National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Mipomersen for the prevention of cardiovascular events due to homozygous or severe heterozygous familial hypercholesterolaemia
Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

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Appropriateness	Genzyme Therapeutics	Mipomersen meets decision making criteria for entry to national commissioning by the Advisory Group for National Specialised Services (AGNSS). It should be referred to AGNSS for consideration as a nationally commissioned service and consequent appraisal through the AGNSS decision making process and should not be considered by NICE. We would ask NICE to consider whether AGNSS referral is appropriate following the scoping discussions with stakeholders and scoping meeting. Please see additional comments section later in this document for rationale for AGNSS inclusion.	Comment noted. AGNSS have previously indicated that they will not be considering this topic. The decision regarding referral of this appraisal to AGNSS is beyond the remit of NICE.
	HEART UK	Definitely	Comment noted. No action required.
	Royal College of Pathologists	This STA is relevant, timely and a high priority issue for severely affected patients.	Comment noted. Consultees agreed that if mipomersen is not going to be considered by AGNSS, then an STA would be the most appropriate process to consider this topic. No action required.
Wording	British Cardiac Society	Wording fine	Comment noted. No action required.
	Genzyme	Yes, the wording of the remit is appropriate, but needs to reflect the planned indication more closely. Please see comments in regulatory	Comment noted. The wording of the UK marketing authorisation is still

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	Therapeutics	section.	uncertain as mipomersen is not currently licenced. The remit broadly describes the disease, the patient population and the technology that will be covered by the appraisal. If the final wording of the marketing authorisation is narrower than the proposed remit, then NICE will only be able to make recommendations in line with the marketing authorisation.
	HEART UK	Yes, but see section on background information below regarding definition of severity	Comment noted. The wording of the UK marketing authorisation is still uncertain as mipomersen is not currently licenced. The remit broadly describes the disease, the patient population and the technology that will be covered by the appraisal. Please see below regarding response on definition of severity.
	Royal College of Pathologists	Yes	Comment noted. No action required.
Timing Issues	British Cardiac Society	Mipomersen is currently being licensed in Europe a NICE technical appraisal soon would be appropriate.	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.
	Genzyme Therapeutics	No comments, other than scheduling the appraisal close to the point of planned license will enable timely advice to the NHS on mipomersen for NHS clinicians, commissioners and patients.	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.

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	HEART UK	Urgent - in time for UK marketing authorisation	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.
	Royal College of Pathologists	Urgent - ideally should be completed in time for UK marketing authorisation	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.

Comment 2: the draft scope

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Background information	British Cardiac Society	Definition of severe heterozygous familial hypercholesterolaemia There are many possible definitions for severe He-FH. The obvious ones are compound heterozygote FH, patients who still have elevated levels of LDL (see reference range) despite maximal treatment with tolerated drug, patients with severe progressive coronary heart disease despite medication and possibly statin intolerant patients. Such patients may be currently candidates for LDL apheresis in the small number of centres throughout the UK that provides such a service. If the price of mipomersen were to be less than that of providing LDL apheresis, this may be an appropriate economic comparator. The role of LDL apheresis should certainly be included within the scope of this technology appraisal.	Comment noted. Attendees at the scoping workshop agreed that the definition of severe He-FH is consistent with the eligibility criteria for the patients enrolled in the mipomersen trials, that is, 'people who are on maximally tolerated lipid lowering therapies with an LDL cholesterol level > 5.2 mmol/L plus coronary heart disease (CHD) or who have an LDL cholesterol level >7.8mmol/L and are at high risk of CHD'.
	Genzyme Therapeutics	Page 1 Background - Paragraph 2 The definition of severe HeFH at the bottom of the second paragraph in the background section, page 1 is incorrect and should reflect the	Comment noted. The background section has been amended.

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		trial entry criteria for Mipomersen. The current definition in the background: "Severe He-FH represents is a small subset of the total He-FH population and includes people with LDL cholesterol levels >5.2 mmol/L while on a maximally tolerated dose of lipid lowering therapy, or >7.8 mmol/L for people with or without coronary heart disease." should be deleted and replaced with the following based on trial entry criteria and patient estimates later in this document: "Severe He-FH represents < 1% of the He-FH population and includes people who are on maximally tolerated lipid lowering therapies with LDL> 5.2 mmol/L (200mg/dl) plus coronary heart disease or LDL>7.8mmol/L (300mg/dl) without coronary heart disease". Page 1 - Paragraph 4, 2nd sentence The sentence "In Ho-FH, LDL cholesterol levels are markedly elevated (typically greater than 13 mmol/l) with other forms of cholesterol remaining normal" is incomplete as other lipid fractions such as Lp(a) and VLDL are also elevated in Ho-FH. Background, Page 2, Paragraph 1 This paragraph states that: "CG71 recommends LDL apheresis for the treatment of people with Ho-FH if they have coronary heart disease or if they are not responding to lipid-modifying drug therapy. CG71 also recommends LDL apheresis for the treatment of people with He-FH in exceptional instances for example when there is progressive, symptomatic coronary heart disease, despite maximal tolerated lipid-modifying drug therapy and optimal medical and surgical therapy." While this is correct it is important to note in the background section that the provision of LDL-apheresis as a treatment option for this patient population is extremely limited with lack of equity in provision of services across England and Wales and limited availability of LDL apheresis even where a service does exist to meet likely patient need.	Comment noted. The background section has been updated. Comment noted. The background section is only intended to briefly describe the disease relevant to the new technology together with appropriate information on the prognosis associated with the condition, epidemiology and alternative treatments currently used in the NHS. The issue of limited availability of the recommended treatment will be presented by the manufacturer in their evidence submission.

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		To illustrate this point, a 2008 NHS Lothian application to establish a national LDL Apheresis Service for Scotland at the Royal Infirmary of Edinburgh (available at http://www.nospg.nhsscotland.com/wp-content/C-LDL-Apheresis-Application.pdf) states that adult LDL-apheresis services are provided in 6 centres across England and Wales to a total of 45 patients as follows - Bristol (5 patients) - Leeds (4 patients) - Birmingham (4 patients) - London Hammersmith (4 patients) - London Harefield (11 patients) - Cardiff (17 patients, including supra-regional referrals from England) This represents a total of 45 patients in 2008 and our own data currently estimates that 69 patients are treated with LDL-aheresis in 2011 in England and Wales under treatment recommendations in CG71. These estimates are a significant shortfall both against our own estimates of the treatable population with mipomersen (381 patients, see later) and the potential population indicated for LDL-apheresis of 200, based on both a UK scientific advisory board held in November 2011 with key clinical opinion leaders in chemical pathology, endocrinology and cardiology and recommendations on the use of LDL apheresis from the Heart UK-LDL Apheresis Working Group (see Thompson G.L et al, Atherosclerosis 198 (2008) 247-255) - please see later for detail. General comment It may be helpful to include a brief paragraph on how FH is diagnosed and managed, as per current recommendations in NICE Clinical Guideline 71 (CG71) as follows: "In the UK, diagnosis of familial hypercholesterolaemia is based on the Simon Broome criteria, which include a combination of family history,	Comment noted. The background section is only intended to provide a brief summary of the disease relevant to the new technology together with appropriate

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		clinical signs (specifically tendon xanthoma) cholesterol concentration and DNA testing. Management of FH aims to reduce LDL-C levels by 50% of baseline and consequent cardiovascular risk with a combination of diet and lifestyle changes, lipid modifying therapy (statins, ezetimibe, bile acid sequestrants, nicotinic acid, and fibrates) and rarely in the UK, LDL apheresis. The percentage reduction is based on the difficulty of getting these patients to goal due to limitations in response to existing lipid lowering therapies (i.e. statin mechanism is not as effective in FH)".	information on the prognosis associated with the condition, epidemiology and alternative treatments currently used in the NHS. A more detailed description of the treatment pathway for Ho-FH and severe He-FH will be included in the evidence submission from the manufacturer.
	HEART UK	1. Paragraph 2, last sentence. The definition of severe He-FH is crucial to the scope and potential numbers who could be treated. We recommend the definition used in NICE CG71 for patients with He-FH in whom LDL-apheresis should be considered ie in exceptional circumstances, for example when there is progressive, symptomatic coronary disease, despite maximal tolerated lipid-modifying drug therapy and optimal medical and surgical therapy. There are other He-FH patients who are poor responders, or have side effects limiting the response to current therapies, who should also be considered for treatment with Mipomersen, dependent on the clinical and cost-effectiveness. They may not be classed as severe but could benefit from this technology. 2. Paragraph 3, sentence 2. Change "forms" to "fractions"	Comment noted. Attendees at the scoping workshop agreed that the definition of severe He-FH is consistent with the eligibility criteria for the patients enrolled in the mipomersen trials, that is, 'people who are on maximally tolerated lipid lowering therapies with an LDL cholesterol level ≥ 5.2 mmol/L plus coronary heart disease (CHD) or who have an LDL cholesterol level ≥7.8mmol/L and are at high risk of CHD'. Comment noted. The sentence has been deleted. .
	Royal College of Pathologists	Paragraph 1 1. Replace "specific genetic defect" with "an autosomal co-dominant genetic defect" 2. Replace "non-familial" with "polygenic" as the latter may be more frequent in other family members 3. Smoking does not interact with genetic factors to increase cholesterol 4. Replace "cholesterol" with "LDL-cholesterol" which is more specific	Comments noted. The draft scope has been updated to reflect suggested changes to points 2-7. For the purpose of brevity and to ensure that the scope is understandable by people who do not have a medical background, point 1 has not been incorporated

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		for FH Paragraph 2. 5. The definition of Severe He-FH is insufficiently precise using the open-ended term "includes" and appears to have been taken form a consensus statement definition of eligibility for LDL apheresis treatment. This definition is and is in conflict with the recommendations in the CG71 FH Guideline para 1.3.3.2 Paragraph 4. 6. According to CG71 Para 1.3.3.1 LDL apheresis for Ho-FH is not restricted to those with coronary disease although this will be taken into account in decision making. Paragraph 3 7. Replace "forms of cholesterol" with "cholesterol fractions"	into the scope. A more detailed description of the patient population will be provided in the evidence submission from the manufacturer.
The technology/ intervention	Genzyme Therapeutics	This section should state that "high levels of Apolipoprotein B-100 containing lipoproteins, such as LDL can lead to the development of atherosclerosis. Mipomersen has been shown to significantly reduce Apo B containing lipoproteins, including LDL". The Technology, pg 2, 2nd paragraph This paragraph should include the comment that mipomersen has been studied as an adjunctive treatment to maximally tolerated conventional lipid lowering therapies. It has been studied in the severe He-FH population as defined in the background section above. We would suggest the following text: "It has been studied as an adjunctive treatment to maximally tolerated conventional lipid lowering therapies compared with placebo plus maximally tolerated lipid lowering therapy in people with HoFH and in people with severe HeFH. It has also been studied in people with severe hypercholesterolemia with Coronary Heart Disease (approx. 88% of patients had FH), and in people with hypercholesterolemia	Comment noted. The scope does not include any results from the clinical trials or promotional claims. This information will be included in the manufacturer's evidence submission to NICE. Comment noted. The clinical trial description has been updated to more accurately describe the trial populations.

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		(LDL-C ≥ 2.6 mmol/L) who are at high risk of coronary heart disease". We would also include the statement in this section that "mipomersen has been shown to significantly reduce Apo B containing lipoproteins, including LDL".	
	HEART UK	1. Paragraph 2, sentence 3. In view of the definition of "severe" as discussed above, we recommend this word is changed to "significant".	Comment noted. Attendees at the scoping workshop agreed that the definition of severe He-FH is consistent with the eligibility criteria for the patients enrolled in the mipomersen trials, that is, 'people who are on maximally tolerated lipid lowering therapies with an LDL cholesterol level ≥ 5.2 mmol/L plus coronary heart disease (CHD) or who have an LDL cholesterol level ≥7.8mmol/L and are at high risk of CHD'.
		2. Intervention(s). We recommend changing to "Mipomersen in combination with maximally tolerated lipid lowering therapy", to not preclude its use along with LDL apheresis.	Comment noted. Attendees at the scoping workshop agreed that there are no data to support mipomersen use in combination with LDL apheresis.
	Royal College of Pathologists	Technology - Suggest change "short nucleic acid polymer " to "short antisense nucleic acid polymer"	Comment noted. The suggested change has been incorporated into the scope.
		Intervention - suggest change to "maximum tolerated doses of high intensity statin therapy alone or in combination with other lipid lowering therapy" to reflect recommendations of CG71.	Comment noted. Scoping workshop attendees agreed that the intervention should be described in line with the proposed licensed indication. No changes to the

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			technology in the scope have been made.
Population	British Cardiac Society	Another group of patients for which mipomersen could be indicators are those with either severe hypercholesterolaemia and/or severe familial hypercholesterolaemia with elevated levels of Lp(a). High concomitant levels of Lp(a) and LDL are considered appropriate criteria for LDL apheresis. Mipomersen will reduce significantly the levels of all ApoB containing lipoproteins and thus, such a group of patients may well have an indication for mipomersen therapy.	Comment noted. Attendees at the scoping workshop agreed that the population in the scope should be described in line with the proposed licensed indication. A detailed description of the population will be included in the evidence submission from the manufacturer.
	Genzyme Therapeutics	We would suggest the following slight alteration, consistent with the planned indication: "People at high risk of cardiovascular events due to homozygous familial hypercholesterolemia or severe heterozygous familial hypercholesterolemia which has not been adequately managed with maximally tolerated lipid lowering treatment".	Comment noted. The scope has been updated.
	HEART UK	It needs to be made clear whether the population of He-FH are only a. genetically, b. clinically "definite" or c. also "possible", as defined by the SimonBroome criteria in NICE CG71.	Comment noted, attendees at the scoping workshop agreed that the population in the scope should be described in line with the proposed licensed indication. A detailed description of the population will be included in the evidence submission from the manufacturer.
	Royal College of Pathologists	CG71 - See comments regarding definition of severe FH - "severely affected" He-FH may be a better form of words to include those with "progressive, symptomatic coronary heart disease, despite maximal tolerated lipid-modifying drug therapy and optimal medical and surgical therapy" as considered eligible for apheresis as per CG71. Basing eligibility for treatment on arbitrary LDL-C cut-offs rather than risk of events is inherently flawed.	Comment noted, attendees at the scoping workshop agreed that the population in the scope should be described in line with the proposed licensed indication. A detailed description of the population will be included in the evidence submission

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			from the manufacturer.
Comparators	British Cardiac Society	The comparators for homozygous and heterozygous FH should certainly be different. Implicit in the diagnosis of homozygous (technically more correct compound heterozygote) FH is the need for LDL apheresis.	Comment noted. Attendees at the scoping workshop agreed that mipomersen is likely to be used instead of LDL apheresis (after maximally tolerated high intensity stations alone or in combination with ezetimibe, a bile acid sequestrant or niacin), therefore LDL apheresis should be included as a comparator. For patients who do not have access to LDL apheresis, best supportive care would be considered, and therefore it should also be included as a comparator. The scope has been amended accordingly.
	Genzyme Therapeutics	Current management options for the treatment population are limited as patients are already on maximally tolerated lipid lowering therapy. The majority receive no further treatment and consequently do not achieve target LDL C reductions and remain at high risk of cardiovascular events. We would therefore suggest "best supportive care" (i.e. no treatment beyond maximally tolerated existing lipid lowering therapies) is the appropriate comparator as the majority of patients do not receive additional therapy beyond maximally tolerated lipid lowering therapy and are not treated with LDL-apheresis (see comments in background section above and later estimates of patient numbers).	Comment noted. Attendees at the scoping workshop agreed that mipomersen is likely to be used instead of LDL apheresis (after maximally tolerated high intensity stations alone or in combination with ezetimibe, a bile acid sequestrant or niacin), therefore LDL apheresis should be included as a comparator. For patients who do not have access to LDL apheresis, best supportive care would be considered, and therefore it should also be included as a comparator. The scope has been amended

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			accordingly.
	HEART UK	Yes. This should include LDL apheresis.	Comment noted. Attendees at the scoping workshop agreed that LDL-apheresis should be included as a comparator. The scope has been amended accordingly.
	Royal College of Pathologists	The appropriate standard treatment comparator is maximum tolerated dose of high intensity statin alone or in combination with ezetimibe, a bile acid sequestrant or niacin with apheresis as a comparator in Ho-FH and severely affected He-FH.	Comment noted. Attendees at the scoping workshop agreed that mipomersen is likely to be used instead of LDL apheresis (after maximally tolerated high intensity stations alone or in combination with ezetimibe, a bile acid sequestrant or niacin), therefore LDL apheresis should be included as a comparator. For patients who do not have access to LDL apheresis, best supportive care would be considered, and therefore it should also be included as a comparator. The scope has been amended accordingly.
Outcomes	Genzyme Therapeutics	Outcome measures are appropriate. As the clinical trial programme for mipomersen does not include measurement of clinical outcome end points, surrogate end points based on LDL cholesterol will need to be used. In addition to LDL C and Apo B, studies have also demonstrated a causal relationship between elevated Lp(a) levels and cardiovascular risk, in both the general population and in subjects with familial hypercholesterolemia, where Lp(a) levels ate typically elevated. (Mbewu et al. Arterioscler Thromb 11 (4):940-946.1991; Danesh et	Comment noted. Attendees at the scoping workshop agreed that a surrogate endpoint where an association with survival or health related quality of life can be clearly demonstrated could be used.

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		al.,Circulation 102 (10):1082-1085 2000; Holmes et al., Clin Chem 51 (11):2067-2073, 2005. Nenseter et al., Atherosclerosis Vol. 216, Issue 2, 426-432, 2011). There is also emerging evidence that lowering Lp (a) may reduce cardiovascular risk (Jaeger et al.Nat Clin Pract Cardiovasc Med. 2009 Mar;6(3):229-39).	
	HEART UK	Yes A further important outcome would be a reduction in the need or frequency of LDL apheresis.	Comment noted. Mipomersen is intended to be used instead of LDL-apheresis (not in combination), therefore workshop attendees did not consider that this outcome needed to be included in the scope.
	Royal College of Pathologists	Avoidance of the need for LDL apheresis is an important outcome which should be included. Non-HDL-cholesterol or apolipoprotein B are superior to calculated LDL-cholesterol as surrogate outcome measures for assessment of response to treatment. Lipoprotein(a) concentration should be included as an additional surrogate outcome.	Comment noted. Attendees at the scoping workshop agreed that a surrogate endpoint where an association with survival or health related quality of life can be clearly demonstrated could be used. Attendees heard from NICE that the list of outcomes in the scope is not exhaustive and other outcome measures not listed can be considered by the manufacturer in their evidence submission if the data permits.
Economic analysis	Genzyme Therapeutics	Lifetime time horizon should be adopted.	Comment noted. No action required.
	HEART UK	Appropriate	Comment noted. No action required.
	Royal College of Pathologists	The proposed economic analysis seems appropriate.	Comment noted. No action required.
Equality	Genzyme	As previously noted, the provision of LDL-apheresis as a treatment	Comment noted. Geographic

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	Therapeutics	option for this patient population is extremely limited with lack of geographical equity in provision of services across England and Wales and limited availability of LDL apheresis even where a service does exist to meet likely patient need. LDL-apheresis requires venous access and the patient usually attends clinic for 2-4 hours every 2 weeks, or more rarely on a weekly basis. As a pharmacotherapy in an area of unmet need, mipomersen may improve equity of access to an effective treatment.	access to the existing treatment is considered an equity issue rather than 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. The Committee will consider when making its decision whether its recommendation on the use of mipomersen will lead to unequal access to treatment for some patients in England and Wales.
	HEART UK	Administration by subcutaneous injection may be difficult in patients with certain disabilities, who may require carer support to access the technology.	Comment noted. Any potential equality issues will be highlighted in the evidence submissions from the manufacturer and other consultees. The Committee will consider when making its decision whether its recommendation on the use of mipomersen will lead to unequal access to treatment for some patients in England and Wales.
	Royal College of Pathologists	Genotyping for FH promotes equality by providing unequivocal confirmation of diagnosis where lipid measures may be equivocal, regardless of gender ethnicity or comorbidities. Equality of access is also important as existing treatment options such as apheresis is currently available in only 5 UK centres and fortnightly travel to these centres from long distances is impractical.	Comment noted. Any potential equality issues will be highlighted in the evidence submissions from the manufacturer and other consultees. The Committee will consider when making its decision whether its recommendation on the use of mipomersen will lead to unequal

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			access to treatment for some patients in England and Wales.
Other considerations	HEART UK	1. There are other He-FH patients who are poor responders, or have side effects limiting the response, to current therapies who should also be considered for treatment with Mipomersen, dependent on the clinical and cost-effectiveness. They may not be classed as severe but could benefit from this technology. 2. There are patients who have either not been proven to have FH or are not thought to have FH, but who have significant hyperlipidaemia and are not currently obtaining adequate reduction of their LDL cholesterol and have progressive vascular disease. They may benefit from this technology.	Comments noted. Attendees at the scoping workshop agreed that the population in the scope should be considered in line with the proposed licensed indication.
	Royal College of Pathologists	Subgroups should include 1. Those with and without vascular disease in coronary, cerebral or peripheral vascular beds - risk being greatest for those with vascular disease at multiple sites 2. Those who are intolerant of statins, particularly those who have muscular toxicity with multiple statins, and/or other lipid lowering therapy. Note that some patients do not tolerate apheresis.	Comments noted. Attendees at the scoping workshop heard from the manufacturer that the entry criteria in the clinical trials were specific to the presence or risk of coronary heart disease. Therefore, as all patients fulfilled this criterion, it does not constitute a subgroup. The manufacturer confirmed that data for people with cerebral and peripheral vascular bed are not available; therefore consideration of this subgroup would not be possible at this time. Attendees heard from the manufacturer that the clinical trials included those who were intolerant to statins but no analysis of this small subgroup was planned.

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			Attendees at the scoping workshop therefore agreed that there is no added benefit to perform a subgroup analysis of those who are intolerant of statins (and would therefore be able to access mipomersen earlier than those who do not have statin intolerance) as they are already covered by the marketing authorisation.
Innovation	British Cardiac Society	Mipomersen is indeed an innovative therapy with enormous potential to make a significant and substantial impact on the health related benefits for a small and focused group of patients. It may indeed provide an alternative to LDL apheresis therapy.	Comment noted. The innovative nature of mipomersen will be highlighted in the manufacturer's submission and will be considered by the Committee during the course of the appraisal.
	Genzyme Therapeutics	Yes, we believe that mipomersen is innovative as it is a novel first in class antisense oligonucleotide (ASO) drug that inhibits the expression of apolipoprotein B-100 (Apo B), the primary structural constituent of all atherogenic lipoproteins. The extreme LDL-C levels in severe FH are the consequence of genetic mutations that profoundly impair LDL particle clearance. High plasma LDL particle concentration also triggers increased hepatic uptake of LDL through non-specific pathways resulting in increased secretion by the liver of Apo B-containing lipoprotein particles, including VLDL, LDL and Lp(a). Current therapeutic interventions such as statins work on a different mechanism but offer limited value in patients with severe FH due to the severe dysfunction of the LDLR clearance pathway in these patients. Mipomersem is targeted to an area of high unmet need as the majority of indicated patients will still have markedly elevated LDL-C levels and	Comment noted. The innovative nature of mipomersen will be highlighted in the manufacturer's submission and will be considered by the Committee during the course of the appraisal.

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		other atherogenic lipid fractions such as Lp(a), despite maximally tolerated lipid lowering therapy and the majority of eligible patients currently do not receive further treatment beyond maximally tolerated lipid lowering therapy. LDL-apheresis is an option for these patients, however it has limited availability and thus considerable geographic inequity of access, requires frequent and chronic vascular access, and is associated with compromised quality of life. By providing an additional, first in class, pharmacological treatment option in this high risk population, mipomersen addresses an unmet need.	
	HEART UK	Yes, this is a potential "step-change" for Ho-FH and severe He_FH patients (and as in other considerations above). No [all benefits expected to be captured in QALY calculation]	Comment noted. The innovative nature of mipomersen will be highlighted in the manufacturer's submission and will be considered by the Committee during the course of the appraisal.
	Royal College of Pathologists	The technology is indeed a 'step-change' in the management of the condition, if issues of tolerability do not limit its use. Better accessibility and long-term adherence to treatment might not be taken into account in QALY calculations. The published data and any as yet unpublished results which may have been presented in abstract form is the only source of evidence of which we are aware.	Comment noted. The innovative nature of mipomersen will be highlighted in the manufacturer's submission and will be considered by the Committee during the course of the appraisal.
Questions for consultation	Genzyme Therapeutics	Is the definition of severe heterozygous familial hypercholesterolaemia appropriate? The definition of severe HeFH according to clinical trial entry criteria should read as: "Severe He-FH represents < 1% of the He-FH population and includes	Comment noted. Attendees at the scoping workshop agreed that the definition of severe He-FH is consistent with the eligibility criteria for the patients enrolled in the

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		people who are on maximally tolerated lipid lowering therapies with LDL> 5.2 mmol/L (200mg/dl) plus coronary heart disease or LDL>7.8mmol/L (300mg/dl) without coronary heart disease" It is important to note that this definition is also clinically supported and defined by LDL-apheresis eligibility criteria from 3 sources, from recommendations in NICE CG71, from consensus from UK clinical experts and with recommendations made on the use of LDL apheresis from the Heart UK-LDL Apheresis Working Group, (see Thompson G.L et al, Atherosclerosis 198 (2008) 247-255). These recommendations are detailed below and mirror the definition of severe HeFH above: 1. Apheresis criteria in NICE CG71 are as follows (section 1.3.3. pg 18-19) - Healthcare professionals should consider offering LDL apheresis for the treatment of adults and children/young people with homozygous FH (see recommendations 1.1.5 and 1.1.16). The timing of initiation of LDL apheresis should depend on factors such as the person's response to lipid-modifying drug therapy and presence of coronary heart disease. - 1.3.3.2 In exceptional instances (such as when there is progressive, symptomatic coronary heart disease, despite maximal tolerated lipid-modifying drug therapy and optimal medical and surgical therapy), healthcare professionals should consider offering LDL apheresis for the treatment of people with heterozygous FH. This should take place in a specialist centre on a case-by-case basis and data recorded in an appropriate registry. As detailed above we estimate 69 patients are currently treated with LDL-apheresis in England and Wales (rising from 45 in 2008), based on these guideline recommendations. 2. Further, UK clinical experts in the management of Familial Hypercholestrolamia were brought together for a Genzyme FH Scientific Advisory Board (19th October 2011). The group's consensus	mipomersen trials, that is, 'people who are on maximally tolerated lipid lowering therapies with an LDL cholesterol level ≥ 5.2 mmol/L plus coronary heart disease (CHD) or who have an LDL cholesterol level ≥7.8mmol/L and are at high risk of CHD'.

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		definition of severe HeFH was as follows: - Patients with defined HeFH (clinically and/or genetically) whose coronary and/or cardiovascular disease progresses and where LDL cholesterol remains >5.0mmol/l or is decreased by <40% with maximal tolerated drug therapy. - All FH homozygotes/Compound HeFH from the age of seven onwards unless their serum cholesterol can be reduced by >50% and/or decreased to <or=9mmol/l by maximally tolerated drug therapy; The advisory board (of 10 key clinical opinion leaders in chemical pathology, endocrinology and cardiology who represented most of the major lipid and endocrinology centres in the UK) estimated that the number of known patients falling within this definition of Severe HeFH is 200 within England and Wales and this population would be defined as LDL-apheresis eligible and be the target population for mipomersen. 3. The advisory board definition of severe HeFH is also consistent with recommendations made on the use of LDL apheresis from the Heart UK-LDL Apheresis Working Group, which also estimates the target population to be 200 (see Thompson G.L et al, Atherosclerosis 198 (2008) 247-255). How many people have severe He-FH in England and Wales? Published estimates of prevalence specific to severe HeFH do not exist. However, an estimated prevalence can be calculated by using data from trials involving FH patients treated with maximally tolerated lipid-lowering therapies. A large, cross-sectional study reported by Pijlman et al. (Pijlman AH et al. Atherosclerosis 209 (1):189-194. 2010) examined maximal statin plus ezetimibe therapy in 1,249 FH patients in the Netherlands. The Dutch FH population is the most well described and studied as screening for familial hypercholesterolemia has been ongoing in the Netherlands since 1994. In this study, the mean on-treatment LDL C level in FH patients was 3.5 mmol/L.	Comment noted. Attendees at the scoping workshop confirmed that mipomersen is likely to be used by up to 500 patients in England and Wales. Specific epidemiological estimates will be included in the manufacturer's evidence submission for the Committee to consider. No changes to the scope required.

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		Assuming a Gaussian distribution for on-treatment LDL-C, approximately 8% of patients on combination therapy would have LDL-C levels above 5.2 mmol/L. The study also reported that 17% of all patients had a history of CVD. Therefore, assuming that these patients are equally distributed in the on-treatment group, 1.36% of on-treatment patients would be expected to meet the criteria of LDL-C levels above 5.2 mmol/L and have a history of cardiovascular disease. Based on the estimated genetic prevalence of HeFH (1 in 500 population), the prevalence of patients with both pre-existing cardiovascular disease and LDL-C levels above 5.2 mmol/L while on lipid-lowering therapy is therefore estimated to be 1.36% of 1 in 500 or 1 per 36,700 population (27 per million population). Further, the indication for mipomersen and the diagnostic criteria for severe FH require that patients are maximally treated with lipid-lowering therapies. In the Pijlman et al., (2010) study, 27% of treated patients were on maximally tolerated lipid-lowering therapy (defined as maximum statin dose combined with ezetimibe), translating to a prevalence of 1 per 135,926 population or 7 per million population. Based on these data and an English and Welsh population estimate of 51,456,400 and 2,990,000 respectively, a total of 381 HeFH patients with cardiovascular disease and LDL-C levels exceeding 5.2 mmol/L while on maximally tolerated lipid-lowering therapy would be considered to be severe HeFH and eligible for therapy with mipomersen. This represents less than 1% of the entire FH population In England and Wales. The prevalence of FH patients with LDL-C ≥ 7.8 mmol/L can be calculated in a similar manner. Using the on-treatment LDL-C levels from Pijlman et al. (2010) and assuming a Gaussian distribution, 0.02% of all FH patients will have LDL-C ≥ 7.8 mmol/L, regardless of CAD status. This corresponds to a prevalence of < 1 per million people in the general population. Based on their LDL-C levels, these patients are consistent with the phenotype of HoFH and meet the	

Section	Consultees	Comments	Action
		definition of severe FH. However, given that the Pijlman et al., (2010) study included all FH patients, and not just HeFH patients, the prevalence estimates above best characterize the entire severe FH population, including both HoFH and severe HeFH patients. It is expected that the majority of the FH patients with on-treatment LDL-C levels above ≥300 mg/dL (7.8 mmol/L) would be HoFH patients. It is important to note that a prevalence of 7 per million population assumes that 100% of severe FH patients are diagnosed. It should be considered that in reality not all patients will be diagnosed, resulting in a prevalence that would be less than 7 per million or below 381 patients in England and Wales Based on the clinical definition of severe HeFH from the UK Scientific Advisory board detailed above, clinicians estimated that approximately 200 patients would fall within their definition of severe HeFH and would be candidates for mipomersen. Based on 2008 clinical criteria for LDL-apheresis established in CG71 which also cover HoFH and severe HeFH, we estimate 69 patients are currently treated in England and Wales (rising from 45 in 2008), indicating that the apheresis eligible population is small. Overall, it is evident that patients with severe FH constitute <1% of the FH population and are a small, well-characterized and clinically distinct population that is easily identifiable via their refractory LDL-C levels and medical history. Would mipomersen also be considered as an appropriate treatment for people with moderate He-FH? No, the current proposed label would re-strict on license prescribing to the HoFH and severe HeFH population. We would not view mipomersen as appropriate for wider usage on an off label basis. Further, given the nature and severity of the disease in the target population, initiation and monitoring of treatment is likely to be restricted to specialist centres. Is mipomersen likely to be used as monotherapy for people with	Comment noted. No action required.

Section	Consultees	Comments	Action
		familiar hypercholesterolaemia? No, the proposed indication will specify that mipomersen should be used in addition to maximally tolerated standard lipid lowering therapy. Mipomersen would thus be used in addition to existing maximally tolerated lipid lowering therapy, as per the proposed license. Again, as above we would not view mipomersen as appropriate for wider usage on an off label basis. Given the nature and severity of the disease in the target population, initiation and monitoring of treatment is likely to be restricted to specialist centres. Have the most appropriate comparators for mipomersen for the prevention of cardiovascular events due to homozygous familial hypercholesterolaemia and severe heterozygous familial hypercholesterolaemia been included in the scope? Yes, we believe standard management (best supportive care with maximally tolerated lipid lowering therapies) should be used as the comparator as it is the most frequent treatment in the defined population. • How should standard management without mipomersen be defined? Standard management should be defined as treatment with maximally tolerated standard lipid lowering therapies. • Should the comparators for Ho-FH and He-FH be different? We believe standard management (best supportive care) should be used as the comparator for both Ho-FH and He-FH.	Comment noted. No action required. Comment noted. Attendees at the scoping workshop agreed that mipomersen is likely to be used instead of LDL apheresis, therefore LDL apheresis should be included as a comparator. For patients who do not have access to LDL apheresis, best supportive care would be considered, and therefore it should also be included as a comparator. The scope has been amended accordingly.
	HEART UK	1. Is the definition of severe He-FH appropriate: The definition of severe He-FH is crucial to the scope and potential numbers who could be treated. We recommend the definition used in	Comment noted. Attendees at the scoping workshop agreed that the definition of severe He-FH is

Section	Consultees	Comments	Action
		NICE CG71 for patients with He-FH in whom LDL-apheresis should be considered ie in exceptional circumstances, for example when there is progressive, symptomatic coronary disease, despite maximal tolerated lipid-modifying drug therapy and optimal medical and surgical therapy. With this definition there are likely to be 100-200 such patients in England & Wales.	consistent with the eligibility criteria for the patients enrolled in the mipomersen trials, that is, 'people who are on maximally tolerated lipid lowering therapies with an LDL cholesterol level ≥ 5.2 mmol/L plus coronary heart disease (CHD) or who have an LDL cholesterol level ≥7.8mmol/L and are at high risk of CHD'.
		2. Would mipomersen also be considered as an appropriate treatment for people with moderate He-FH: Again this depends on the definition of moderate however there are other He-FH patients who are poor responders, or have side effects limiting the response to current therapies, in whom it should be considered.	Comment noted. Attendees at the scoping workshop agreed that the population in the scope should be described in line with proposed licensed indication. The scope has been amended accordingly.
		3. Is mipomersen likely to be used as monotherapy in people with FH: Yes, occasionally, where no other treatments are tolerated or available.	Comment noted. Attendees at scoping workshop heard from manufacturer that the proposed licensed indication for mipomersen will not cover its use as monotherapy. Instead it will be considered in combination with maximum tolerated doses of lipid lowering therapy.
		4. Most appropriate comparators: For Ho-FH and severe HeFH as we have defined it - standard management is maximal achieved dose of high potency statin plus ezetimibe plus other lipid lowering therapy, including LDL apheresis, where appropriate.	Comment noted. Attendees at the scoping workshop agreed that including best supportive care without mipomersen and LDL-apheresis as comparators is appropriate.
		5. Suggested subgroups: are appropriate, but note issues around definition of severity as above.	

Section	Consultees	Comments	Action
	Royal College of Pathologists	Additional questions Q: Would mipomersen also be considered as an appropriate treatment for people with moderate He-FH? A: Unlikely but again this depends on the definition of moderate He-FH as well as acceptability to patients, safety, efficacy and cost considerations Q: Is mipomersen likely to be used as monotherapy for people with familiar hypercholesterolaemia? A: Only those who are intolerant of statins and perhaps other lipid lowering therapy.	Comments noted. Attendees at the scoping workshop agreed that mipomersen would only be considered for severe patients in line with the anticipated marketing authorisation. Comment noted. Attendees at scoping workshop heard from the manufacturer that the proposed licensed indication for mipomersen will not cover its use as monotherapy. Instead it will be considered in combination with maximum tolerated doses of lipid lowering therapy.

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

Department of Health
Medicines and Healthcare products Regulatory Agency
Royal College of Nursing
Society for Vascular Technology

NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Mipomersen for the prevention of cardiovascular events due to homozygous or severe heterozygous familial hypercholesterolaemia

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.	We would also include: European Atherosclerosis Society Interchol (International Cholesterol Foundation as stakeholders)	Genzyme		Not included	Organisations that are invited to participate in a technology appraisal are national organisations based in the UK/Wales. These organisations are international and therefore cannot be included on the matrix of consultees and commentators.

2.	The Association of Clinical Biochemistry should be consulted as there are implications for Clinical Biochemistry laboratories	Royal College of Pathologists		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. The Association of Clinical Biochemistry has been added to the matrix of consultees and commentators under 'professional groups'.
3.	Add the Allied Health Professionals Federation to the matrix of consultees and commentators as a General commentator.	NICE Secretariat		Added	This organisation has requested to be included on all appraisal matrices and meets the selection criteria to participate in this appraisal. The Allied Health Professionals Federation has been added to the matrix of consultees and commentators as a 'general commentator'.
4.	Remove Heart Disease and Diabetes Research Trust as a relevant research group.	NICE Secretariat		Removed	This organisation has disbanded.