National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	Amgen	We support the referral of this topic to the Institute for appraisal.	Comment noted. No changes required.
	Merck Sharp and Dohme	MSD feels that it is appropriate to refer this topic for appraisal	Comment noted. No changes required.
	Royal College of Pathologists	This drug addresses an important unmet need that doesn't yet have marketing authorisation however this could be within 2 years and this TA is therefore timely	Comment noted. No changes required.
	HEART UK	Very appropriate	Comment noted. No changes required.
Wording	Amgen	We recommend amending the remit to reflect the anticipated marketing authorisation for evolocumab (see Section 4: regulatory issues). We recommend the following wording with amendments underlined and deleted: "To appraise the clinical and cost effectiveness of evolocumab within its licensed indication for ~~hyperlipidaemia~~ primary hypercholesterolaemia (heterozygous familial and non-familial) and mixed dyslipidaemia (excluding	Comment noted. The draft remit has been updated to reflect the anticipated marketing authorisation.

Section	Consultee/ Commentator	Comments	Action
		homozygous familial hypercholesterolaemia)."	
	Merck Sharp and Dohme	No comment	Response noted.
	Royal College of Pathologists	The remit wording should include "treatment of". The term "hyperlipidaemia" could mean either hypercholesterolaemia or hypertriglyceridaemia, the latter not being intended. Dyslipidaemia is often taken to mean elevated triglyceride with low HDL-C, which is also not intended. It would be better to use the term "primary hypercholesterolaemia or mixed hyperlipidaemia" which is less ambiguous.	Comment noted. The draft remit has been updated to reflect the anticipated marketing authorisation.
	HEART UK	Yes	Comment noted. The draft remit has been updated to reflect the anticipated marketing authorisation.
Timing Issues	Amgen	We believe that this topic is an area of urgency for the NHS based on the current unmet need associated with inadequately controlled hypercholesterolaemia in England and Wales (as described in the scope background). This unmet need is also reflected in the current NHS Outcomes Framework improvement area for reducing premature mortality from the major causes of death (1.1 Under 75 mortality rate from cardiovascular disease).[1] Therefore, we recommend that the commencement of this topic occurs as soon as possible to ensure timely guidance for the NHS following marketing authorisation. References:	Comment noted. NICE aims to provide guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.

Section	Consultee/ Commentator	Comments	Action
		1. Department of Health. NHS Outcomes Framework 2014/15. 2013	
	Merck Sharp and Dohme	No comment	Response noted.
	Royal College of Pathologists	It will be important to have this in place by the time these new agents are available as treatment gaps and inequalities of access may quickly arise	Comment noted. NICE aims to provide guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
	HEART UK	As soon as possible after licensed indication is available.	Comment noted. NICE aims to provide guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
Additional comments on the draft remit	Royal College of Pathologists	It is not clear why homozygous FH has been excluded from the remit. There is evidence that this treatment is effective in a substantial proportion of homozygous and compound heterozygous FH (who are clinically indistinguishable) who do not have two receptor negative LDLR mutations.	Comment noted. Heterozygous FH and homozygous FH have different treatment pathways, and therefore it was felt that it would be appropriate for this

Section	Consultee/ Commentator	Comments	Action
			appraisal to consider heterozygous FH only.
	HEART UK	There are other members of the same drug class i.e. PCSK9 inhibitors which are also in clinical trials and which are likely to be applying for a license shortly after Evolocumab. Consideration should be given to appraise these simultaneously.	Comment noted. Attendees at the scoping workshop agreed that because of the different regulatory timings and the need for timely guidance to the NHS it is appropriate to consider these new technologies separately.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Amgen	The background information describes lipid modification to prevent cardiovascular disease with regard to NICE clinical guideline 67. We recommend an amendment to this section to reflect the recent publication of the NICE clinical guideline for lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease (NICE CG181 issued July 2014).	Comment noted. The background section has been updated.
	Merck Sharp and Dohme	In the last paragraph of the background, when discussing lipid-modifying drugs for dyslipidaemia and prevention of cardiovascular disease, the drugs should be amended to reflect the recent publication of CG181. The following	Comment noted. The background section has

Section	Consultee/ Commentator	Comments	Action
		drugs should be removed from the lipid-modifying drugs detailed in this section as they are not recommended in CG181: nicotinic acid and bile acid sequestrants. The reference to CG67 should also be changed as CG181 has now been published. When discussing CG71 in the background section ezetimibe should also be highlighted after reference to "NICE clinical guideline 71 recommends statins as the initial treatment". In CG71 sections 1.3.1.6 to 1.3.1.9 gives clear recommendations for ezetimibe use for the treatment of adults with heterozygous-familial hypercholesterolaemia. For accuracy this should be reflected in the background section of the scope. Also, a review of whether to update CG71 is being taken in August 2014. This should be reflected in the background section.	been updated.
	Royal College of Pathologists	The distinction between homozygous FH and heterozygous FH is not quite so clear cut as portrayed. Although vascular disease with onset in childhood is seen only in severely affected homozygous and compound heterozygous FH, LDL-C concentrations may overlap with severe heterozygous FH and treatment pathways leading to maximal combination lipid lowering therapy and LDL-apheresis are common to both. The management of dyslipidaemia section is now out of date in that it refers to NICE CG67 which has been superseded by CG181. The latter does not recommend the use of fibrates, nicotinic acid or resins for those who do not tolerate statins and these should be removed. Nicotinic acid is no longer recommended by EMEA except for severe hypertriglyceridemia. Resins may have a role in FH as per CG71.	Comment noted. The background section has been updated.
	HEART UK	NICE CG 181 should be referenced rather than CG 67.	Comment noted. The background section has been updated.

Section	Consultee/ Commentator	Comments	Action
The technology/ intervention	Amgen	We recommend a minor addition to the description of the mechanism of action to provide a more accurate description of the technology (suggested wording underlined): "Evolocumab (brand name unknown, Amgen) is a fully human monoclonal antibody which targets an enzyme involved in the regulation of lipid levels in the blood, known as proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 significantly impacts lipid metabolism by inhibiting the recycling of low-density lipoprotein receptors; reducing their expression on hepatic cells surfaces. Inhibition of PCSK9 therefore increases hepatic LDL receptor density and lowers LDL-C."	Comment noted. The description of the technology has been updated.
	Merck Sharp and Dohme	No comment	Response noted.
	Royal College of Pathologists	The monoclonal antibody inhibits PCSK9, a circulating enzyme involved in the down-regulation of LDL receptor activity	Comment noted. The description of the technology has been updated.
	HEART UK	Yes	Comment noted.
Population	Amgen	Current NICE guidelines (CG181: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease) recommend prescribing lipid-lowering therapies based on patients' CVD status or risk. Additionally, NICE CG71 recommends lipid-lowering therapies in patients with familial hypercholesterolaemia. As such, we recommend evolocumab is considered within the context of these populations with the greatest need of additional treatment options to adequately control LDL-C (in combination with	Comment noted. Attendees at the scoping workshop agreed that wording of the population should be updated to reflect the anticipated marketing authorisation.

Section	Consultee/ Commentator	Comments	Action
		statins, or for treatment where patients are statin-intolerant or for whom a statin is not considered clinically appropriate).	
	Merck Sharp and Dohme	It would be helpful if Amgen could clarify what the intended license will be. Is hyperlipidaemia and/or mixed dyslipidaemia in the label?	Comment noted. The company clarified that the anticipated marketing authorisation is for primary hypercholesterolaemia and mixed dyslipidaemia.
	Royal College of Pathologists	The relevant population are people with "primary hypercholesterolaemia or mixed hyperlipidaemia" who are either intolerant of inadequately responsive to high intensity statin treatment in line with current NICE guidance. The definition of an adequate response and statin intolerance require definitions. Patients with heterozygous FH should be considered separately. Consideration should be given to identification of a subgroup with severe heterozygous FH e.g. those with baseline LDL-C >8.0 - 8.5 mmol/L who are unlikely to achieve an adequate response to conventional therapy. Patients who have heterozygous FH caused by gain-of-function mutations in the PCSK9 gene have severe FH and typically poor response to statins but may be expected to respond better to this therapy Patients who are intolerant of statins should be considered separately from those who are poorly responsive. Patients who have established cardiovascular disease (secondary prevention) and are therefore at the highest level of risk should be considered separately from those requiring treatment for primary prevention.	Comment noted. Attendees at the scoping workshop agreed that wording of the population should be updated to reflect the anticipated marketing authorisation. They also agreed to include people with heterozygous familial hypercholesterolaemia, those with statin intolerance, and those with, or at risk of, cardiovascular disease as subgroups for separate consideration if the evidence allows.

Section	Consultee/ Commentator	Comments	Action
	HEART UK	Appropriate	Comment noted.
Comparators	Amgen	The draft scope clearly defines the relevant lipid-modifying drugs for lipid modification currently used in the NHS. We recommend the removal of statins as a comparator since evolocumab is anticipated to be added to background statin therapy for patients who cannot adequately control LDL-C with optimal statin therapy. Whilst statins are not an appropriate comparator for evolocumab in patients that are statin-intolerant or for whom a statin is not consider clinically appropriate. Evolocumab was primarily studied in patients receiving statins (high and moderate intensity) with other lipid-lowering therapies. This anticipated use and clinical studies is also reflected in the anticipated marketing authorisation (see Section 4: regulatory issues). We also recommend the inclusion of LDL-apheresis as an adjunctive treatment (alongside lipid-lowering therapies) since it is used to treat some patients with severe heterozygous familial hypercholesterolaemia in the UK.	Comment noted. Attendees at the scoping workshop agreed that statins are not a relevant comparator for evolocumab. However, LDL apheresis was not included as a comparator because it will be used after failure with lipid lowering drug therapy. Attendees at the scoping workshop agreed, however, that requirement of procedures including LDL apheresis and revascularisation should be included as an outcome.
	Merck Sharp and Dohme	Nicotonic acid and bile acid sequestrants are not standard of care in the NHS. Please refer to the recent publication of CG181.	Comment noted. Attendees at the scoping workshop agreed that nicotinic acid, fibrates and bile acid sequesterants

Section	Consultee/ Commentator	Comments	Action
			were not appropriate comparators for evolocumab.
	Royal College of Pathologists	Ezetimibe is the current standard of care for this indication. Nicotinic acid is no longer recommended for those who do not tolerate or achieve an inadequate response statins and should be removed as a comparator. Resins and fibrates may have limited roles in FH (as per CG71) and mixed hyperlipidaemia with a major component of hypertriglyceridemia, respectively.. Other similar anti-PCSK9 monoclonal antibodies at a similar stage of development should be included e.g. alirocumab, bozocizimab. Other emerging technologies in a similar stage of development include the oral CETP inhibitor anacetrapib which has substantial LDL-C lowering effect, apparently exceeding that achievable with ezetimibe. Apheresis should also be included as it is used for the same population for the same indication	Comment noted. Attendees at the scoping workshop agreed that nicotinic acid, fibrates and bile acid sequesterants were not appropriate comparators for evolocumab. However, LDL apheresis was not included as a comparator because it will be used after failure with lipid lowering drug therapy. Attendees at the scoping workshop agreed, however, that requirement of procedures including LDL apheresis and revascularisation should be included as an outcome. Technologies in development do not represent established practice, and so cannot

Section	Consultee/ Commentator	Comments	Action
			be considered relevant comparators.
	HEART UK	Fibrates and Bile acid sequestrants are not standard treatments (see CG 181) and appropriate formulations of Nicotinic acid no longer available in BNF. Currently Statins and / or Ezetimibe would be "best alternative care".	Comment noted. Attendees at the scoping workshop agreed that nicotinic acid, fibrates and bile acid sequesterants were not appropriate comparators for evolocumab.
Outcomes	Amgen	We believe the outcomes are appropriately defined. **Fatal and non-fatal cardiovascular events:** There are five evolocumab LDL-C lowering phase 3,multi-centre, double-blind, randomised, stratified, controlled clinical trials supporting the hypercholesterolaemia and mixed dyslipidaemia (excluding homozygous familial hypercholesterolaemia) indication. The primary efficacy endpoints for these phase 3 studies encompass:[1-5] ▪ Mean percent change from baseline in LDL-C at weeks 10 and 12 (4/5 studies) ▪ Percent change from baseline in LDL-C at week 12 (4/5 studies) ▪ Percent change from baseline in LDL-C at week 52 (1/5 studies) Fatal and non-fatal CV events were collected in the phase 2 and 3 clinical programme for the purposes of assessing safety. There is an ongoing phase 3, multicentre, randomised, double-blind, placebo-controlled study (FOURIER: **F**urther Cardiovascular **O**utcomes **R**esearch with PCSK9	Comment noted. Clinical outcomes that reflect survival or health-related quality of life are preferred over surrogate outcomes in technology appraisals. If surrogate outcomes are used to model the effect of treatment on mortality and/or health-related quality of life, the relationship between the surrogate and final outcome should be explained and justified, and this would be associated

Section	Consultee/ Commentator	Comments	Action
		Inhibition in Subjects With **E**levated **R**isk; Study 20110118) designed to evaluate the effect of additional LDL-C reduction on major CV events when evolocumab is used in combination with statin therapy in patients with clinically evident CV disease. The FOURIER trial was initiated in January 2013 with an estimated study completion date of February 2018. Therefore, we plan to provide estimations based on established data sources for the translation of LDL-C changes to reductions in CV events to enable consideration of this outcome measure and to support the economic evaluation. This approach will be consistent with methodologies used for other lipid-lowering therapies in the absence of CV event data (for example, NICE TA132: Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia issued 2007). **Health-related quality of life:** Health-related quality of life data has not been directly collected in the five evolocumab phase 3 studies. Health related benefits in terms of published utility data for cardiovascular events will be presented to support the economic evaluation. References: 1. Koren et al;J Am Coll Cardiol. 2014;63(23):2531-2540 2. Robinson et al; JAA.2014; 311(18):1870-1882 3. Stroes et al; J Am Coll Cardiol.2014; doi:10.1016/j.jacc.2014.03.019. 4. RUTHERFORD-2 AMGEN data on file. 5. Blom et al: N Engl J Med.2014; 370(19): 1809-1819	with some degree of uncertainty. Please see Guide to the methods of technology appraisal (2013) for further details. No changes required.
	Merck Sharp and Dohme	No comment	Response noted.
	Royal College of	Non-HDL-Cholesterol should be specified as an outcome which is a superior predictor of on-treatment cardiovascular events than LDL-C. Lipoprotein(a)	Comment noted. The outcomes section has

Section	Consultee/ Commentator	Comments	Action
	Pathologists	should be included as it may contribute to poor statin response and may respond better to this treatment than to statins or ezetimibe. Requirement for revascualarisation procedures, transplants (cardiac or liver) and LDL-apheresis treatments should be included	been updated. Attendees at the scoping workshop agreed that non-HDL-cholesterol, lipoprotein (a) and requirement of procedures including LDL apheresis and revascularisation are relevant outcomes. However, organ transplants are rare in the population under consideration, and therefore were not considered relevant outcomes for this appraisal.
	HEART UK	Yes	Comment noted. No action required
Economic analysis	Amgen	No comments on the aspects described within the draft scope. We wish to have the opportunity to provide supplementary data and analyses to support a Value Based Assessment of evolocumab if any amendments to the Guide to Methods of Technology Appraisal are implemented and this proposed appraisal is referred and eligible. To enable this, we would welcome notification of anticipated timelines and eligibility in order for us to include this within the manufacturer submission.	Comment noted. No amendments to the Guide to Methods of Technology Appraisal have been issued, and so the methods of technology appraisal are those specified in

Section	Consultee/ Commentator	Comments	Action
			the Guide.
	Merck Sharp and Dohme	It is important to consider where evolocumab is initiated. It is anticipated that it would be initiated and administered in secondary care, which brings with it associated costs.	Comment noted. The economic analysis is expected to include all relevant cost, in accordance with the NICE reference case. Please see Guide to the methods of technology appraisal (2013) for further details. No changes required.
	Royal College of Pathologists	The time horizon should be up to 80 years of age, with 5 and 10 year cardiovascular risk being considered	Comment noted. The NICE reference case stipulates that the time horizon should be long enough to reflect all important differences in costs or outcomes between the technologies being compared. Please see Guide to the methods of technology appraisal (2013) for further details.

Section	Consultee/ Commentator	Comments	Action
	HEART UK	No comment	Response noted.
Equality and Diversity	Amgen	No comments.	Response noted.
	Merck Sharp and Dohme	No comment	Response noted.
	Royal College of Pathologists	Inequality of access to LDL-apheresis is a major issue owing to the high set up costs for treatment and the existence of few established centres with appropriate expertise. The fact that the treatment is an injection-only treatment will exclude people who will not accept injection based therapies, including many from ethnic minority groups	Comment noted. Access to the existing treatment is not considered an issue which impacts on one of the protected characteristics (age, gender [including marital status], race, disability, religion & belief and sexual orientation) defined by the current Equality Act. Any potential equality issues will be highlighted in the evidence submissions from the company and other consultees. The Committee will consider when making its decision whether its recommendation on the

Section	Consultee/ Commentator	Comments	Action
			use of evolocumab will lead to unequal access to treatment for some patients. No changes required.
	HEART UK	No impact	Comment noted.
Innovation	Amgen	***Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?*** We believe that due to its novel, targeted mechanism of action, evolocumab offers a significant medical advance with an associated step-change in the treatment of patients with hypercholesterolaemia and mixed dyslipidaemia who are at increased risk of CV events. Evolocumab is a fully human monoclonal immunoglobulin G2 (IgG2) antibody that binds with high affinity and specificity to human proprotein convertase subtilisin/kexin type 9 (PCSK9), a protein that plays an essential role in lipid metabolism by recycling and regulating hepatic cell-surface LDL receptors (LDLR). LDLRs regulate the level of plasma low-density lipoprotein cholesterol (LDL-C).[1-2] Following secretion, PCSK9 directly binds LDLRs and causes them to be routed for degradation; this in turn reduces the liver's ability to remove LDL-C from blood and leads to increased levels of circulating LDL-C. By binding to PCSK9, evolocumab inhibits interaction of PCSK9 with LDLR, which results in increased hepatic expression of LDLR and subsequently, decreased circulating concentrations of serum LDL-C. Further supporting the notion of LDL-lowering by PCSK9 inhibition are epidemiological data from heterozygous patients with PCSK9 loss-of-function	Comment noted. The innovative nature of evolocumab will be considered by the Committee during the appraisal.

Section	Consultee/ Commentator	Comments	Action
		mutations (inherent low circulating PCSK9 levels), showing them to have significantly lower CHD risk than wild type controls.[3] Evolocumab has demonstrated clinically meaningful and consistent reductions in LDL-C with magnitudes not previously demonstrated across various hyperlipidaemic subjects at increased risk of CV events. In clinical studies, the magnitude of effect on lowering LDL-C was around 3-fold greater than the current preferred second-line treatment after statins (ezetimibe). The observed effect size of evolocumab was consistent when evolocumab was used in combination with commonly used statins at various doses, when added to optimised standard of care lipid lowering therapy in patients with familial hypercholesterolaemia, and also when used in statin intolerant patients. Despite the availability of lipid-lowering therapies, some patients are unable to achieve adequate LDL-C control and remain at increased risk of CV events (e.g. severe familial and non-familial hypercholesterolaemia). Therefore, evolocumab, alone or in combination with other lipid-modifying therapies, can provide a medical step-change compared to current treatments due to the magnitude and consistent reductions in LDL-C, enabling patients to lower their risk of CV events. References: 1. Horton et al. Trends Biochem Sci. 2007;32:71-77. 2. Brown et al. Science. 2006;311:1721-1723. 3. Cohen J et al. N Engl J Med 2006;354:1264-72 ***Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?*** We believe that evolocumab can provide health-related benefits that are	

Section	Consultee/ Commentator	Comments	Action
		unlikely to be included in the QALY estimate when compared to existing treatment patterns. LDL-apheresis is an adjunctive treatment option for some patients to support reductions in LDL-C (e.g. severe heterozygous familial hypercholesterolaemia). LDL-apheresis typically requires attendance at specialist clinics requiring venous cannulation and takes typically 2-4 hours every 1-2 weeks. Due to the requirement for ongoing care with LDL-apheresis for patients to enable reductions in LDL-C. It is expected to contribute to health-related disutility due to the patient burden associated with receiving this treatment. Treatment with evolocumab is anticipated to reduce or remove the requirement for adjunctive LDL-apheresis due to the demonstrated magnitude of LDL-C reduction. ***Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.*** Published literature regarding the patient burden associated with LDL-apheresis.	
	Merck Sharp and Dohme	No comment	Response noted.
	Royal College of Pathologists	This treatment represent a major innovation in lipid management with the potential to improve the prognosis of those who have failed to achieve a satisfactory response to statin therapy, and therefore face therapeutic nihilism or limited access to LDL-apheresis I think the QALY should capture the benefits I understand that Phase I and II data versus placebo and or ezetimibe are available and much of it published, and that Phase III RCT data as add on therapy to statins +/- ezetimibe in HoFH and HeFH, and versus ezetimibe in	Comment noted. The innovative nature of evolocumab will be considered by the Committee during the appraisal.

Section	Consultee/ Commentator	Comments	Action
		statin intolerance are in development	
	HEART UK	Yes, this is a step-change.	Comment noted. The innovative nature of evolocumab will be considered by the Committee during the appraisal.
Other considerations	Amgen	No comments.	Response noted.
	Merck Sharp and Dohme	No comment	Response noted.
	Royal College of Pathologists	The definition of statin intolerance and adequacy of response to statin therapy would be important as such issues may determine who will be eligible for such treatment	Comment noted. The definition of statin intolerance and adequacy of response to statin therapy are expected to be in line with the definitions in NICE clinical guideline 71 (sections 1.3.1.10 and 1.3.1.11) and will be considered by the Committee during the appraisal.
	HEART UK	There are other members of the same drug class i.e. PCSK9 inhibitors which are also in clinical trials and which are likely to be applying for a license	Comment noted. Attendees at the

Section	Consultee/ Commentator	Comments	Action
		shortly after Evolocumab. Consideration should be given to appraise these simultaneously.	scoping workshop agreed that technologies in development which are not anticipated to get marketing authorisation by the time evolocumab will be available do not represent established practice and would not be considered appropriate comparators in this appraisal.
NICE Pathways [Delete section if not relevant]	Amgen	**Where do you consider evolocumab will fit into the *existing NICE pathway, Familial hypercholesterolaemia?*** We believe evolocumab could be used in the 'drug treatment in adults' section for use in patients unable to achieve the recommended 50% reduction in LDL-C with initial statin therapy.	Comment noted. No action required.
	Royal College of Pathologists	The treatment would clearly fit into the NICE FH pathway as an alternative to apheresis in heterozygous FH and some homozygous FH (prior to consideration of LDL-apheresis, or lomitapide). It would also fit into the CG181 pathway for statin intolerant patients. It will be important to decide on definitions of statin intolerance and inadequate response for the above indications and to consider whether the treatment should be prescribed only after specialist assessment/under specialist supervision.	Comment noted. The definition of statin intolerance and adequacy of response to statin therapy are expected to be in line with the definitions in NICE clinical guideline 71 (sections 1.3.1.10

Section	Consultee/ Commentator	Comments	Action
			and 1.3.1.11) No action required.
	HEART UK	It should fit into the NICE FH pathway after statins and ezetimibe, and used by a specialist:" If treatment with the maximum tolerated dose of a high-intensity statin and ezetimibe does not reduce LDL-C concentrations by greater than 50% from baseline, offer a referral to a specialist in familial hypercholesterolaemia."	Comment noted. No action required.
Questions for consultation	Amgen	***For which patient groups would evolocumab be used in clinical practice? Would it be considered only for people for whom statins are contraindicated, not tolerated or unable to provide appropriate control of LDL-C?*** Please refer to our comments regarding population and comparators (Section 1). ***Have all relevant comparators for evolocumab been included in the scope?*** Please refer to our comments regarding comparators (Section 1) and the anticipated marketing authorisation (Section 4). ***Which treatments are considered to be established clinical practice in the NHS for hyperlipidaemia and dyslipidaemia?*** Statins are the established initial treatment for primary hypercholesterolaemia and mixed dyslipidaemia as reflected in the recommendations from the recently issued NICE CG181. Evolocumab is not being studied as an alternative to statin therapy except in conditions of statin-intolerance or contraindications. Ezetimibe (also in accordance with NICE TA132) is used for LDLC lowering in combination with statins or monotherapy in those unable to tolerate statins. Other lipid-lowering therapies (e.g. fibrates, nicotinic acid or bile acid sequestrants) are believed to be used to a lesser extent in clinical	Comment noted.

Section	Consultee/ Commentator	Comments	Action
		practice in the NHS. If an appraisal is undertaken, we plan to provide supporting NHS treatment patterns data for lipid-lowering therapies. ***Is nicotinic acid commonly used for treating these conditions?*** We believe that nicotinic acid (other than in very small doses as part of multivitamin supplements) may not be currently available in the UK for the treatment of lipid disorders. As per above, if an appraisal is undertaken, we plan to provide supporting NHS treatment patterns data for lipid-lowering therapies such as nicotinic acid. ***How frequently is LDL-C apheresis used to treat heterozygous familial hypercholesterolaemia?*** Our understanding is that of the approximately 120 people receiving LDL-apheresis treatment in the UK. Around 70 of them have severe heterozygous familial hypercholesterolaemia (the rest being homozygous familial hypercholesterolaemia). This service is currently limited as a consequence of resources and local availability of apheresis services. ***Have all relevant outcomes been included in the scope?*** Yes, we believe all the relevant outcomes have been included in the scope. Please refer to our comments regarding outcomes.	
	Merck Sharp and Dohme	***For which patient groups would evolocumab be used in clinical practice?*** It is anticipated that evolocumab is to be initiated and administered in secondary care. As hyperlipidaemia and mixed dyslipidaemia is mainly cared for in primary care it is assumed (subject to appraisal) that statins and ezetimibe would retain first and second line treatment in line with CG181, with evolocumab initiated in specialist centres for specific patients once referred by the GP.	Comment noted.

Section	Consultee/ Commentator	Comments	Action
		Is nicotinic acid commonly used for treating these conditions? In the new lipid modification guideline CG181 nicotonic acid is not recommended for use in these patients. ***How frequently is LDL-C apheresis used to treat heterozygous familial hypercholesterolaemia?*** LDL-C apheresis is only used to treat compound heterozygous familial hypercholesterolaemia. This compound population should be included in the evolocumab, ezetimibe and lomitapide for treating homozygous familial hypercholesterolaemia MTA if this goes ahead.	
	Royal College of Pathologists	Existing LDL-apheresis units should be able to provide activity data. How many patients are eligible for LDL-apheresis but do not receive treatment because of lack of access.	Comment noted. No action required.
	HEART UK	It should only be considered when statins are contraindicated, not tolerated, or unable to provide appropriate control of LDLC or Non-HDLC. Nicotinic acid is no longer used. LDL-C apheresis is used to treat heterozygous FH on very rare occasions (Less than 50 patients currently in UK) Other subgroups should include patients who are intolerant to statins.	Comment noted. No action required.
Additional comments on the draft scope	Amgen	No additional comments.	Comment noted. No action required.
	Merck Sharp and Dohme	The list of related NICE recommendations and NICE pathways should be updated: - TA94 should be removed as this was updated as part of CG181.	Comment noted. The scope has been updated to incorporate

Section	Consultee/ Commentator	Comments	Action
		- Please update CG67 to reflect the publication of CG181.	suggested changes.
	Royal College of Pathologists	Homozygous FH should have been included	Comment noted. Heterozygous FH and homozygous FH have different treatment pathways, and therefore it was felt that it would be appropriate for this appraisal to consider heterozygous FH only.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
Genetic Alliance UK
Healthcare Improvement Scotland

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Somerville Foundation	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria and equalities commitments. Therefore the Somerville Foundation Trust have been added to the matrix under 'patient/carer' groups.

2.	Vascular Society of Great Britain and Ireland	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria and equalities commitments. Therefore the Somerville Foundation Trust have been added to the matrix under 'professional' groups.
3.	Muslim Health Network	NICE Secretariat		Removed	The organisation has now disbanded
4.	Somerville Foundation	PIP		Removed	PIP recommended removal at scoping matrix sign-off as this organisation are not directly relevant to the appraisal