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Mipomersen and its use in Familial Hypercholesterolemia

Johnathon Seth Parham, MD

Clinical Fellow in Endocrinology, Division of Endocrinology, Metabolism, and Lipid Research, Department of Medicine, Washington University School of Medicine, Campus Box 8127, 660 South Euclid, St. Louis, MO 63110, USA

Abstract

Introduction—Familial Hypercholesterolemia (FH) is an inherited disorder characterized by a defect in the binding and internalization of low-density lipoprotein (LDL) particles, resulting in markedly elevated LDL levels and premature atherosclerosis. It is one of the most common inherited disorders of lipid metabolism. Many FH patients, especially those with homozygous FH do not reach LDL goals with traditional LDL therapies and may require additional, less often used, therapies.

Areas covered—Mipomersen is an anti-sense oligonucleotide that prevents production of apolipoprotein B leading to decreased levels of very low-density lipoprotein (VLDL) and LDL. In this review the authors discuss the pharmacokinetics of the drug, the clinical trials evaluating its efficacy and safety, and risks and challenges associated with its clinical implementation. Its use as therapy for the treatment of FH is also discussed.

Expert opinion—Mipomersen is approved for use only in homozygous FH. It has frequent adverse effects, such as injection site reactions, flu-like symptoms and hepatoxicity. It is useful only in patients who have failed other therapies, and it faces competition from other medications that have more tolerable side effect profiles.

Keywords

Antisense oligonucleotide; Familial hypercholesterolemia; Lomitapide; Mipomersen

Corresponding author: Anne Carol Goldberg, MD, Professor of Medicine, Division of Endocrinology, Metabolism, and Lipid Research, Department of Medicine, Washington University School of Medicine, Campus Box 8127, 660 South Euclid, St. Louis, MO 63110, USA, Tel: +1 314 362 4332; fax: +1 314 362 4833, agoldber@wustl.edu.

Declaration of Interest

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1. Introduction:

The burden of coronary heart disease in developed nations remains overwhelming, as heart disease continues to be the leading cause of death in the United States and worldwide. Inherited disorders of lipid metabolism make up a substantial portion of patients affected by atherosclerotic cardiovascular disease, and of these, familial hypercholesterolemia (FH) is one of the most common and well-described disorders [1]. FH is an inherited disorder characterized primarily by a defect in the ability to bind and internalize low density lipoprotein (LDL) particles, resulting in markedly elevated LDL levels and premature atherosclerosis. It has an autosomal dominant inheritance pattern, and clinical severity is in part dependent on homozygosity versus heterozygosity of the inherited mutation. The most common form is a mutation in the gene that encodes the LDL receptor (*LDLR* gene). Over 1700 mutations, of which at least 900 are pathogenic, in this gene have been described [1,2], leading to the LDL receptor having decreased ability to clear LDL from the circulation. Mutations in alleles of three other genes also create the phenotype of FH. These include defects in the LDL-receptor-binding region of apolipoprotein B (APOB) [1] and rare gain of function proprotein convertase subtilisin/kexin type 9 (PCSK9) gene mutations [3]. A rare autosomal recessive form of FH caused by loss-of-function mutations in the LDL receptor adaptor protein 1 (LDLRAP1), which encodes a protein required for clathrin-mediated internalization of the LDL receptor, has also been described [4]. Though single gene disorders play a crucial role in the etiology of FH, linkage studies suggest that some cases are caused by the presence of multiple single nucleotide polymorphisms [5]. Therefore, FH can be considered to be a group of inherited disorders that produce a similar phenotype.

FH homozygotes have the same mutation in both alleles of the same gene. Compound heterozygotes have different mutations in each allele of the same gene and, double heterozygotes have mutations in two different genes affecting LDL receptor function. Patients who are homozygotes (or compound heterozygotes) have much higher LDL-C levels and earlier clinical atherosclerosis than heterozygotes [4]. Historically, the prevalence of homozygous FH (HoFH) has been estimated at 1 in 1,000,000, but recent data from the Netherlands suggest that this number could be as low as 1 in 160,000 and is likely to be about 1 in 250,000 [6]. Studies based on the Dutch Lipid Clinic Network criteria suggest the prevalence of heterozygous FH (HeFH) may be as high as 1 in approximately 250 patients [4]. Because of its prevalence and impact on cardiovascular events, the CDC Office of Public Health Genomics recommends Tier 1 genomic application of cascade screening for FH [7].

Untreated heterozygotes have LDL-C in the range of 155 to 500 mg/dl whereas untreated homozygotes (or compound heterozygotes) typically have LDL-C greater than 500 mg/dl although the level may be lower, particularly in children [4, 8]. Diagnosis of FH is made based on lipid levels, physical exam findings, family history and if available, genetic testing. Arcus corneae before age 45 is typical in HoFH. Cutaneous and tuberous xanthomas are suggestive of but not limited to homozygous FH patients, who tend to have early presence of tendinous xanthomas. Heterozygous patients may have tendon xanthomas and early arcus corneae (before age 45) [1]. However, physical exam findings can be absent in patients with FH. Three clinical diagnostic tools for HeFH include: The US Make Early Diagnoses

Prevent Early Deaths Program Diagnostic Criteria (MEDPED), the Dutch Lipid Clinic Network Criteria and the Simon Broome Register Diagnostic Criteria. In untreated HoFH, the first major atherosclerotic event is typically in adolescence. Patients with HeFH are typically asymptomatic in childhood but suffer a high number of atherosclerosis cardiovascular disease (ASCVD) events prior to age 60 [1].

Homozygous patients require treatment as soon as the diagnosis is made, usually in early childhood, and need lifestyle, medication and additional modalities [8]. Treatment of homozygous FH patients can delay major cardiovascular events and early death [4,9]. Reducing LDL-C levels in HoFH is critical. Patients should be encouraged to follow a low-saturated fat, low-cholesterol diet. Treating modifiable risk factors, such as smoking, diabetes and high blood pressure is important. However, despite adherence, diet has little impact on the severity of hypercholesterolemia [4]. Treatment for HoFH starts at the time of diagnosis and involves age-appropriate diet, statin, ezetimibe, bile acid sequestrants, PCSK9 inhibitors and often apheresis [4,10]. According to the European Atherosclerosis Society Consensus panel, LDL-C goals in HoFH are less than 100 mg/dL in adults, less than 135 mg/dL in children and less than 70 mg/dL in adults with clinical ASCVD [11]. Lomitapide and mipomersen are approved by the FDA as adjunct therapy for HoFH. Both drugs affect the production and secretion of apoB-containing lipoproteins, rather than increasing their removal from circulation.

2. Overview of the market:

Treatment modalities for HoFH and HeFH largely focus on a single aspect of treatment, enhancing the removal of LDL-C from the circulation. LDL apheresis represents the most direct approach to this solution, offering dramatic, but temporary reductions in LDL-C. Patients with HoFH often require multiple drug regimens to achieve target LDL-C levels, and even patients without FH on high potency statins may not reach an LDL-C level less than 70 mg/dL [12]. Newer therapies with more significant reductions in LDL-C would allow for fewer medications to be taken daily, with the hope of reducing costs and potential adverse reactions and drug interactions for the patient. The PCKS9 inhibitor, evolocumab was approved in 2015 for HeFH and HoFH, and acts by blocking the effect of proprotein convertase subtilisin kexin 9, which degrades LDL receptors, decreasing LDL receptor recycling to the cell surface. The monoclonal antibody interferes the binding of PCSK9 to LDL receptors, allowing increased availability of LDL receptors and greater LDL uptake. HoFH mutations are either LDL-R negative with less than 2% of normal function or LDL-R defective, with 2–25% of normal function. Thus, LDL-R negative patients experience little to no benefit from PCSK9 inhibitor therapy [13]. Medications that target the production of LDL-C rather than enhancing its elimination do not require the presence of LDL receptor activity. One of these, lomitapide, was approved in the United States in 2012, and mipomersen was approved in 2013. Lomitapide inhibits microsomal triglyceride transfer protein, which is required for hepatic production of very-low density lipoprotein (VLDL) particles from the liver. Mipomersen is an anti-sense oligonucleotide that inhibits synthesis of apolipoprotein B, an essential component of VLDL. An investigational drug, ETC-1002, is a new LDL-C lowering agent in development at Esperion Therapeutics, Inc. The molecule targets two hepatic enzymes: adenosine triphosphate-citrate lyase (ACL) and adenosine

monophosphate-activated protein kinase (AMPK), thus inhibiting sterol and fatty acid synthesis and promoting mitochondrial long-chain fatty acid oxidation. ETC-1002 has been studied in phase I and phase II clinical trials and has been shown to decrease LDL-C levels significantly (but it also works by upregulating LDL receptors) [14].

3. Introduction to the compound:

Mipomersen is an antisense oligonucleotide (ASOs), a single-stranded synthetic oligonucleotide that binds to RNA through sequence-specific base-pair interactions. Once bound, ASOs can affect the metabolism of the target RNA and subsequently inhibit the production of specific proteins. Mipomersen targets apolipoprotein B-100 production, an essential structural component of LDL and VLDL [15,16].

4. Chemistry:

Mipomersen sodium is a synthetic phosphorothioate oligonucleotide sodium salt, 20 nucleotides in length with the following sequence: 5'-$\underline{G^{Me}C^{Me}C^{Me}U^{Me}C}AGT^{Me}CTG^{Me}CTT^{Me}C\ \underline{G^{Me}CA^{Me}C^{Me}C}$-3', where the underlined residues are 2'-*O*-(2-methoxyethyl) nucleosides and all other residues are 2'-deoxynucleosides. Cytosine (C) and Uracil (U) bases are modified at the 5 position with a methyl group. The molecular weight is 7,594.9g/mol [17]. Mipomersen is formulated in a pre-filled syringe containing 200 mg of mipomersen sodium in 1 mL of aqueous solution (pH 7.5–8.5) without any added preservative. It is administered as a once weekly subcutaneous injection.

5. Pharmacodynamics and clinical efficacy:

Mipomersen demonstrated a dose- and time-dependent reduction of apolipoprotein B-100 messenger RNA in the liver in all animal species studied. The first phase I study in humans was conducted in volunteers with mild dyslipidemia, and the 200 mg dose produced an approximate 50% reduction in circulating apo B after four weeks of treatment. The drug concentrations increased during treatment and were cleared from plasma with an approximate 31-day half-life after stopping the drug. After cessation of dosing, apo B levels remained low for several weeks and slowly returned to baseline over several months [18]. In four phase I and II studies the pharmacodynamics of mipomersen were evaluated. These studies included patients with mild dyslipidemia who were not on lipid lowering therapy [19], patients with mild to moderate hyperlipidemia [20], patients with hypercholesterolemia receiving stable statin therapy [21] and patients with FH who were on stable lipid lowering medication [22]. In all of these studies mipomersen produced dose-dependent reduction in all apo B-containing lipoproteins. Mipomersen has demonstrated efficacy in both homozygous and heterozygous FH patients in phase III trials. In the pivotal phase III study, patients aged 12 years and older with a clinical diagnosis or genetic confirmation of homozygous FH, who were already receiving maximum tolerated dose of a lipid lowering drug, were randomly assigned to mipomersen 200 mg subcutaneously every week or placebo. 28 subjects randomized to mipomersen completed the 6-month trial with a mean percentage change in LDL of −24.7%. However, responses to mipomersen with LDL

reduction were variable, ranging from essentially no change to 82% LDL cholesterol decrease, and independent of baseline LDL-C, age, race or sex [23]. Another multicenter phase III trial studied mipomersen in patients with clinical severe hypercholesterolemia, with randomization to weekly mipomersen or placebo for twenty six weeks. This trial demonstrated reduction in LDL in the mipomersen group by 36%, along with statistically significant reduction in apolipoprotein-B and lipoprotein (a), with no change in HDL [24]. Mipomersen was also effective in heterozygous FH. One phase III study randomized patients with heterozygous FH and coronary artery disease on lipid lowering treatment to mipomersen 200 mg weekly or placebo for twenty six weeks. The mean reduction of LDL-C was −28% and of lipoprotein (a) was −21.1% [25]. Lastly, a phase III trial studied mipomersen in patients with LDL-C over 100 and CHD or at high risk for CHD per National Cholesterol Education Program Adult Treatment Panel III guidelines. These patients were randomized to 200 mg mipomersen weekly or placebo for 26 weeks. Mean baseline LDL-C levels were 122.7 and 122.6 mg/dl in the placebo and mipomersen patients, respectively. Results showed a reduction of LDL by −36.9% with mipomersen compared to −4.5% with placebo [26]. An open label extension of a phase III study involving 141 patients with FH demonstrated sustained reductions in LDL-C and apoB with mipomersen [27]. In addition to this, a post hoc analysis of prospectively collected data of three trials demonstrated that long-term mipomersen treatment may also be associated with a reduction in cardiovascular events in FH patients [28]. Another study demonstrated that mipomersen reduced LDL-C and lipoprotein(a) in patients on lipid lowering therapy and apheresis, and might reduce the necessity for apheresis [29]. Finally, a meta-analysis of randomized controlled trials showed mipomersen was effective for lowering ApoB-containing lipoproteins [30].

6. Pharmacokinetics:

Following administration, mipomersen peak plasma concentrations are reached within 3–4 hours. Mipomersen is metabolized to chain-shortened metabolites within tissues. This is done initially by endonucleases, producing oligonucleotides that no longer have pharmacological action. These smaller oligonucleotides are further digested by exonucleases [31]. The metabolites are predominantly excreted in the urine, the major route of whole-body clearance of the drug. Mipomersen is not metabolized by traditional drug-metabolizing enzymes, such as cytochrome P450 and therefore does not interact with molecules cleared through oxidative metabolic pathways [31].

7. Safety, tolerability and regulatory affairs:

Mipomersen was evaluated in a phase I clinical study designed to test its effects on CYP enzyme activity. No clinically significant interactions were seen when mipomersen was administered with simvastatin, ezetimibe or warfarin [32,33]. An additional, long term study showed no significant changes in QTc measurements in patients treated for up to two years [27]. In a large double blinded study of mipomersen in HoFH patients, the most commonly reported adverse effects were flu-like symptoms, typically two days after injection and injection site reactions (76% of patients), some of which were long-lasting. Injection site reactions were the most prevalent adverse effect, and can result in erythema, pain, pruritis, swelling and skin color changes and resulted in discontinuation of therapy in 5% of patients

in pooled phase 3 trials. Elevations in liver enzymes were also reported during mipomersen treatment, including 12% of patients who had elevations greater than 3 times the upper limit of normal. Due to the risk for hepatotoxicity, mipomersen is approved for restricted use for physicians registered in a Risk Evaluation and Mitigation Strategy (REMS) [17]. In one 13-week trial there was a doubling of intrahepatic triglyceride on 1H magnetic resonance spectroscopy, though the trial did not result in clinically significant hepatic steatosis [34]. In addition, in the longest trial to date, 16 of 65 patients on at least one occasion had an increase in liver fat content that exceeded 20% on hepatic MRI [27]. However, one study in which liver biopsies of patients treated with mipomersen were performed revealed hepatic steatosis without inflammation, similar to the steatosis seen in familial hypobetalipoproteinemia and distinct from the inflammatory steatosis of non-alcoholic fatty liver disease [35]. The long-term implications of the increased liver fat are unknown and are a concern in the use of a medication that could potentially be administered for many years. Although mipomersen is approved for use by the FDA, Europe's Committee for Medicinal Products for Human (CMHP) determined the risk of side effects outweighed the benefit of the drug and did not approve mipomersen for marketing authorization [36].

8. Conclusion:

The armamentarium available to the clinician treating HoFH includes multiple medications. Because several of the most potent medications, such as statins and PCSK9 monoclonal antibodies work by increasing LDL receptor function, most patients with HoFH do not achieve recommended LDL-C targets. For these patients, additional treatment regimens, including mipomersen, which target different pharmacologic mechanisms, should be considered as adjunct therapy in patients who do not meet LDL-C goals and remain at high risk for cardiovascular disease. In addition, adverse effects, particularly hepatotoxicity, local site injection reactions, and concern for hepatic steatosis with long term use may be limit use significantly.

9. Expert Opinion:

Mipomersen has demonstrated significant efficacy in reducing LDL-C in patients with both homozygous FH and heterozygous FH. Mipomersen is approved only for homozygous FH and as such faces a limited market for its use. In addition, the response to mipomersen varied substantially among patients with homozygous FH. Mipomersen use is also complicated by its adverse effects, such as hepatotoxicity. Injection site reactions can lead to patient discontinuation of the drug. In practice, the side effects can be daunting since they may be persistent, with skin reactions causing long-lasting cosmetic problems and the flu-like symptoms interfering with work and other activities. Use of an injection compared with an oral medication is also a drawback, however, it may be an advantage over apheresis. The long term implications of the drug induced increase in hepatic fat are unknown at this time, and this is a concern in a therapy that could be used for many years, including use in younger patients. REMS monitoring of hepatic transaminases can also add to cost and inconvenience. The drug is further limited by the fact that it remains an alternative to patients who have failed other therapies. In addition, the significant cost of the medication (initially over $150,000 per year) is a limiting factor. Mipomersen faces competition from

other agents that produce similar reductions in LDL-C (lomitapide) with more easily managed adverse effects. Lomitapide is costlier and also has disadvantages with regard to hepatic steatosis, gastrointestinal side effects, and potential drug interactions. It is also only indicated for homozygous FH.

The treatment of severe hypercholesterolemia including familial hypercholesterolemia will continue moving forward with the development of new treatment modalities that use a variety of methodologies including further generations of antisense nucleotides, monoclonal antibodies to various targets, and RNA silencing. The ultimate goal in the treatment of familial hypercholesterolemia is to be able to lower LDL-C levels significantly with few side effects given the lifelong nature of the treatment. Treatment of homozygous FH can be particularly difficult, and the need is great in these patients to lower LDL-C from an early age. The viability of mipomersen, an early generation antisense oligonucleotide, with its cutaneous and systemic reactions as well as the concerns about hepatic fat is questionable. Outcomes trials in patients with homozygous familial hypercholesterolemia are probably not feasible given the low numbers of these patients. For those HoFH patients with some LDL receptor activity, the PCSK9 monoclonal antibodies can offer some benefit. Newer therapies including those involving other targets probably hold more promise for the future treatment of HoFH than mipomersen. Although mipomersen did show efficacy in treatment of heterozygous FH, it has not been marketed for use in the HeFH population and has clearly been superseded by the currently marketed alirocumab and evolocumab with their ease of use, every two-week dosing, and fewer side effects. These PCSK9 monoclonal antibodies have also been shown to reduce cardiovascular events in randomized cardiovascular outcomes trials, although the trials were not specifically done in patients with familial hypercholesterolemia.

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Abbreviation list

(FH)	Familial hypercholesterolemia
(HoFH)	Homozygous familial hypercholesterolemia
(HeFH)	Heterozygous familial hypercholesterolemia
(LDL)	low density lipoprotein
(VLDL)	Very low density lipoprotein
(APOB)	Apolipoprotein B
(PCSK9)	proprotein convertase subtilisin/kexin type 9

(LDLRAP1)	LDL receptor adaptor protein 1
(ASCVD)	Atherosclerosis cardiovascular disease
(ASO)	Antisense oligonucleotide
(CHD)	Coronary heart disease

References

1. Hopkins P, Toth P. Familial hypercholesterolemias: prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011 6;5(3 Suppl):S9–17. [PubMed: 21600530]
2. Reiner Z Management of patients with familial hypercholesterolaemia. Nat Rev Cardiol. 2015:12:565–75. [PubMed: 26076948]
3. Abifadel M, Elbitar S, El Khoury P, et al. Living the PCSK9 Adventure: from the Identification of a New Gene in Familial Hypercholesterolemia Towards a Potential New Class of Anticholesterol Drugs. Curr Atheroscler Rep. 2014 9;16(9):439. [PubMed: 25052769]
4. Cuchel M, Bruckert E, Ginsberg H. Homozygous Familial Hypercholesterolaemia: New Insights and Guidance for Clinicians to Improve Detection and Clinical Management. Eur Heart J. 2014;35(32):2146–2157. [PubMed: 25053660] **Important review of homozygous familial hypercholesterolemia providing suggested diagnostic criteria.
5. Talmud PJ, Shah S, Whittall R, et al. Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study. Lancet. 2013 4 13;381(9874):1293–301. [PubMed: 23433573]
6. Sjouke B, Kusters D, Kindt I, et al. Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype–phenotype relationship, and clinical outcome. Eur Heart J. 2014 2 28. doi:10.1093/eurheartj/ehu058
7. More Detailed information on Key Tier 1 applications – Familial Hypercholesterolemia. Center for Surveillance, Epidemiology and Laboratory Services (CSELS), public health genomics. Atlanta, GA: CDC, 2014 Available at https://www.cdc.gov/genomics/implementation/toolkit/fh_1.htm
8. Reiner Z Treatment of children with homozygous familial hypercholesterolaemia. Eur J Prev Cardiol. 2018;25(10):1095–1097. [PubMed: 29873241]
9. Raal FJ, Pilcher GJ, Panz VR, et al. Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy circulation. 2011;124:2202–2207. [PubMed: 21986285]
10. Watts GF, Gidding S, Wierzbicki AS et al. Integrated guidance on the care of familial hypercholesterolemia from the International FH Foundation. J Clinical Lipidology 2014; 8:148–172.
11. Nordestgaard B, Chapman M, Humphries S. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. Consensus Statement of the European Atherosclerosis Society. Eur Heart J 2013;34(45):3478–90a. [PubMed: 23956253] *Consensus statement that is widely cited, showing the problems of diagnosing FH.
12. Boekholdt SM, Hovingh GK, Mora S, et al.: Very low levels of atherogenic lipoproteins and the risk for cardiovascular events. J Am Coll Cardiol 2014, 64:485–494. [PubMed: 25082583]
13. Raal FJ, Honarpour N, Blom DJ, et al.: Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet (London, England) 2015, 385:341–350.*This study demonstrates the difference in effect of evolocumab in patients with and without residual LDL receptor activity.
14. Nikolic D, Mikhailidis DP, Davidson MH, et al.: ETC1002: A future option for lipid disorders? Atherosclerosis 2015, 237:705–710.

15. Bennett CF, Swayze EE. RNA targeting therapeutics: molecular mechanisms of antisense oligonucleotides as a therapeutic platform. Annu Rev Pharmacol Toxicol. 2010;50:259–293. [PubMed: 20055705]
16. Davis RA. Cell and molecular biology of the assembly and secretion of apolipoprotein B-containing lipoproteins by the liver. Biochim Biophys Acta. 1999;1440:1–31. [PubMed: 10477822]
17. Genyzme Corporation. KYNAMRO® (mipomersen sodium) injection prescribing information. 2013 Available from: http://www.kynamro.com/~/media/Kynamro/Files/KYNAMRO-PI.pdf
18. Yu RZ, Lemonidis KM, Graham MJ, et al. Cross-species comparison of in vivo PK/PD relationships for second-generation antisense oligonucleotides targeting apolipoprotein B-100. Biochem Pharmacol. 2009;77:910–919. [PubMed: 19056355]
19. Kastelein JJ, Wedel MK, Baker BF, et al. Potent reduction of apolipoprotein B and low-density lipoprotein cholesterol by short-term administration of an antisense inhibitor of apolipoprotein B. Circulation. 2006;114:1729–1735. [PubMed: 17030687]
20. Akdim F, Tribble DL, Flaim JD, et al. Efficacy of apolipoprotein B synthesis inhibition in subjects with mild-to-moderate hyperlipidaemia. Eur Heart J. 2011;32:2650–2659. [PubMed: 21593041]
21. Akdim F, Stroes ES, Sijbrands EJ, et al. Efficacy and safety of mipomersen, an antisense inhibitor of apolipoprotein B, in hypercholesterolemic subjects receiving stable statin therapy. J Am Coll Cardiol. 2010;55:1611–1618. [PubMed: 20378080]
22. Akdim F, Visser ME, Tribble DL, et al. Effect of mipomersen, an apolipoprotein B synthesis inhibitor, on low-density lipoprotein cholesterol in patients with familial hypercholesterolemia. Am J Cardiol. 2010;105:1413–1419. [PubMed: 20451687]
23. Raal FJ, Santos RD, Blom DJ, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. Lancet. 2010;375:998–1006. [PubMed: 20227758] **Key study showing the effect of mipomersen in patients with homozygous familial hypercholesterolemia.
24. McGowan MP, Tardif JC, Ceska R, et al. Randomized, placebo-controlled trial of mipomersen in patients with severe hypercholesterolemia receiving maximally tolerated lipid-lowering therapy. PLoS One. 2012;7:e49006. [PubMed: 23152839]
25. Stein EA, Dufour R, Gagne C, et al. Apolipoprotein B synthesis inhibition with mipomersen in heterozygous familial hypercholesterolemia: results of a randomized, double-blind, placebo-controlled trial to assess efficacy and safety as add-on therapy in patients with coronary artery disease. Circulation. 2012;126:2283–2292. [PubMed: 23060426]
26. Thomas GS, Cromwell WC, Ali S, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, reduces atherogenic lipoproteins in patients with severe hypercholesterolemia at high cardiovascular risk: a randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol. 2013;62:2178–2184. [PubMed: 24013058]
27. Santos RD, Duell PB, East C, et al.: Long-term efficacy and safety of mipomersen in patients with familial hypercholesterolaemia: 2-year interim results of an open-label extension. Eur Heart J. Eur Heart J. 2015 3 1;36(9):566–75. [PubMed: 24366918]
28. Duell PB, Santos RD, Kirwan BA, et al.: Long-term mipomersen treatment is associated with a reduction in cardiovascular events in patients with familial hypercholesterolemia. J Clin Lipidol. 2016 Jul-Aug;10(4):1011–1021. [PubMed: 27578134]
29. Waldmann E, Vogt A, Crispin A, et al. Effect of mipomersen on LDL-cholesterol in patients with severe LDL-hypercholesterolaemia and atherosclerosis treated by lipoprotein apheresis (the MICA study). Atherosclerosis. 2017(259):20–25.
30. Li N, Li Q, Tian XQ, et al. Mipomersen is a promising therapy in the management of hypercholesterolemia: a meta-analysis of randomized controlled trials. Am J Cardiovasc Drugs. 2014(5):367–376. [PubMed: 25027352]
31. Yu RZ, Kim TW, Hong A, et al. Cross-species pharmacokinetic comparison from mouse to man of a second-generation antisense oligonucleotide, ISIS 301012, targeting human apolipoprotein B-100. Drug Metab Dispos. 2007;35(3):460–468. [PubMed: 17172312]

32. Yu RZ, Geary RS, Flaim JD, et al. Lack of pharmacokinetic interaction of mipomersen sodium (ISIS 301012), a 2′-O-methoxyethyl modified antisense oligonucleotide targeting apolipoprotein B-100 messenger RNA, with simvastatin and ezetimibe. Clin Pharmacokinet. 2009;48:39–50. [PubMed: 19071883]

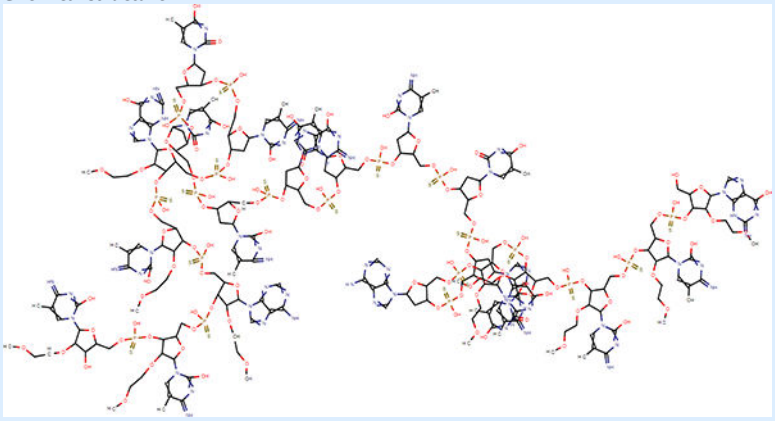
33. Li Z, Hard ML, Grundy JS, et al. Lack of clinical pharmacodynamic and pharmacokinetic drug-drug interactions between warfarin and the antisense oligonucleotide mipomersen. J Cardiovasc Pharmacol. 2014;64:164–171. [PubMed: 24691275]

34. Rader DJ, Kastelein JJ. Lomitapide and mipomersen: Two first-in-class drugs for reducing low density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia. Circulation. 2014;129:1022–32. [PubMed: 24589695]

35. Hashemi N, Odze RD, McGowan MP, et al.: Liver histology during Mipomersen therapy for severe hypercholesterolemia. J Clin Lipidol. 2014 Nov-Dec;8(6):606–11. [PubMed: 25499943]

36. Husten Larry. Europe and US Diverge on Two New Drugs. Forbes. 3 2013 Available at: https://www.forbes.com/sites/larryhusten/2013/03/22/europe-and-us-diverge-on-two-new-drugs/#30f97169246

Drug summary box

Drug name - Mipomersen
Phase: Launched
Indication - Homozygous Familial Hypercholesterolemia
Pharmacology - Anti-sense oligonucleotide inhibits mRNA production of apolipoprotein B-100
Route of administration - Subcutaneous injection once per week
Chemical structure – 
Pivotal trial(s) [23]