovascular (non-familial) population			
Alirocumab + Statin vs. Statin	Inc. Cost Inc. QALY ICER	14,325 0.90 15,833	13,958 1.15 12,179
Alirocumab + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	12,447 0.73 16,973	12,349 0.91 13,640
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	14,749 0.90 16,301	14,492 1.15 12,645
Secondary prevention Recurrent events / polyvascular (non-familial) population			
Alirocumab + Statin vs. Statin	Inc. Cost Inc. QALY ICER	13,693 1.10 12,400	13,377 1.37 9,740
Alirocumab + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	12,137 0.91 13,399	12,146 1.10 11,020
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	14,256 1.10 12,910	14,075 1.37 10,248

Revised base-case results using CTTC rate ratios as applied in different appraisals

A comparison of CTTC-derived risk reductions per 1 mmol/L reduction in LDL-c for major coronary events and death employed in recent appraisals suggests that modelling of CTTC in the original alirocumab submission,[1] is more conservative than the use of CTTC accepted for other appraisals (**Error! Reference source not found.**).

To understand the implications of using alternative estimates, rate ratios for the main events were similarly sourced for from the same 2010 CTTC meta-analysis as detailed in **Error! Reference source not found.**.[2] Some adjustments were required due to the differing applications/models. For the adoption of CTTC as applied in the appraisal of evolocumab, 'CHD Death' and 'Stroke Death' were used, whereas the equivalent event in the alirocumab model was 'Any Vascular Death'. This value was therefore sourced from the 2010 CTTC meta-analysis.

For the adoption of CTTC as applied in the appraisal of ezetimibe, to be consistent, the rate ratio utilised for 'Any Stroke' was applied in the alirocumab model in place of 'Ischaemic Stroke'. In addition the rate ratio for 'Coronary Revascularisation', which although not applied in the ezetimibe analysis, was similarly sourced from the 2010 CTTC meta-analysis (Table 9).

Table 9 CTTC Rate Ratio (95% CI) per 1mmol/L reduction in LDL-c mapped from evolocumab and ezetimibe appraisals

	Rate Ratios in the base case for alirocumab	Rate Ratios mapped from ezetimibe	Rate Ratios mapped from evolocumab
Non-Fatal MI (ACS)	0.74 (0.71, 0.77)	0.74 (0.69, 0.78)	0.71 (0.58, 0.87)
Coronary Revascularisation	0.76 (0.73, 0.78)	0.76 (0.73, 0.80)	0.66 (0.60, 0.73)
Stroke*	0.79 (0.74, 0.85)	0.85 (0.80, 0.90)	0.69 (0.50, 0.95)
Any Vascular Death	0.88 (0.84, 0.91)	0.86 (0.82, 0.90)	0.86 (0.82, 0.90)

* Any stroke from the ezetimibe appraisal and Ischeaemic Stroke from the alirocumab/evolocumab appraisals

Table 10 presents the revised base-case ICERs (with incremental costs and QALYs) for each population, at one of four intervention thresholds, adopting the CTTC rate ratio strategies applied for the appraisal of evolocumab (ID765) and ezetimibe (ID627 - review TA132). The comparisons are presented as in the original alirocumab submission, however alirocumab plus ezetimibe and a statin is also compared with ezetimibe and a statin for the non-familial populations analyses.

Table 10 ICERs (£/QALY) for key patient populations and comparators (Deterministic–using ERG/CTTC variants)

Population / CTTC used in other appraisals		Appraisal ID 779 >= 3.0 mmol/L	Appraisal ID 627 >= 3.0 mmol/L	Appraisal ID 765 >= 3.0 mmol/L	Appraisal ID 779 >= 4.0 mmol/L	Appraisal ID 627 >= 4.0 mmol/L	Appraisal ID 765 >= 4.0 mmol/L
Primary prevention heterozygous-familial population							
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	16,773 0.37 45,004	16,912 0.39 43,466	16,386 0.46 35,319	16,531 0.44 37,228	16,707 0.46 35,966	15,997 0.56 28,456
Secondary prevention heterozygous-familial population							
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	13,368 0.59 22,600	13,657 0.65 20,902	12,846 0.69 18,618	13,092 0.66 19,973	13,417 0.72 18,513	12,434 0.77 16,208
Secondary prevention High-risk cardiovascular (non-familial) population							
Alirocumab + Statin vs. Statin	Inc. Cost Inc. QALY ICER	13,394 0.38 35,471	13,599 0.41 33,054	12,992 0.45 28,559	12,789 0.52 24,408	13,076 0.57 22,901	12,067 0.64 18,849
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	13,556 0.38 35,899	13,781 0.41 33,497	13,184 0.45 28,981	13,012 0.52 24,835	13,329 0.57 23,343	12,337 0.64 19,269
Secondary prevention Recurrent events / polyvascular (non-familial) population							
Alirocumab + Statin vs. Statin	Inc. Cost Inc. QALY ICER	12,051 0.44 27,184	12,404 0.49 25,423	11,455 0.53 21,726	11,312 0.60 18,831	11,797 0.66 17,828	10,311 0.72 14,384
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	12,255 0.44 27,644	12,638 0.49 25,903	11,692 0.53 22,175	11,588 0.60 19,291	12,115 0.66 18,308	10,631 0.72 14,832

Revised scenario analyses for statin intolerant populations

Error! Reference source not found. presents revised scenario analyses ICERs (with incremental costs and QALYs) for both the non-HeFH and HeFH statin intolerant populations, at a range of LDL-c cut-offs (>=2.5mmol/L; >=3mmol/L; >=3.5mmol/L and >=4mmol/L).

Table 11 Revised ICERs (£/QALY) for statin intolerant populations and comparators (Deterministic – using ERG/CTTC)

Population		>= 2.5 mmol/L	>= 3.0 mmol/L	>= 3.5 mmol/L	>= 4.0 mmol/L
Primary prevention heterozygous-familial population					
Alirocumab + Ezetimibe vs. Ezetimibe	Inc. Cost Inc. QALY ICER	16,628 0.40 41,639	16,571 0.42 39,887	16,465 0.45 36,949	16,208 0.52 31,330
Alirocumab vs. Ezetimibe	Inc. Cost Inc. QALY ICER	13,286 0.43 30,565	13,286 0.43 30,565	13,286 0.43 30,565	13,216 0.45 29,298
Secondary prevention heterozygous-familial population					
Alirocumab + Ezetimibe vs. Ezetimibe	Inc. Cost Inc. QALY ICER	12,878 0.68 18,926	12,785 0.70 18,244	12,610 0.74 17,085	12,195 0.82 14,799
Alirocumab vs. Ezetimibe	Inc. Cost Inc. QALY ICER	9,872 0.67 14,831	9,872 0.67 14,831	9,872 0.67 14,831	9,762 0.68 14,267
Secondary prevention High-risk cardiovascular (non-familial) population					
Alirocumab + Ezetimibe vs. Ezetimibe	Inc. Cost Inc. QALY ICER	13,338 0.42 31,882	13,204 0.45 29,132	12,942 0.52 24,890	12,716 0.58 22,081
Alirocumab vs. Ezetimibe	Inc. Cost Inc. QALY ICER	10,984 0.34 32,635	10,924 0.35 31,183	10,820 0.37 28,928	10,631 0.42 25,532
Secondary prevention Recurrent events / polyvascular (non-familial) population					
Alirocumab + Ezetimibe vs. Ezetimibe	Inc. Cost Inc. QALY ICER	11,994 0.49 24,685	11,832 0.52 22,628	11,518 0.59 19,440	11,250 0.65 17,316
Alirocumab vs. Ezetimibe	Inc. Cost Inc. QALY ICER	9,848 0.39 25,407	9,777 0.40 24,320	9,654 0.43 22,628	9,432 0.47 20,070

References

1. CTT et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 376, 1670-1681 (2010).

2. CTT et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 380, 581-590 (2012).

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

Critique of the new PAS ICERs and additional sensitivity analyses, which have been submitted by the company in response to the ACD

Produced by Aberdeen HTA Group

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Date completed 04 March 2016

Contains CIC/AIC

This report provides the ERG's commentary on an updated PAS submitted by the company (Sanofi) on 29/02/2016 as document: ID779 Alirocumab Sanofi PAS submisson v0.3 011215 JE [CIC] in response to the ACD and in advance of the second Appraisal Committee meeting for this appraisal. The ERG received these revised analyses on 1 March 2016. The results are discussed in the following sections.

The company's revised analysis

The Company provided a set of economic analyses applying a new patient access scheme. This takes the form of further simple discount on the list price, such that the drug price in the new analysis comes to [redacted] per pen irrespective of dose (75mg or 150mg) or pack size (1 or 2 pen pack). Thus, the annual cost for the drug in the model now comes to [redacted]

For the new set of analyses, the company has also applied the committee's preferred set of modelling assumptions, as outlined in section 3.46 of the ACD:

- applied annual post-cardiovascular event costs (such as care for stroke) over the entire modelled time horizon (lifetime) instead of 3 years
- applied follow-up costs to the second half of first year costs following a cardiovascular event
- applied an updated cost of £8,618 for stroke and an annual care cost for stroke of £1,769
- applied a rate ratio of 0.79 per 1 mmol/L reduction in LDL-c for ischaemic stroke based on results from CTTC meta-analysis, instead of assuming the same rate ratio of 0.64 per 1 mmol/L reduction
- applied an annual discontinuation rate of 8% instead of 0% so that it is consistent with discontinuation observed in ODYSSEY and LONG-TERM
- applied the effects of ezetimibe on LDL-c reduction using rate ratios from the CTTC.

With the exception of one set of analyses presented for comparison, the revised analyses used the CTTC meta-analyses to determine the link between alirocumab induced LDL-c reductions and effects on all cardiovascular outcomes.

In addition to the above changes, the company has also changed the LDL-C treatment thresholds applied in the model. Previously, the LDL-C thresholds were ≥1.81 mmol/L; ≥2.59 mmo/l; ≥3.36 mmol/L ; and ≥4.13 mmol/L (in line with the sub-groups considered in the ODDESEY trials). In the updated analyses, these thresholds have been changed to ≥ 2.5 mmol/L; ≥ 3 mmol/L ; ≥ 3.5 mmol/L ; and ≥ 4.0 mmol/L. The justification provided by the company is that these new thresholds are pragmatic and aligned to UK clinical practice, and

should assist the Committee's decision-making in light of feedback received regarding justification for the original treatment thresholds.

In order to implement these new treatment thresholds in the economic model, the company also had to estimate new mean LDL-C concentrations for patients remaining above them. The mean LDL-C levels above the original thresholds were originally estimated from the THIN dataset, using data for individuals with a valid LDL-C measure irrespective of lipid modifying treatment received (uncertainty surrounding this approach was noted in the ERG's main report (section 5.2.3). In order to estimate the mean LDL-C concentrations above the new thresholds, the company noted that they did not have time to estimate these from the THIN data. Therefore they have used the TREND function in Excel to fit a linear relationship (using least squares) between the original mean LDL-C values and the original cut-off thresholds, and then interpolated the mean LDL-C values above the new thresholds. It is difficult to comment on the validity of this approach, but it can be noted that all the new thresholds do lie within the range of original thresholds, so there is no extrapolation beyond the data observed in the THIN dataset. Finally, in order to estimate mean LDL-C levels for those intolerant to statins and remaining above the new thresholds, the company has used data from the ALTERNATIVE trial.

All the updated mean LDL-C values, for each of the new modelled thresholds in each population, are replicated in Table 1 (statin tolerant) and Table 2 (statin intolerant) below. The ERG have been able to replicate all the interpolated mean LDL-C values reported in Table 1, but do not have access to the raw data to verify the values reported for statin intolerant patients in Table 2. Furthermore, since the mean LDL-C values reported for statin intolerant patients were only reported to two decimal places, the ERG have been unable to exactly replicate the company's updated cost-effectiveness results for statin intolerant patients.

Table 1. Mean LDL-c values used to calculate baseline risk at different intervention cut-off thresholds (replicates Table 5, Appendix 2, of the company's response to the ACD)

Population	Intervention thresholds				
Primary prevention heterozygous-familial population					
Original submission thresholds for intervention	**>= 1.81 mmol/L**	**>= 2.59 mmol/L**	-	**>= 3.36 mmol/L**	**>= 4.13 mmol/L**
Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	4.50 0.125 1.81-7.20	4.82 0.131 2.59-7.05	-	5.28 0.139 3.36-7.20	5.59 0.143 4.13-7.05
Revised thresholds for ACD consultation [Approximated y = 0.4809x + 3.6188]	**>= 2.0 mmol/L**	**>= 2.5 mmol/L**	**>= 3.0 mmol/L**	**>= 3.5 mmol/L**	**>= 4.0 mmol/L**
Revised Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	4.58 0.127 2.00-7.16	4.82 0.131 2.50-7.14	5.06 0.135 3.00-7.12	5.30 0.139 3.50-7.10	5.54 0.143 4.00-7.08
Secondary prevention heterozygous-familial population					
Original submission thresholds for intervention	**>= 1.81 mmol/L**	**>= 2.59 mmol/L**	-	**>= 3.36 mmol/L**	**>= 4.13 mmol/L**
Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	4.40 0.123 1.81-6.98	4.56 0.126 2.59-6.52	-	4.80 0.131 3.36-6.25	5.23 0.138 4.13-6.33
Revised thresholds for ACD consultation [Approximated by = 0.3557x + 3.6893]	**>= 2.0 mmol/L**	**>= 2.5 mmol/L**	**>= 3.0 mmol/L**	**>= 3.5 mmol/L**	**>= 4.0 mmol/L**
Revised Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	4.40 0.123 2.00-6.80	4.58 0.127 2.50-6.66	4.76 0.130 3.00-6.51	4.93 0.133 3.50-6.37	5.11 0.136 4.00-6.22
Secondary prevention High-risk cardiovascular (non-familial) population					
Original submission thresholds for intervention	**>= 1.81 mmol/L**	**>= 2.59 mmol/L**	-	**>= 3.36 mmol/L**	**>= 4.13 mmol/L**
Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	2.68 0.082 1.81-3.54	3.31 0.100 2.59-4.02	-	4.03 0.116 3.36-4.70	4.76 0.130 4.13-5.38
Revised thresholds for ACD consultation [Approximated by y = 0.9012x + 1.0136]	**>= 2.0 mmol/L**	**>= 2.5 mmol/L**	**>= 3.0 mmol/L**	**>= 3.5 mmol/L**	**>= 4.0 mmol/L**
Revised Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	2.82 0.086 2.00-3.63	3.27 0.099 2.50-4.03	3.72 0.109 3.00-4.43	4.17 0.119 3.50-4.84	4.62 0.128 4.00-5.24
Secondary prevention Recurrent events / polyvascular (non-familial) population					
Original submission thresholds for intervention	**>= 1.81 mmol/L**	**>= 2.59 mmol/L**	**-**	**>= 3.36 mmol/L**	**>= 4.13 mmol/L**
Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	2.66 0.082 1.81-3.52	3.31 0.100 2.59-4.03	-	4.05 0.117 3.36-4.73	4.78 0.130 4.13-5.43
Revised thresholds for ACD consultation [Approximated by y = 0.9162x + 0.9766]	**>= 2.0 mmol/L**	**>= 2.5 mmol/L**	**>= 3.0 mmol/L**	**>= 3.5 mmol/L**	**>= 4.0 mmol/L**
Revised Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	2.81 0.086 2.00-3.62	3.27 0.099 2.50-4.04	3.73 0.110 3.00-4.45	4.18 0.119 3.50-4.87	4.64 0.128 4.00-5.28

Table 2. Mean LDL-c values used to calculate baseline risk at different intervention cut-off thresholds – statin intolerants (replicates Table 6, Appendix 2, of the company's response to the ACD)

Population	**Intervention thresholds**				
Primary & Secondary prevention heterozygous-familial population					
Revised thresholds for ACD consultation	**>= 2.0 mmol/L**	**>= 2.5 mmol/L**	**>= 3.0 mmol/L**	**>= 3.5 mmol/L**	**>= 4.0 mmol/L**
Alirocumab plus ezetimibe vs. ezetimibe					
Revised Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	N/A	5.25 0.138 2.5 – 7.99	5.36 0.140 3.0 – 7.71	5.55 0.143 3.5 – 7.60	5.99 0.149 4.0 – 7.98
Alirocumab vs. ezetimibe					
Revised Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	N/A	7.18 0.164 2.5 – 11.87	7.18 0.164 3.0 – 11.37	7.18 0.164 3.5 – 10.87	7.33 0.166 4.0 – 10.65
Secondary prevention High-risk cardiovascular (non-familial) population & Recurrent events / polyvascular (non-familial) populations					
Revised thresholds for ACD consultation	**>= 2.0 mmol/L**	**>= 2.5 mmol/L**	**>= 3.0 mmol/L**	**>= 3.5 mmol/L**	**>= 4.0 mmol/L**
Alirocumab plus ezetimibe vs. ezetimibe					
Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	N/A	3.98 0.115 2.5 – 5.46	4.20 0.120 3.0 – 5.39	4.60 0.127 3.5 – 5.69	4.91 0.133 4.0 – 5.83
Alirocumab vs. ezetimibe					
Mean LDL-c used to calculate baseline risk (SE; min/max informing log-normal distribution for PSA)	N/A	4.60 0.127 2.5 – 6.70	4.72 0.129 3.0 – 6.45	4.94 0.133 3.5 – 6.88	5.31 0.139 4.0 – 6.62

Revised deterministic results

Table 3 below replicates the company's updated deterministic results for those tolerant to statins for each patient population. The ERG has checked these and can verify that they are all consistent with the changes the company has described. Given that the cut-off treatment threshold approach applied by the company may lead to some confusion about where exactly the cost-effectiveness baseline LDL-C threshold lies, the ERG have added an extra column to Table 1, which determines the actual mean baseline LDL-C level above which the ICER drops below £30,000 for each population in the company's model. These were estimated by increasing the mean baseline LDL-C level in increments of 0.1 mmol/L in each population, until the ICER dropped below £30,000. It should be noted that these cost-effectiveness thresholds are higher than the modelled cut-off thresholds of 2.5 and 3 mmol/L.

Table 4 replicates the company's updated deterministic results for statin intolerant patients. As noted above, the ERG do not have the exact mean LDL-C values applied for these sub-populations, and as such cannot replicate the ICERs exactly. However, applying the mean LDL-C concentrations (reported to 2 decimal places in Table 2), the ERG has obtained ICERs that are very close (within a maximum of ~£50) to those reported in Table 4. The small discrepancies can be attributed to rounding.

Further to the updated main analyses, the company also provided a new sensitivity analysis in Appendix 2 of their response to the ACD. The company noted that in paragraph 4.13 of the ACD, it is suggested that the Committee had concerns regarding the validity of the estimated ICERs for the HeFH primary prevention population, which were much lower than those for the HeFH secondary prevention population. It was noted in the ACD that "*the Committee understood from the clinical expert that this would not necessarily be expected, given that the lifetime risk of an event is high for these populations regardless of whether a previous event has already been experienced*." In response the company noted that the real-world data used to estimate the baseline risks in the model, may have led to underestimation of risk in the HeFH primary prevention population. Therefore, they provided a new sensitivity analysis exploring the baseline risk threshold, above which alirocumab, as an add-on to statin + ezetimibe, may become cost-effective in this population. This suggested that for patients with LDL-c $\geq$ 4mmol/L, the ICER for alirocumab could fall below £30,000 with a 50% increase in composite 1st year CV event risk; i.e. from 2.26% to 3.43% (see Table 8 of the company's response to the ACD for further details).

Table 3. Revised ICERs (£/QALY) for key patient populations and comparators (Deterministic – using ERG/CTTC) (replicates Table 7, Appendix 2, of the company's response to the ACD)

Population		>= 2.5 mmol/L	>= 3.0 mmol/L	>= 3.5 mmol/L	>= 4.0 mmol/L	Mean baseline LDL-C threshold (mmol/L) for ICER ≤ £30,000 per QALY*
Primary prevention heterozygous-familial population						
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	16,883 0.34 **49,682**	16,773 0.37 **45,004**	16,656 0.41 **40,880**	16,531 0.44 **37,228**	
Secondary prevention heterozygous-familial population						
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	13,500 0.56 **24,091**	13,368 0.59 **22,600**	13,232 0.62 **21,233**	13,092 0.66 **19,973**	~4.0
Secondary prevention High-risk cardiovascular (non-familial) population						
Alirocumab + Statin vs. Statin	Inc. Cost Inc. QALY ICER	13,659 0.31 **43,880**	13,394 0.38 **35,471**	13,105 0.45 **29,220**	12,789 0.52 **24,408**	~4.1
Alirocumab + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	11,665 0.17 **69,430**	11,514 0.20 **56,334**	11,352 0.24 **46,787**	11,179 0.28 **39,566**	
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	13,792 0.31 **44,308**	13,556 0.38 **35,899**	13,297 0.45 **29,647**	13,012 0.52 **24,835**	~4.1
Secondary prevention Recurrent events / polyvascular (non-familial) population						
Alirocumab + Statin vs. Statin	Inc. Cost Inc. QALY ICER	12,381 0.37 **33,527**	12,051 0.44 **27,184**	11,696 0.52 **22,469**	11,312 0.60 **18,831**	~3.5
Alirocumab + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	10,683 0.20 **53,137**	10,491 0.24 **43,276**	10,290 0.28 **36,105**	10,078 0.33 **30,686**	
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	12,551 0.37 **33,987**	12,255 0.44 **27,644**	11,935 0.52 **22,929**	11,588 0.60 **19,291**	~3.5

Note; *ERG calculation, exact baseline LDL-C concentration above which the ICER for alirocumab drops below £30,000 per QALY in the model

Table 4. Revised ICERs (£/QALY) for statin intolerant populations and comparators (Deterministic – using ERG/CTTC) (replicates Table 14, Appendix 2, of the company's response to the ACD)

Population		>= 2.5 mmol/L	>= 3.0 mmol/L	>= 3.5 mmol/L	>= 4.0 mmol/L	Mean baseline LDL-C threshold (mmol/L) for ICER ≤ £30,000 per QALY*
Primary prevention heterozygous-familial population						
Alirocumab + Ezetimibe vs. Ezetimibe	Inc. Cost Inc. QALY ICER	16,628 0.40 **41,639**	16,571 0.42 **39,887**	16,465 0.45 **36,949**	16,208 0.52 **31,330**	~6.1
Alirocumab vs. Ezetimibe	Inc. Cost Inc. QALY ICER	13,286 0.43 **30,565**	13,286 0.43 **30,565**	13,286 0.43 **30,565**	13,216 0.45 **29,298**	~7.2
Secondary prevention heterozygous-familial population						
Alirocumab + Ezetimibe vs. Ezetimibe	Inc. Cost Inc. QALY ICER	12,878 0.68 18,926	12,785 0.70 18,244	12,610 0.74 17,085	12,195 0.82 14,799	~3.9
Alirocumab vs. Ezetimibe	Inc. Cost Inc. QALY ICER	9,872 0.67 **14,831**	9,872 0.67 **14,831**	9,872 0.67 **14,831**	9,762 0.68 **14,267**	~4.7
Secondary prevention High-risk cardiovascular (non-familial) population						
Alirocumab + Ezetimibe vs. Ezetimibe	Inc. Cost Inc. QALY ICER	13,338 0.42 **31,882**	13,204 0.45 **29,132**	12,942 0.52 **24,890**	12,716 0.58 **22,081**	~4.1
Alirocumab vs. Ezetimibe	Inc. Cost Inc. QALY ICER	10,984 0.34 **32,635**	10,924 0.35 **31,183**	10,820 0.37 **28,928**	10,631 0.42 **25,532**	~4.8
Secondary prevention Recurrent events / polyvascular (non-familial) population						
Alirocumab + Ezetimibe vs. Ezetimibe	Inc. Cost Inc. QALY ICER	11,994 0.49 **24,685**	11,832 0.52 **22,628**	11,518 0.59 **19,440**	11,250 0.65 **17,316**	~3.5
Alirocumab vs. Ezetimibe	Inc. Cost Inc. QALY ICER	9,848 0.39 **25,407**	9,777 0.40 **24,320**	9,654 0.43 **22,628**	9,432 0.47 **20,070**	~4.1

Note; *ERG calculation, exact baseline LDL-C concentration above which the ICER for alirocumab drops below £30,000 per QALY in the model

Revised probabilistic results

The company also provided updated probabilistic analyses using the new LDL-C thresholds and mean LDL-C values for the main comparisons and patient populations. The results of these are replicated in Tables 5 and 6 below. All the probabilistic analyses were presented for LDL-C cut-off thresholds of 3 mmol/L and 4 mmol/L for all four patient populations (tolerant to statins). It is worth pointing out that the probabilistic ICERs are similar to the deterministic ones. The ERG has checked and rerun the probabilistic results, and has verified very similar findings, subject to random variation in the simulation process.

The company also provided selected scatter plots and CEACs for comparisons at various LDL-C thresholds (Figures 1-4 of Appendix 2 of their response to the ACD), but these have not been replicated here.

Table 5. Company's probabilistic results by willingness to pay threshold (replicates Table 9, Appendix 2, of the company's response to the ACD)

Population/Comparison	WTP £20,000 / QALY		WTP £30,000 / QALY	
	>= 3.0 mmol/L	>= 4.0 mmol/L	>= 3.0 mmol/L	>= 4.0 mmol/L
Primary prevention heterozygous-familial population				
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	0.2%	1.8%	9.0%	21.9%
Secondary prevention heterozygous-familial population				
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	31.6%	51.8%	88.4%	95.6%
Secondary prevention High-risk cardiovascular (non-familial) population				
Alirocumab + Statin vs. Statin	0.0%	17.8%	22.4%	81.0%
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	0.0%	14.6%	18.8%	78.2%
Secondary prevention Recurrent events / polyvascular (non-familial) population				
Alirocumab + Statin vs. Statin	5.4%	59.0%	67.2%	98.2%
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	5.8%	55.4%	62.6%	98.8%

Table 6. Revised ICERs (£/QALY) for key patient populations and comparators (Probabilistic – using ERG/CTTC) (replicates Table 10, Appendix 2, of the company's response to the ACD)

Population		>= 3.0 mmol/L	>= 4.0 mmol/L
Primary prevention heterozygous-familial population			
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	16,708 0.38 **43,439**	16,466 0.45 **36,650**
Secondary prevention heterozygous-familial population			
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	13,245 0.60 **22,192**	12,976 0.66 **19,662**
Secondary prevention High-risk cardiovascular (non-familial) population			
Alirocumab + Statin vs. Statin	Inc. Cost Inc. QALY ICER	13,272 0.37 **35,858**	12,667 0.52 **24,486**
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	13,386 0.37 **35,748**	12,909 0.52 **25,048**
Secondary prevention Recurrent events / polyvascular (non-familial) population			
Alirocumab Statin vs. Statin	Inc. Cost Inc. QALY ICER	11,878 0.44 **27,289**	11,225 0.60 **18,743**
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	12,077 0.44 **27,535**	11,486 0.59 **19,467**

Deterministic results applying variants of hazard ratios obtained from the CTT meta-analysis

The company provided some new scenario analyses using hazard ratios obtained from different versions of the CTT meta-analysis (CTTC, 2010; CTTC, 2012). They noted that the version used in previous NICE appraisals was not exactly the same. Table 7 below replicates the company's illustration of the different rate ratios that have been used across the appraisals for alirocumab, ezetimibe, and evolocumab. Table 8 presents the company's revised ICERs for each population (at LDL-C thresholds of 3 and 4 mmol/L), for each set of rate ratios obtained from different versions of the CTT meta-analysis.

The rate ratios applied in the appraisal for alirocumab and ezetimibe are quite similar (Table 7), and that they lead to modest differences in the ICER (Table 8). Applying the rate ratios obtained from the version of the CTT meta-analysis used in the evolocumab submission has a greater impact on the ICERs. For comparison with the mean baseline LDL-C cost-effectiveness threshold in Table 3 above, the ERG has calculated the same model based thresholds for the different populations when applying the more favourable rate ratios as applied for the evolocumab appraisal (final column of Table 8 below).

The rate ratios reportedly used in the evolocumab appraisal, appear to have been derived from the CTTC 2010 publication (CTTC, 2010), using a subset of 5 trials comparing more intensive statin treatment with less intensive statins. This publication concluded that per 1 mmol/L reduction in LDL-C, further reductions in LDL-C with more versus less intensive statin resulted in similar reductions in the risk of major vascular events to the proportional reduction observed in trials of statin versus control. In fact the proportional reduction in CV events tended to be larger with more versus less statin, and was significantly so for the reduction in the risk of revascularisation (per 1 mmol/L reduction in LDL-C). The ezetimibe appraisal, on the other hand, applied the rate ratios reported in the CTTC 2010 meta-analysis for trials of statin versus control. Finally, for the alirocumab appraisal, the company have applied rate ratios from the more recent 2012 publication (CTTC, 2012), which included data from 27 statin trials (including more versus less statin, and statin versus control combined).

Table 7. CTTC Rate Ratio (95% CI) per 1mmol/L reduction in LDL-c mapped from evolocumab and ezetimibe appraisals (replicates Table 12, Appendix 2, of the company's response to the ACD)

	Rate Ratios in the base case for alirocumab	Rate Ratios mapped from ezetimibe	Rate Ratios mapped from evolocumab
Non-Fatal MI (ACS)	0.74 (0.71, 0.77)	0.74 (0.69, 0.78)	0.71 (0.58, 0.87)
Coronary Revascularisation	0.76 (0.73, 0.78)	0.76 (0.73, 0.80)	0.66 (0.60, 0.73)
Stroke*	0.79 (0.74, 0.85)	0.85 (0.80, 0.90)	0.69 (0.50, 0.95)
Any Vascular Death	0.88 (0.84, 0.91)	0.86 (0.82, 0.90)	0.86 (0.82, 0.90)

* Any stroke from the ezetimibe appraisal and Ischeaemic Stroke from the alirocumab/evolocumab appraisals

Table 8. ICERs (£/QALY) for key patient populations and comparators (Deterministic– using ERG/CTTC variants) (replicates Table 13, Appendix 2, of the company's response to the ACD)

Population / CTTC used in other appraisals		Appraisal ID 779 >= 3.0 mmol/L	Appraisal ID 627 >= 3.0 mmol/L	Appraisal ID 765 >= 3.0 mmol/L	Appraisal ID 779 >= 4.0 mmol/L	Appraisal ID 627 >= 4.0 mmol/L	Appraisal ID 765 >= 4.0 mmol/L	Mean baseline LDL-C threshold (mmol/L) for ICER ≤ £30,000 per QALY*
Primary prevention heterozygous-familial population								
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	16,773 0.37 45,004	16,912 0.39 43,466	16,386 0.46 35,319	16,531 0.44 37,228	16,707 0.46 35,966	15,997 0.56 28,456	~5.4
Secondary prevention heterozygous-familial population								
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	13,368 0.59 22,600	13,657 0.65 20,902	12,846 0.69 18,618	13,092 0.66 19,973	13,417 0.72 18,513	12,434 0.77 16,208	~3.6
Secondary prevention High-risk cardiovascular (non-familial) population								
Alirocumab + Statin vs. Statin	Inc. Cost Inc. QALY ICER	13,394 0.38 35,471	13,599 0.41 33,054	12,992 0.45 28,559	12,789 0.52 24,408	13,076 0.57 22,901	12,067 0.64 18,849	~3.6
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	13,556 0.38 35,899	13,781 0.41 33,497	13,184 0.45 28,981	13,012 0.52 24,835	13,329 0.57 23,343	12,337 0.64 19,269	~3.6
Secondary prevention Recurrent events / polyvascular (non-familial) population								
Alirocumab + Statin vs. Statin	Inc. Cost Inc. QALY ICER	12,051 0.44 27,184	12,404 0.49 25,423	11,455 0.53 21,726	11,312 0.60 18,831	11,797 0.66 17,828	10,311 0.72 14,384	~3.0
Alirocumab + Ezetimibe + Statin vs. Ezetimibe + Statin	Inc. Cost Inc. QALY ICER	12,255 0.44 27,644	12,638 0.49 25,903	11,692 0.53 22,175	11,588 0.60 19,291	12,115 0.66 18,308	10,631 0.72 14,832	~3.1

Note; *ERG calculation, exact baseline LDL-C concentration above which the ICER for alirocumab drops below £30,000 per QALY, applying the more favourable rate ratios for alirocumab (i.e. from ID765).

ERG critique and summary of the company's updated analyses

The revised analyses submitted by the company in response to the ACD appear to have been implemented in accordance with described changes, which are in line with the Committee's preferred modelling assumptions (including the use of the CTT meta-analysis to model the effects of alirocumab on CV events). The revised analyses, with newly agreed patient access scheme, indicates that for certain subpopulations with LDL-C above modelled treatment thresholds, the ICER for alirocumab as an add on to maximally tolerate LLT, may fall within ranges considered cost-effective. The following points should be taken into consideration:

- The ICERs remain above £30,000 per QALY gained for Alirocumab as an-add on to statin + ezetimibe in the HeFH primary prevention population, at all the modelled LDL-C treatment thresholds.
- The company's sensitivity analysis indicates that for those in the HeFH primary prevention population with LDL-C ≥ 4 mmol/L, the baseline risk would have to increase by ~50% for the ICER for alirocumab, as a an add on to statin, to drop below £30,000 per QALY.
- For the HeFH primary prevention population intolerant to statins, the ICERs for alirocumab + ezetimibe, versus ezitimibe alone, also remain above £30,000 for all the modelled LDL-C treatment thresholds. For those with an untreated LDL-C level ≥ 4 mmol/L (mean LDL-C = 7.33 mmol/L), the ICER for alirocumab monotherapy versus ezetimibe monotherapy falls below £30,000 (£29,298).
- In the HeFH secondary prevention population, the estimated ICERs for alirocumab as an add-on to statin + ezetimibe fall below £30,000 for subpopulations with LDL-C greater or equal to all the modelled treatment thresholds. It is worth noting that the actual mean baseline LDL-C, above which the ICER for alirocumab drops below £30,000 per QALY, is ~ 4 mmol/L in this population.
- For the HeFH secondary prevention population intolerant to statins, the ICERs are below £20,000 for subpopulations with LDL-C greater or equal to all the modelled treatment cut-off thresholds (both as an add-on to ezetimibe, and as monotherapy in head-to-head comparison with ezetimibe). However, the exact mean LDL-C thresholds, above which the ICERs drop below £30,000 per QALY, are ~3.9 mmol/L for alirocumab as an add-on to ezetimibe, and ~ 4.7 mmol/L for alirocumab versus ezetimibe.

- In the high risk secondary prevention cohort, the ICERs for alirocumab as an add-on to statin (or statin + ezetimibe), fall below £30,000 in subpopulations with LDL-C ≥ 3.5 mmol/L (on maximally tolerate LLT). The actual mean baseline LDL-C cost-effectiveness thresholds, above which the ICER drops below £30,000, are ~4.1 mmol/L for both these comparisons.
- In the head-to-head comparison with ezetimibe + statin, the ICER for alirocumab + statin remains above £30,000 for all modelled LDL-C treatment thresholds.
- For the high risk secondary prevention cohort intolerant to statins, the ICER for alirocumab drops below £30,000 in subpopulations with LDL-C ≥ 3 mmol/L (as an add-on to ezetimibe) or ≥ 3.5 mmol/L (versus ezetimibe). The mean LDL-C thresholds, above which the ICERs drop below £30,000, are ~4.1 and ~4.8 mmol/L for these comparisons, respectively.
- For the recurrent CV event/polyvascular disease population, the ICERs for alirocumab as an add-on to statin (or statin + ezetimibe), fall below £30,000 in subpopulations with LDL-C ≥ 3.0 mmol/L. The mean LDL-C cost-effectiveness thresholds, above which the ICERs drop below £30,000, are ~3.5 mmol/L for both these comparisons.
- In the head-to-head comparison with ezetimibe + statin, the ICER for alirocumab + statin remains above £30,000 for all modelled LDL-C treatment thresholds in the recurrent event/polyvascular disease population.
- For the recurrent events/polyvascular disease cohort intolerant to statins, the ICER for alirocumab (as an add-on to ezetimibe or versus ezetimibe) is below £30,000 for subpopulations with LDL-C ≥ 2.5 mmol/L. The mean LDL-C thresholds, above which the ICERs drop below £30,000, are ~3.5 and ~4.1 mmol/L respectively for these comparisons.

It is worth taking into account, as the company have appropriately pointed out, that there has been some inconsistency with respect to the version of the CTT meta-analysis used to derive rate ratios in different NICE appraisals of hypercholesterolaemia drugs. The rate ratios used in the current appraisal lead to more conservative estimates of the ICERs for alirocumab as compared to the use of rate ratios used in previous appraisals (Table 8). They also reduce the mean baseline LDL-C cost-effectiveness thresholds.

References

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