CANACCORD Genuity

Equity Research

Ritu Baral
1.212.849.3917
rbaral@canaccordgenuity.com

Life Sciences -- Biotechnology

Aegerion Pharmaceuticals

Second chance with an orphan indication and powerful efficacy data in hand

BUY

AEGR : NASDAQ : US$10.84

TARGET PRICE: US$16.00

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Investment recommendation

Initiating with BUY, $16 target on lomitapide's potential as a best-in-class HoFH drug. Lomitapide is Aegerion's Phase 3 oral MTP inhibitor for homozygous familial hypercholesterolemia (HoFH). We think lomitapide may become the best-in-class HoFH drug on strong LDL lowering and good safety and tolerability. We think final pivotal data will be positive and that Aegerion will submit the lomitapide NDA for HoFH in late 2011 and receive FDA approval mid-2012. Our $16 target is based on a pNPV analysis.

Investment highlights

Lomitapide has shown best-in-class LDL lowering of ~50% on top of optimized background therapy. Lomitapide's open-label pivotal trial is ongoing but has already yielded primary endpoint data showing 50% LDL reduction from baseline with optimized background therapy. 35% of patients were able to achieve LDL<100 mg/dL despite mean baseline LDL of 354 mg/dL, suggesting a very clinically meaningful benefit.

We think lomitapide has shown good safety and acceptable tolerability given HoFH's severity and unmet medical need. No pivotal patients discontinued due to changes in liver enzymes. We think that lomitapide has a mild, transient impact on liver enzymes, and that drug-associated liver fat elevations are transient and may not be clinically meaningful. We also think GI side effects are manageable and improve with duration of treatment.

We think lomitapide has a high chance of regulatory and commercial success. We think lomitapide will successfully complete the remaining safety portion of a pivotal trial and other small PK safety studies. Given HoFH's unmet medical need, we think lomitapide will receive expedited review and approval in 2012 with a broad label. We think the drug will be appropriate for ~4,000-6,000 patients worldwide and predict worldwide peak sales of over $400M in HoFH alone.

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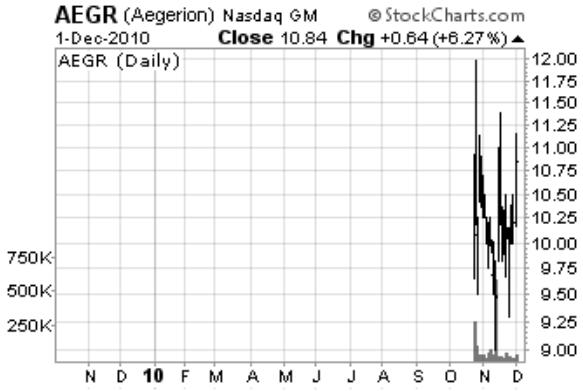
Company Statistics

Market Cap (M):	US$171.9
52-week Range:	US$9.00 - 12.00

Price Chart



Earnings Summary

FYE Dec		2009A	2010E	2011E
Revenue:		0.0	0.0	0.0
EPS:		(9.19)	(3.17)	(1.87)
Revenue:	Q1	-	0.0A	-
	Q2	-	0.0A	-
	Q3	-	0.0A	-
	Q4	-	0.0	-
Total		0.0	0.0	0.0
EPS:	Q1	-	(1.41)A	-
	Q2	-	(1.37)A	-
	Q3	-	(3.60)A	-
	Q4	-	(0.38)	-
Total		(9.19)	(3.17)	(1.87)

Company Description

Aegerion Pharmaceuticals, Inc. is an emerging biopharmaceutical company focused on the development and commercialization of novel therapeutics to treat severe but rare genetic lipid disorders. The company's lead drug is an MTP inhibitor-class drug, lomitapide, that is currently in pivotal development for homozygous familial hypercholesterolemia, which is characterized by very high LDL levels that do not respond well to statin therapy. Efficacy and interim safety data has been positive and final trial data is due around the end of 2011. Aegerion plans to submit the lomitapide approval application to FDA in late 2011.

Figure 1: Aegerion pipeline

Drug/Program	Disease	Licensing/ Partnership	Preclinical	Phase 1	Phase 2	Phase 3	Regulatory Filing	Commercialization
Lomitapide	HoFH	Wholly owned						
Lomitapide	FC	Wholly owned						

Source: Company reports and Canaccord Genuity

INVESTMENT THESIS

Aegerion's MTP-1 inhibitor lomitapide is a promising Phase 3 drug for homozygous familial hypercholesterolemia (HoFH)

Lomitapide is an oral, small molecule MTP inhibitor therapy in Phase 3 development for HoFH. We think that all efficacy and safety data for lomitapide in HoFH at its current dose and treatment regimen are very positive. HoFH, a rare genetic disease that leads to very high cholesterol and LDL levels, represents a significant unmet medical need. Due to the nature of the disease, HoFH patients do not experience the same proportionate amount of cholesterol reduction with standard drugs and treatment as normal high cholesterol patients do. As a result, most HoFH patients have very poor disease control, which in turn leads to very poor disease prognosis. We believe that lomitapide may help a substantial proportion of HoFH patients reach their LDL goals and reduce cardiovascular risk and events.

Lomitapide may be the best-in-class late clinical development-stage HoFH drug

There are currently only two late-stage drugs in development for treatment of HoFH. Isis Pharmaceuticals and partner Genzyme are developing a Phase 3 antisense drug called mipomersen, which may also be approved in 2012. However, we believe that of these two development-stage treatments, lomitapide is more effective in lowering LDL and has a superior safety and tolerability profile. We think lomitapide has significant potential to become the gold standard HoFH treatment for use in conjunction with statins and LDL apheresis (a type of blood filtering similar to dialysis).

Lomitapide Phase 3 clinical efficacy shows very strong LDL lowering in HoFH

Phase 2 and 3 lomitapide data, both from the current pivotal trial as well as previous Phase 2 and 3 trials, have consistently shown ~50% LDL reduction with drug treatment. This compares to ~25% LDL reduction seen in Phase 3 trials of Isis' mipomersen. 35% of patients were able to achieve LDL<100 mg/dL despite mean baseline LDL of 354 mg/dL, suggesting very clinically meaningful benefit. Additionally, lomitapide has consistently shown 50%-60% reduction in triglyceride (TG) levels, which is another key blood fat level for heart health. We think that the current lower-dose lomitapide treatment regimen (compared to previous trials) will continue to show these levels of LDL and TG reduction in real-world clinical experience. In addition, we think that lomitapide has the potential to induce incremental weight loss in HoFH, which may improve patients' metabolic profiles and cardiac risk.

Final Phase 3 safety data will likely resemble current positive safety data

Safety and tolerability have previously been a concern for lomitapide. Its key safety and tolerability issues are hepatic fat, liver enzyme elevations and diarrhea, which occurred at problematic rates in Phase 2 trials. We note these trials were in broader populations and used a higher dose (100mg) than that of the current Phase 3 trial (60mg). In addition, the previous trials did not employ dose titration in the treatment protocol (dose titration is part of the current protocol). Aegerion has already substantially completed the pivotal lomitapide trial, and 22 patients who had hepatic fat measurements taken had modest increases in hepatic fat from a mean of 1.2% to 8.7% at 26 weeks. Fourteen patients had a 56-week mean hepatic fat level of 5.1%. Median change in hepatic fat

from baseline in these patients was 5.48% at 26 weeks of treatment and 2.14% at 56 weeks of treatment. Data consistently suggests that hepatic fat rises initially but stabilizes and then falls around 26 weeks of therapy, likely due to an inherent desensitization mechanism. Furthermore, based on our conversations with lipid experts, we do not think that these elevations in hepatic fat are clinically meaningful. No patients have discontinued thus far due to liver enzyme elevations. So far, four trial patients had ALT elevations (>5x but <11x the upper limit of normal), three of whom had a temporary dose reduction and have since been re-challenged at higher doses. One patient discontinued lomitapide for seven weeks, but was then safely put back on the drug.

Experts familiar with lomitapide believe that lomitapide is tolerable; patients may manage common treatment side effects with relative ease

Phase 2 lomitapide trial data showed that diarrhea and GI distress were the common side effects of therapy, and very likely a result of the drug's direct mechanism of action. We note that Phase 2 diarrhea rates were around 50% and led to significant drop-outs in the patient population (which we note is significantly more broad with much less severe disease than HoFH). Aegerion has noted that this side effect profile is similar in the current Phase 3 trial, but with lower incident rates and severity. Only three patients (~10%) have dropped out thus far due to GI side effects. Experts who have experience with lomitapide note that patient diarrhea is significantly less severe with dose titration and that there appears to be some degree of desensitization. They have indicated that patients tend to experience significantly fewer and less severe episodes of diarrhea and GI distress with continued lomitapide treatment. They believe that patient compliance will not be a major issue with lomitapide given the degree of clinical benefit widely seen with the drug.

We see lomitapide's risk/benefit profile as very acceptable given HoFH's unmet medical need and think the drug will receive FDA and EMEA approval in 2012

HoFH is a very severe and poorly managed disease. The average age of a HoFH patient's first cardiovascular adverse event (usually stroke or heart attack) is about 20, and most patients die of a heart attack before reaching the age of 30. Statins have limited efficacy in these patients due to disease mechanism. Regular LDL apheresis sessions can markedly improve disease; however, most patients are not treated at optimal frequencies due to logistical and tolerability difficulties as well as treatment cost. We think that given this very significant need for better HoFH treatments and lomitapide's strong efficacy in lowering LDL, the drug will be approved in a straightforward and accelerated manner. We think the drug will receive Fast Track Status and priority review. We think FDA will convene an advisory committee meeting for lomitapide in H1/12, which we predict will go very favorably. We anticipate lomitapide approval by both the FDA and EMEA in 2012.

Lomitapide may become an appropriate treatment for 4,000-6,000 FH patients

We think that lomitapide will see very broad use in almost all patients with genotypically diagnosed HoFH, estimated at about 1,000 patients worldwide. We also think that it will see significant use in patients with "phenotypically diagnosed" FH, where fibroblast cell cultures show malfunctioning LDL receptors, and in patients with familial histories of hypercholesterolemia (despite lack of mutation identification). We estimate this patient population to be an additional 2,000 patients worldwide. Finally, we also think that some number of patients with "functional FH" will also received treatment with lomitapide.

These patients have very high total cholesterol and LDL levels that are resistant to statin treatment, suggesting LDL receptor dysfunction despite no identified FH mutation or well documented family history of high cholesterol. We think that these patients represent another 3,000 total worldwide population, and believe that some meaningful proportion will be treated with lomitapide.

We estimate peak annual worldwide Lomitapide sales of ~$500M with rapid uptake

As Aegerion is developing lomitapide to address an orphan population of HoFH and closely related populations, we think the company will be able to employ the orphan pricing model with little difficulty. We think that lomitapide will be priced at lowest around $100,000 annually, and at highest around $250,000. We think that the more restricted lomitapide's final label is, the higher the treatment price, resulting in about the same approximate $500M annual revenue rate to Aegerion regardless of pricing.

INVESTMENT RISKS

Development risk – Previous clinical trials have shown problematic safety/tolerability

Previous higher dose non-titration lomitapide trials have shown rates of liver fat and liver enzyme elevations that were deemed unacceptable by clinicians for treatment of a broad patient population with moderately elevated LDL levels. Additionally, GI tolerability in these trials was very poor. As a result, lomitapide clinical development was discontinued for some time. Although safety and tolerability data to date is significantly better due to lower dose and titration, some patients still experience significant changes in hepatic fat and liver enzyme levels as well as diarrhea. These side effects could reach problematic levels, but we think the data thus far suggests the drug, at its current dose and treatment schedule, will be a safe and relatively well-tolerated therapy.

Regulatory risk – Despite unmet need, a single, open-label, uncontrolled Phase 3 trial may not be sufficient to secure FDA or European approval

The FDA normally requires two randomized placebo-controlled pivotal trials for drug approval. Aegerion plans to submit the lomitapide NDA with data from a single uncontrolled open-label Phase 3 trial with a small number of patients. Also, the company does not have a Special Protocol Assessment (SPA) from the FDA, although it has had extensive discussions with the agency as part of the SPA process. We believe the FDA will still approve lomitapide despite its limited Phase 3 data set due to the orphan nature of HoFH as well as the disease's unmet medical need. We think that a placebo-controlled trial would have been unethical, and that a larger trial was not feasible due to the small HoFH patient population. Furthermore, the FDA has previously approved orphan therapies with serious unmet medical needs based on single open-label uncontrolled trials.

Commercial risk – Lomitapide may not have as large a market as estimated, since current market assumptions are relatively new and as yet unproven

While there is little dispute on the number of HoFH patients with definitive genotypic diagnosis (600-1,000 patients worldwide), there is controversy over the additional number of HoFH patients whose exact genetic mutations have not yet been identified. Lomitapide may not be approved or reimbursed for patients with LDL levels characteristic of HoFH but without genotypic, cell culture or familial history diagnosis.

Furthermore, Aegerion may face pricing pressure on lomitapide's orphan pricing. As such, the exact potential patient population and market size for lomitapide is uncertain.

Competitive risk – Lomitapide may compete with Isis' mipomersen, which is partnered with Genzyme, a large-cap biotechnology with an established orphan business unit.

We believe that lomitapide may be approved for HoFH around the same time as Isis Pharmaceuticals' mipomersen, which is partnered with Genzyme. We note that Genzyme has pioneered the orphan disease business model and has considerable experience at launching and commercializing orphan drugs. However, while Genzyme would represent significant commercial competitive entity, we think that lomitapide still has a very good chance at becoming the gold standard HoFH treatment based on its superior efficacy, safety and ease of use, as well as its (at worst) comparable tolerability.

VALUATION

We have built our valuation of Aegerion using a model that we believe is the appropriate method of capturing the value of Aegerion's potential pipeline.

Figure 2: Aegerion pNPV analysis)

Drug name	Indication	Status	Launch	Success	Peak sales ($M)	Royalty Rate	Profitability	NPV
Lomitapide	Genotypically diagnosed HoFH	Phase 3	2012	65%	$89	90%	75%	$3.93
Lomitapide	Expanded (Phase 3) HoFH	Phase 3	2012	65%	$187	90%	75%	$8.26
Lomitapide	Functional HoFH	Phase 3	2012	40%	$140.5	90%	75%	$3.81
TOTAL								**$16.00**

Source: Canaccord Genuity estimates

Potential upside to valuation

We see the following as potential drivers of upside to our model:

- **Stronger-than-expected clinical safety data from lomitapide.** Lomitapide's side effects are very much related to the drug's mechanism of action. Side effect rates are currently well within expected and relatively safe parameters. Should side effect rates or severity fall toward trial completion, it could mean significant upside to our chances of approval, market estimates (especially in the functional HoFH population) and valuation.
- **Delays in the clinical or commercial development of lomitapide's major competitor.** We expect that Isis/Genzyme's HoFH drug mipomersen will be approved around 2012. However, carcinogenicity tests are still ongoing and side effects have raised questions on the drug's commercial viability. Genzyme is currently the subject of a hostile takeover attempt by Sanofi Aventis, and change of control could jeopardize the mipomersen commercial strategy. Any delay to mipomersen would mean upside to our market model for lomitapide.
- **Acquisition at a significant premium to current market value.** We think that Aegerion represents a compelling acquisition candidate, as lomitapide is a very promising drug candidate and Aegerion as a company represents a very therapeutically focused and discrete acquisition candidate. We note that many large pharma companies are currently launching new orphan drug business units and

looking to fill pipelines with late-stage drug candidates. Should Aegerion be acquired, the purchase price may represent upside to our target price.

Potential downside to valuation

As with all companies in preclinical or clinical development, there always exists the risk of failed or inconclusive clinical trials, which would lead to downward pressure on the stock.

RECOMMENDATION

We think that Aegerion's lomitapide is a very promising new therapy for patients who are homozygous for familial hypercholesterolemia (HoFH) or have the HoFH cholesterol profile phenotype without the formally diagnosed genotypic mutation.

The lomitapide Phase 3 pivotal study has already yielded very positive efficacy data, with primary endpoint of LDL reduction of ~50%. Secondary endpoint triglyceride reduction has also been very positive. Safety data has shown hepatic fat and liver enzyme level changes that we think are transient and not clinically significant, and we think the tolerability profile thus far will be manageable and acceptable to patients. We think that final safety and efficacy data (due H1/11) will be very similar to data released thus far.

We think that Aegerion will successfully complete additional preclinical requirements before the end of 2011 and will submit the lomitapide NDA to the FDA shortly thereafter. We expect that the FDA will schedule an advisory committee for lomitapide in H1/12 that will be a key event in the drug's approval pathway. Given the unmet medical need in HoFH, we expect this advisory committee meeting to go positively, with the panel recommending approval.

We see lomitapide's chances of approval as high (65%+). We expect that the drug will be approved by the FDA around mid-year 2012 with a label for treatment of genotypically and phenotypically diagnosed HoFH patients. We think the drug has a good chance for approval (45%) for use in "functional" HoFH patients as well.

We believe that lomitapide will see very rapid market uptake given the unmet medical need and orphan disease treatment dynamics of HoFH. We think that Aegerion will commercialize the drug itself using a very small, efficient sales force targeting the small number of doctors and tertiary care centers that provide treatment for HoFH patients. We think that Aegerion will also set up very effective clinician and patient outreach programs and develop strong relationships with FH patient advocacy groups. We believe the company will also set up effective patient assistance and coverage assistance programs to help with securing insurance coverage of lomitapide, especially for patients with functional HoFH. Overall, we expect peak worldwide lomitapide sales to reach $400-$500M.

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Figure 3: Lomitapide market and sales estimates

Sales forecasts	2010E	2011E	2012E	2013E	2014E	2015E
US Genotype Diagnosed HoFH						
# US pts	300	308	315	323	331	339
growth rate (increasing diagnosis/survival)	*2.5%*	*2.5%*	*2.5%*	*2.5%*	*2.5%*	*2.5%*
Estimated lopitamide market penetration	*0.0%*	*0.0%*	*75.0%*	*90.0%*	*95.0%*	*95.0%*
# of US HoFH patients on lopitamide	0	0	236	291	315	322
US lopitamide revenue per patient (3% yoy $ increase)	$0.0	$0	$150,000	$154,500	$159,135	$163,909
US genotype HoFH lopitamide revenues to Aegerion	$0	$0	$35,458,594	$44,922,492	$50,061,750	$52,852,693
EU/SA Genotype Diagnosed HoFH						
# EU pts	300	305	309	314	318	323
growth rate (increasing diagnosis/survival)	*1.5%*	*1.5%*	*1.5%*	*1.5%*	*1.5%*	*1.5%*
Estimated market penetraion	*0.0%*	*0.0%*	*75.0%*	*90.0%*	*95.0%*	*95.0%*
# of EU HoFH patients on lopitamide	0	0	232	282	302	307
EU lopitamide revenue per patient (3% yoy $ increase)			$150,000	$154,500	$159,135	$163,909
EU/SA genotype HoFH lopitamide revenues to Aegerion			$34,770,094	$43,620,473	$48,136,525	$50,324,330
[redacted]						
US Inheritance Pattern/Fibroblast Assay FH						
# US pts	1,000	1,025	1,051	1,077	1,104	1,131
growth rate (increasing diagnosis/survival)	*2.5%*	*2.5%*	*2.5%*	*2.5%*	*2.5%*	*2.5%*
Estimated lopitamide market penetration	*0.0%*	*0.0%*	*25.0%*	*45.0%*	*55.0%*	*60.0%*
# of US HoFH patients on lopitamide	0	0	263	485	607	679
US lopitamide revenue per patient (3% yoy $ increase)	$0.0	$0	$150,000	$154,500	$159,135	$163,909
US Lopitamide IP/FA Revenues	$0	$0	$39,398,438	$74,870,821	$96,610,395	$111,268,827
EU/SA Inheritance Pattern/Fibroblast Assay FH						
# EU/SA pts	1,000	1,015	1,030	1,046	1,061	1,077
growth rate (increasing diagnosis/survival)	*1.5%*	*1.5%*	*1.5%*	*1.5%*	*1.5%*	*1.5%*
Estimated lopitamide market penetration	*0.0%*	*0.0%*	*25.0%*	*45.0%*	*55.0%*	*60.0%*
# of EU/SA HoFH patients on lopitamide	0	0	258	471	584	646
EU/SA lopitamide revenue per patient (3% yoy $ increase)			$150,000	$154,500	$159,135	$163,909
EU/SA lopitamide IP/FA Revenues			$38,633,438	$72,700,789	$92,895,049	$105,945,959
[redacted]						
US Functional FH						
# US pts	1,500	1,538	1,576	1,615	1,656	1,697
growth rate (increasing diagnosis/survival)	*2.5%*	*2.5%*	*2.5%*	*2.5%*	*2.5%*	*2.5%*
Estimated lopitamide market penetration	*0.0%*	*0.0%*	*10.0%*	*20.0%*	*25.0%*	*30.0%*
# of US HoFH patients on lopitamide	0	0	158	323	414	509
US lopitamide revenue per patient (3% yoy $ increase)	$0.0	$0	$150,000	$154,500	$159,135	$163,909
US lopitamide Functional Revenues	$0	$0	$23,639,063	$49,913,880	$65,870,724	$83,451,620
EU/SA Functional FH						
# EU/SA pts	1,500	1,523	1,545	1,569	1,592	1,616
growth rate (increasing diagnosis/survival)	*1.5%*	*1.5%*	*1.5%*	*1.5%*	*1.5%*	*1.5%*
Estimated lopitamide market penetration	*0.0%*	*0.0%*	*10.0%*	*20.0%*	*25.0%*	*30.0%*
# of EU/SA HoFH patients on lopitamide	0	0	155	314	398	485
EU/SA lopitamide revenue per patient (3% yoy $ increase)			$150,000	$154,500	$159,135	$163,909
EU/SA lopitamide IP/FA Revenues			$23,180,063	$48,467,193	$63,337,533	$79,459,469
[redacted]						

Source: Canaccord Genuity

COMPANY OVERVIEW

Aegerion is an emerging biopharmaceutical company focused on the development and commercialization of novel therapeutics to treat severe lipid disorders. Lipids are naturally occurring blood fat particles, such as cholesterol and triglycerides. Aegerion's lead compound, lomitapide, is a microsomal triglyceride transfer protein inhibitor, or MTP inhibitor class drug. MTP-1 inhibitors limit secretion of cholesterol and triglycerides into the blood from the intestines and the liver, the main sources of lipids in the body.

Aegerion is initially developing lomitapide as an oral, once-a-day treatment for patients with a rare genetic lipid disorder called homozygous familial hypercholesterolemia, or HoFH. As a result of extremely elevated of LDL cholesterol levels in the blood, HoFH patients are at very high risk of experiencing life-threatening cardiac events such as heart attacks and strokes at an early age. Aegerion believes that lomitapide, either as a monotherapy or taken in combination with other treatments, could be a key treatment option for HoFH patients for LDL cholesterol reduction.

Lomitapide has orphan drug status in the US and is now in a single-arm, open-label Phase 3 pivotal trial for the treatment of patients with HoFH. Aegerion is planning additional studies to assess various other safety and tolerability aspects of lomitapide's profile. The company plans to submit a US NDA approval application for lomitapide in H2/11 and a European MAA approval application in 2012. Aegerion currently plans to build its own specialized sales force to commercialize lomitapide in the US and EU.

In addition to HoFH, Aegerion is currently developing a protocol for a Phase 2/3 trial of lomitapide for a severe genetic form of elevated triglycerides, or hypertriglyceridemia, called familial chylomicronemia (FC).

DYSLIPIDEMIA

Dyslipidemia is the medical term for abnormal levels of naturally occurring blood fats (cholesterol and triglycerides). In the developed world, the disorder is almost always marked by higher-than-normal levels these blood fats (also called blood lipids). Dyslipidemia is most often a disorder of blood fat metabolism, including overproduction by the liver, or deficiencies (either underproduction or dietary deficiencies).

There are different types of dyslipidemia which can be characterized by abnormal levels of the different types of blood fats. Some patients have elevations of the "bad" low-density lipoprotein (LDL) cholesterol, or very low density (VLDL) cholesterol. Others have decreases in the "good" high-density lipoprotein (HDL) cholesterol. Still other dyslipidemia patients have increases in their total cholesterol, or just in their concentrations of triglyceride (a non-cholesterol blood lipid). Dyslipidemia contributes to the development of atherosclerosis: heart disease characterized by fatty deposits inside blood vessels. These deposits narrow the vessels, impeding blood flow, and can sometime cause complete blocks. These blocks are what cause heart attacks, strokes and other acute clotting events.

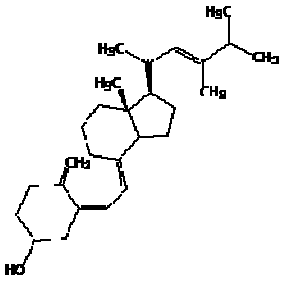
BLOOD LIPIDS: CHOLESTEROLS AND TRIGLYCERIDES

Blood lipids are fat particles in the blood that can be either free or bound to other types of molecules (like sterols or proteins). Most blood lipids are transported in the blood inside a protein capsule. The vast majority of blood lipids are either uncoated fatty acid compounds like triglycerides or coated cholesterol particles. The density of the lipids on the inside of the particle and type of protein capsule determine the type and fate of the particle and its impact on blood vessel and heart health. The concentration of blood lipids depends on metabolism, dietary intake as well as excretion from the intestine, and uptake/secretion from cells.

Cholesterol and other blood lipids are required for vital function. Cholesterol is a waxy steroid metabolite (specifically a steroid alcohol) found in cell membranes and, as mentioned before, transported in particles in the plasma. It is an essential structural component of mammalian cell membranes, where it is required to establish proper membrane permeability and fluidity and to stabilize a cell against stress. In particular, it is incorporated into the myelin sheath that insulates the nerves from the surrounding tissue. In addition, cholesterol is an important component for the manufacture of bile acids, steroid hormones (such as the female sex hormone estradiol, and the male sex hormone, testosterone) and fat-soluble vitamins including Vitamin A, Vitamin D, Vitamin E, and Vitamin K.

Cholesterol comes from two sources: endogenous production by the liver and from food. The liver (and select other cells) make about 75 percent of blood cholesterol. Nearly all body tissues are capable of making cholesterol, but the biggest producers are the liver and intestines. Together all body tissues including the liver and intestines make about a gram of cholesterol daily. The other 25 percent of cholesterol comes from dietary sources. Because triglycerides and cholesterol can't dissolve in blood, they circulate throughout the body with the help of particle surface proteins that enable transport in the blood.

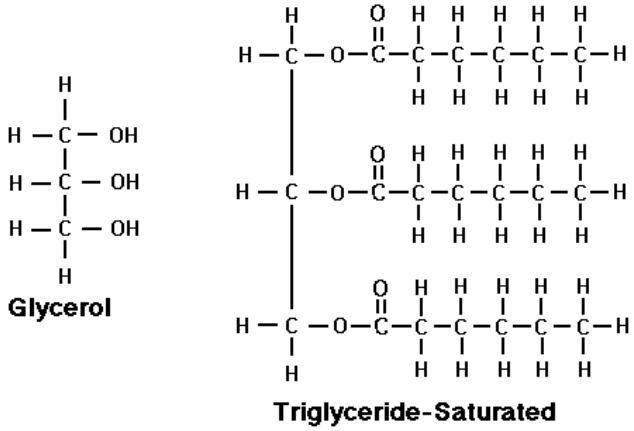
Figure 4: Cholesterol



Source:AHA

Triglycerides. Triglycerides are formed from a single molecule of glycerol that is chemically connected (or esterified) to three fatty acid chains (Figure 5). Most of the fats digested by humans are triglycerides. They also account for about 95% of the body's fatty tissue and are the form of fat found inside various cholesterol particles (also called lipoproteins) in the bloodstream.

Figure 5: Structure of triglycerides

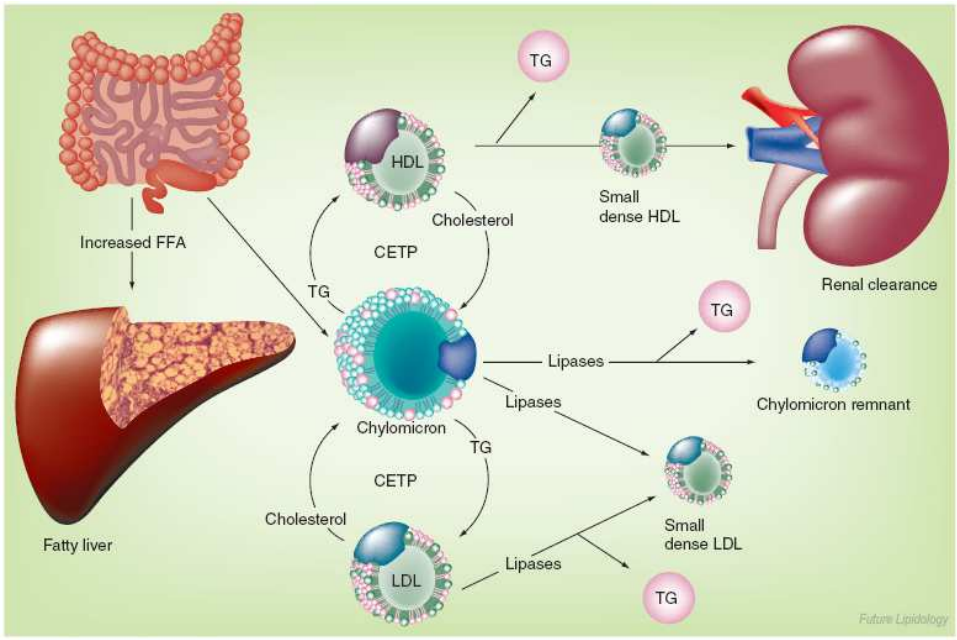


Source: American Heart Association Web site

LIPID METABOLISM AND LIPOPROTEINS

Fat digestion and absorption require that complex fat molecules be broken down into smaller, more manageable molecules. The first step is emulsification of fats in the intestines by bile. Large particles of fat are dispersed into small droplets which then become suspended in the watery contents of the gut. Emulsification allows the digestive enzyme lipase to gain easier access to the fat molecules and accelerate their breakdown and digestion. Lipase enters the duodenum (part of the small intestine) from the pancreas, which the main source of enzymes for digesting fats and proteins. Lipase chops up lipid molecules (including dietary triglycerides) into single fatty acid chains and glycerol molecules. Absorption of these fat molecules into the body, which takes 10-15 minutes, occurs in the villi – millions of finger-like projections that cover the walls of the small intestine. Hydrolyzed dietary fatty acids enter intestinal cells (enterocytes) of these villi via fatty acid (FA) transporters such as intestinal FA-binding protein (IFABP), CD36 and FA-transport protein-4 (FATP4).

Figure 6: Plasma lipid metabolism, processing and clearance

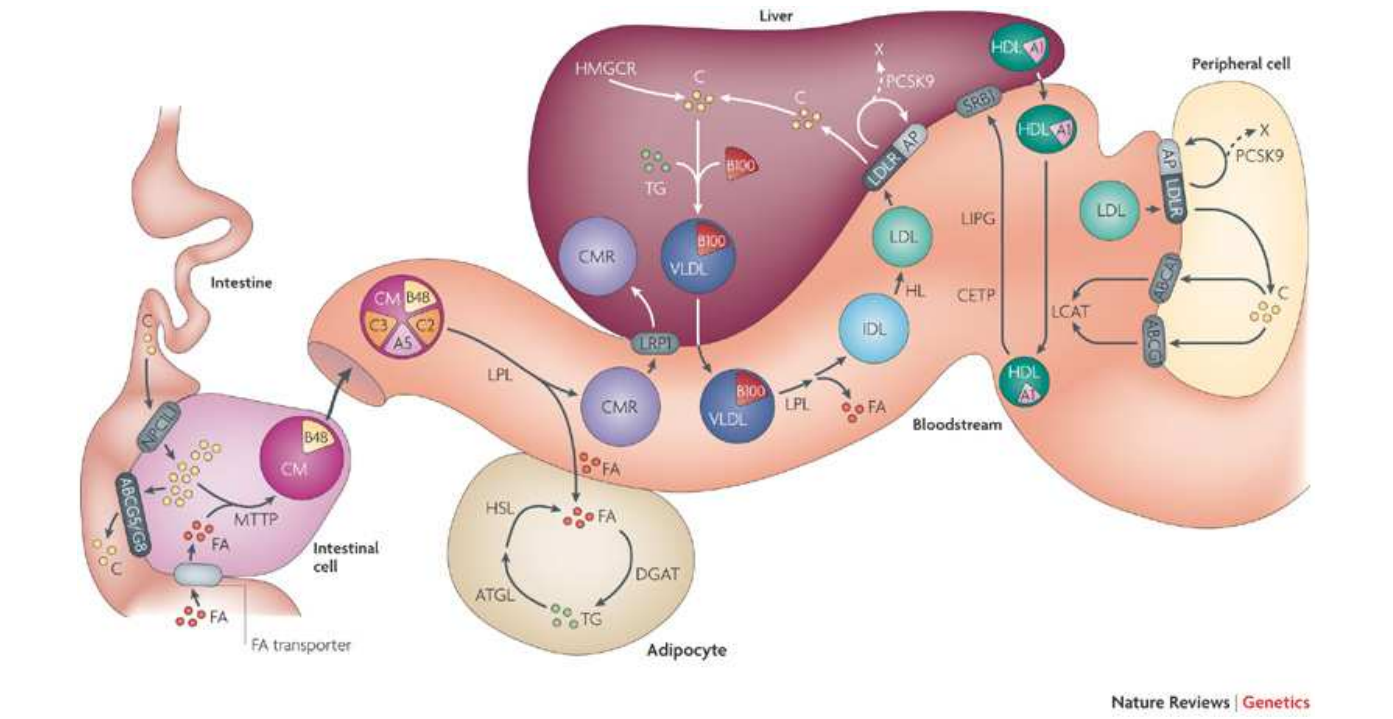


Source: Company reports

The fatty acid chains and glycerol molecules are then re-esterified inside the endocytes by MAG acyltransferase (MGAT) and diacylglycerol acyltransferase (DGAT) to re-form triglycerides. Phospholipids from the diet and bile are also converted into triglycerides in the gut. Dietary cholesterol is acylated by acyl-CoA:cholesterol acyltransferase (ACAT) to cholesterol esters. Facilitated by microsomal triglyceride transfer protein (MTP), triglyceride, cholesterol and apolipoprotein B (Apo-B, usually isoform B48) are packaged into chylomicrons (discussed in the next section) that are released into the lymphatic system and then are delivered into the plasma.

The breakdown and reconstitution of triglycerides and generation of low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol particles are shown in Figure 7 below.

Figure 7: Detailed overview of lipoprotein metabolism.



Source: Hegele R. Plasma lipoproteins: genetic influences and clinical implications. Nature Reviews Genetics 10, 109-121 (February 2009)

Lymphatic chylomicrons enter the vena cava (a major blood vessel located in the trunk) and circulate in the plasma until they interact with lipoprotein lipase (LPL). LPL is attached to blood vessel wall endothelium by proteoglycans and glycosylphosphatidylinositol-anchored HDL-binding protein 1. Chylomicrons also contain other apoliproteins, including Apo-AV (A5), Apo-CII (C2) and Apo-CIII (C3).

Released free FAs incompletely enter peripheral cells. In adipocytes, enzymes including acyl CoA:diacylglycerol acyltransferase (DGAT) resynthesize TG, which is hydrolysed by adipose TG lipase (ATGL) and hormone sensitive lipase (HSL).Chylomicron remnants (CMRs) are taken up by hepatic LDL receptors (LDLR). In the absence of LDLR they are taken up by LDLR-related protein-1 (LRP1).

In liver cells (hepatocytes), TG is packaged with cholesterol and the Apo-B isoform B100 into very low-density lipoprotein (VLDL). The TG contained in VLDL is hydrolyzed by LPL, releasing FAs and VLDL remnants (IDL) that are hydrolysed by hepatic lipase (HL), thereby yielding LDL. In LDL cholesterol metabolism, sterols in the intestinal lumen enter enterocytes via the Niemann-Pick C1-like 1 (NPC1L1) transporter and some are re-secreted by heterodimeric ATP-binding cassette transporter G5/G8 (ABCG5/G8). In enterocytes, cholesterol is packaged with TG into CM. In hepatocytes, cholesterol is recycled or synthesized de novo, with 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) being rate-limiting. LDL transports cholesterol from the liver to the periphery. LDL is endocytosed by peripheral cells and hepatocytes by LDLR, assisted by an adaptor protein (AP). Proprotein convertase subtilisin/kexin type 9 (PCSK9), when complexed to LDLR, short-circuits recycling of LDLR from the endosome, leading to its degradation (X). In HDL cholesterol metabolism, HDL, via Apo-AI (A1), mediates reverse cholesterol

transport by interacting with ATP-binding cassette A1 (ABCA1) and ABCG1 transporters on non-hepatic cells. Lecithin-cholesterol acyltransferase (LCAT) esterifies cholesterol so it can be used in HDL cholesterol, which, after remodeling by cholesterol ester transfer protein (CETP) and by endothelial lipase (LIPG), enters hepatocytes via scavenger receptor class B type I (SRB1).

Figure 8: Dyslipidemia patterns

Lipoprotein Patterns (Fredrickson Phenotypes)		
Phenotype	Elevated Lipoprotein(s)	Elevated Lipids
I	Chylomicrons	TGs
IIa	LDL	Cholesterol
IIb	LDL and VLDL	TGs and cholesterol
III	VLDL and chylomicron remnants	TGs and cholesterol
IV	VLDL	TGs
V	Chylomicrons and VLDL	TGs and cholesterol

Source: AHA

Chylomicrons

Chylomicrons are the largest (1000 nm) and least dense (<0.95) of all lipoproteins. They contain only 1-2% protein. The rest of these particles are 85-88% triglycerides, ~8% phospholipids, ~3% cholesteryl esters and ~1% cholesterol. Chylomicrons contain several types of apolipoproteins including Apo-AI,II & IV, Apo-B48, Apo-CI, II and III, Apo-E and Apo-H. Chylomicrons transport dietary triglycerides and cholesterol absorbed by intestinal epithelia. In the plasma, chylomicrons acquire Apo-CII and Apo-E from HDL. Once transported to tissues, triglycerides contained in chylomicrons are hydrolyzed by Apo-CII-dependent activation of lipoprotein lipase contained on the endothelial cell walls. The chylomicron remnant, including residual cholesterol, is taken up by the liver via receptor-mediated endocytosis. Endocytosis occurs through the LDL receptor protein through recognition of Apo-E in the chylomicron remnant.

Very low density lipoproteins (VLDL)

Very low density lipoproteins are the next step in lipid particles by size and lipid content. They are approximately 25-90 nm in size (MW 6-27 million), with a density of ~0.98. They contain 5-12% protein, 50-55% triglycerides, 18-20% phospholipids, 12-15% cholesteryl esters and 8-10% cholesterol. VLDL also contains several types of apolipoproteins including Apo-B100, Apo-CI, II and III and Apo-E. VLDL also obtains Apo-CII and Apo-E from plasma HDL. VLDL assembly in the liver involves the early association of triglycerides with Apo-B100 mediated by microsomal triglyceride transfer protein (MTP) while Apo-B100 is translocated to the lumen of the ER. Lipoprotein lipase

also removes triglycerides from VLDL in the same way as from chylomicrons. VLDL production is stimulated by insulin resistance, one of the hallmarks of diabetes, which is thought to be the reason many diabetics have elevated VLDL levels.

Intermediate density lipoproteins (IDL)

Intermediate density lipoproteins are smaller than VLDLs (40 nm) and more dense (~1.0). They contain the same apolipoproteins as VLDL and essentially an intermediate state particle between VLDL and LDL particles (discussed in the next section). They are composed of 10-12% protein, 24-30% triglycerides, 25-27% phospholipids, 32-35% cholesteryl esters and 8-10% cholesterol. IDLs are derived from triglyceride depletion of VLDL. IDLs can be taken up by the liver for reprocessing, or upon further triglyceride depletion, become LDL.

Low density lipoproteins (LDL) and lipoprotein(a)

Low-density lipoproteins (LDL) are composed mainly of cholesterol and have very little protein. LDLs have depleted triglyceride contents compared to VLDLs and IDLs, and are the main type of transport particle for cholesterol and cholesteryl esters, carrying 45% to 50% of total plasma cholesterol to peripheral tissues. LDL particles make up more than half of the total lipoprotein in plasma. They are often referred to as "bad cholesterol" because they are primarily responsible for fatty deposits within arteries that obstruct blood flow and lead to heart attacks, strokes and other cardiovascular diseases. These fatty deposits are referred to atheromas, and as a result LDLs are referred to as atherogenic. High levels of LDLs are associated with an increased risk for coronary heart disease that is thought to be caused in large part by these fatty plaques. Low density lipoproteins are smaller than IDL (22-28 nm) (MW approximately 3.5 million) and more dense (~1.04). They contain the apolipoprotein Apo-B100. LDL contains 20-22% protein, 10-15% triglycerides, 20-28% phospholipids, 37-48% cholesteryl esters and 8-10% cholesterol.

Figure 9: Definitions for small, dense LDL

Lipoproteins	VLDL	LLDLD	sdLDL	HDL
Diameter (nm)	30-80	25.5 - 28.0	22.0 -25.5	7 -10
Density (g/mL)	<1.006	1.019-1.044	1.044 - 1.053	1.053 - 1.210
* Definition used by Denka Seiken				

Source: American Heart Association

Importantly, LDL particles themselves are heterogeneous in size, density, lipid composition and clinical significance. Two subclass patterns (A and B) of LDL particles have been identified: small dense LDL particles (sdLDL) and larger, less dense LDLs. Small, dense low-density lipoprotein-cholesterol is a recently recognized marker of cardiovascular disease risk. sdLDLs are thought to be even more atherogenic than overall normal less dense LDL. Individuals with a predominance of small dense LDL (i.e. pattern B) have a three-fold increased risk of heart attacks. Pattern B, small dense LDL (sdLDL) particles, are thought to be more atherogenic because of increase penetration of

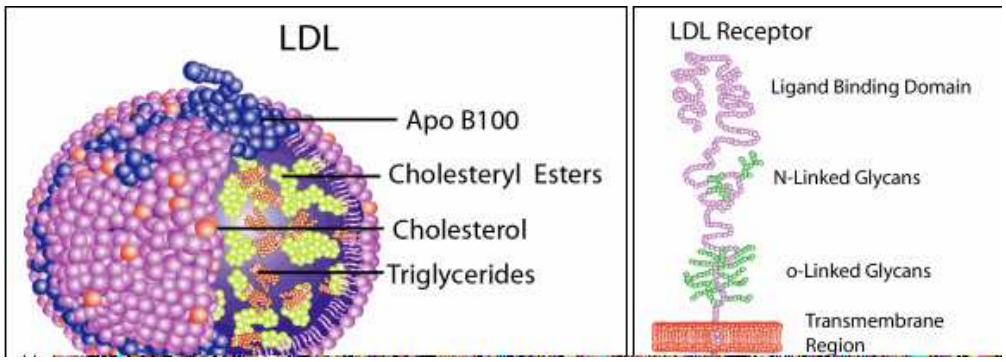
the arterial wall, lower binding affinity for the LDL receptor, longer plasma half-life, and weaker resistance to oxidative stress.

LDL becomes even more clinically dangerous when oxidized. Oxidized LDL can produce inflammation in arteries, promoting atherosclerosis and increasing the risk of heart attack or stroke. LDL oxidation occurs when the LDL particles react with free radicals. Oxidized LDL is more reactive with the surrounding tissues, which can produce tissue damage and clotting (which can directly lead to heart attack or strokes). Once LDL becomes oxidized, it can migrate to the inner lining (endothelium) of an artery, including the carotid artery, the coronary artery or a major peripheral artery of the legs or arms. Once there, it encourages the accumulation of inflammatory cells, like macrophages and platelets, at the site of the vessel and promotes their adhesion to the damaged area. More macrophages, cholesterol and other lipids begin to accumulate at the site, forming an atheroma or plaque that begins to grow thicker and leads to vessel blockage. A diet that is high in trans fats, smoking, poorly controlled diabetes or metabolic syndrome appear to increase levels of oxidized LDL

Normally, LDL is absorbed out of the plasma by the liver and other tissues via specific cell membrane-spanning LDL receptor-mediated endocytosis. The outside, cytoplasmic side (or domain) of the LDL receptor facilitates the formation of coated pit-like formations on the cell membrane surface, which become receptor-rich regions of the membrane as the individual receptors cluster together. The ligand-binding domain of the receptor recognizes and attaches to the Apo-B100 on LDL surfaces, resulting in the formation of a clathrin-coated vesicle. Once the LDL is folded into (or endocytosed) into a vesicle, ATP-dependent proton pumps lower the pH inside the vesicle, resulting in the dissociation of LDL from its receptor. After loss of the clathrin coat, the vesicles fuse with lysosomes, resulting in peptide and cholesteryl ester enzymatic hydrolysis. Normally, the LDL receptor, now part of the vesicle, can then be recycled back to the cell membrane surface. Insulin, tri-iodothyronine and dexamethasome have been shown to be involved with the regulation of LDL receptor-mediated uptake.

Diets high in saturated fat can cause plasma LDL levels to increase. This is due to decreased receptor-mediated plasma LDL clearance and catabolism due to excess fat levels in liver cells (which interferes with LDL transport). Clinical evidence points to LDL cholesterol as the key factor in the pathogenesis of the number and size of vascular atheromas, atherosclerosis and coronary heart disease. HDL cholesterol has been observed to have a protective effect (discussed in the next section). Increases in LDL cholesterol are associated with increased risk for CHD, although total cholesterol concentration is within the reference range. The Adult Treatment Panel (ATP) of the National Cholesterol Education Program (NCEP) recommends using LDL cholesterol levels as the basis for decisions to treat patients for CHD risk. CHD treatment attempts to reduce LDL cholesterol levels.

Figure 10: Structure of LDL and receptor



Source: Company reports

Lipoprotein(a) is similar in structure to LDL. However, it contains an additional protein, apolipoprotein(a) (Apo-(a) or LP(a)), covalently bound to Apo-B. Studies have identified Lp(a) as a putative risk factor for atherosclerotic diseases such as coronary heart disease (CHD), cerebrovascular disease (CVD), atherosclerosis, thrombosis, and stroke. Apo-(a) has been found to have a high sequence homology with plasminogen (an enzyme that degraded blood clots). It contains variable amounts of repeating kringle regions and more than 40 isoforms with a MW range of 400-700 kD. Its function is thought to be related to triglyceride metabolism and possibly thrombotic and atherogenic pathways.

The physiological function of Lp(a)/apo(a) is still unknown. Given its similar structure to plasminogen as well as with tPA (tissue plasminogen activator), a role in coagulation seems plausible. Lp(a) competes with plasminogen for its binding site and accumulates in the vessel wall, inhibiting plasminogen binding to the cell surface, which reduces plasmin generation. This is turn leads to increased clotting due to reduced fibrinolysis (breakdown of clots). Lp(a) also stimulates secretion of PAI-1, which can directly lead to thrombogenesis (generation of clots). Lp(a) mediated inhibition of plasminogen also promotes proliferation of smooth muscle cells. In addition, because of LDL cholesterol content, Lp(a) contributes to atherosclerosis. Other potential functions have been related to recruitment of inflammatory cells through interaction with Mac-1 integrin, angiogenesis, and wound healing. Individuals without Lp(a) or with very low Lp(a) levels seem to be healthy, so Lp(a) does not seem too essential under normal environmental conditions.

High Lp(a) predicts risk of early atherosclerosis similar to high LDL, but in advanced atherosclerosis, Lp(a) is an independent risk factor from LDL. Lp(a) then indicates a coagulant risk of plaque thrombosis. Lp(a) concentrations may be affected by disease states, but are only slightly affected by diet, exercise, and other environmental factors. Commonly prescribed lipid-reducing drugs have little or no effect on Lp(a) concentration. Niacin (nicotinic acid) and aspirin are two drugs known to significantly reduce the levels of Lp(a) in some individuals with high Lp(a).

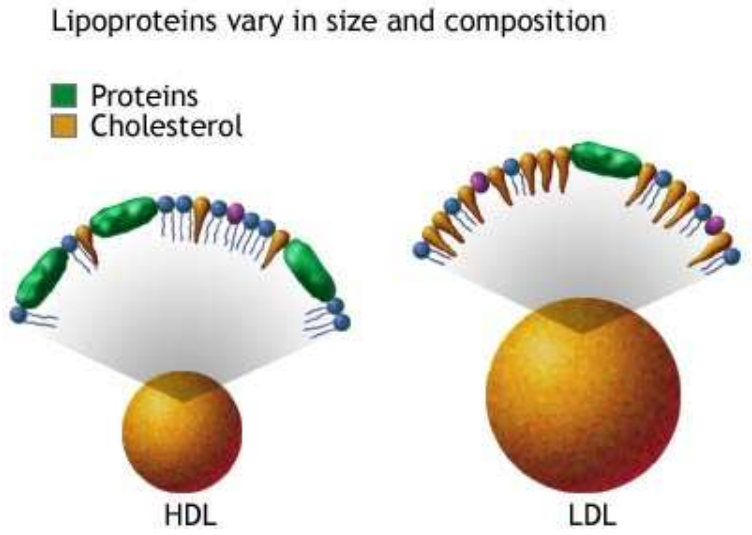
Population data suggests that pharmacologic amounts of fish oil supplements may be helpful in lowering the levels of Lp(a). Some studies have shown that regular consumption of moderate amounts of alcohol leads to significant decline in plasma levels of Lp(a) while other studies have not.

Figure 11: ATP-3 LDL management guidelines

Risk category	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug therapy optional)*
2+ Risk Factors (10-year risk 20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130mg/dL 10-year risk <10%: ≥160 mg/dL
0-1 Risk Factor**	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

Source: American Heart Association

Figure 12: Lipoproteins' membrane composition



Source: A.D.A.M

FAMILIAL HYPERCHOLESTEROLEMIA

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder caused by a genetic mutation or mutations that cause severe elevations in total cholesterol and LDL. As mentioned before, although moderately elevated total cholesterol and LDL is common in industrialized countries, patients with even the mildest forms of FH can have total cholesterol levels of over 300 mg/dL, including LDL levels of 200 mg/dL or more. Patients with the most severe types of FH, when untreated, can have LDL levels of between 500 and 1,000 mg/dL.

Because FH is associated with a high risk for premature coronary artery disease (CAD), health professionals should be alert to the signs found during physical examination and to laboratory values suggestive of FH. Early detection and aggressive management to lower LDL levels helps prevent or slow the progression of coronary atherosclerosis. Moreover, if first-degree relatives of a patient with FH are screened, other gene carriers can be identified and treated.

PATHOPHYSIOLOGY

FH is a disorder of absent or grossly malfunctioning low-density lipoprotein (LDL) receptors which are responsible for clearing LDL particles from the blood. The LDL receptor gene is located on the short arm of chromosome 19, and the protein that makes up the LDL receptor itself is composed of 860 amino acids. The receptor is the primary determinant of hepatic LDL uptake, and normally processes approximately 70% of circulating LDL. Two ligands on LDL particles bind to the receptor: apolipoprotein B-100 (apoB-100) and apoE.

ApoE is found on lipoproteins other than LDL, including VLDL particles, chylomicrons and their IDL remnants, and a subclass of high-density lipoprotein (HDL). The LDL receptor binds to apoE with higher affinity than apoB-100, and some mutations in the receptor may alter the receptor such that it excessively binds to apoE and no longer effectively clears LDL.

Mutations: The LDL receptor was first discovered in the 1970s and it was soon after determined that FH was caused by an autosomal dominant mutation. More than 700 mutations have been identified that have a meaningful impact on receptor function. Some of these mutations change the LDL receptor itself, while other mutations impact the receptor's function through other signaling molecules and pathways. Currently identified mutations can lead to LDL receptor function ranging from none to approximately 25% of normal receptor activity. Additionally, some patients clearly exhibit the highly elevated LDL and total cholesterol levels as well as abnormally low LDL receptor activity characteristic of FH, but with no as-yet identifiable mutation.

Five classes of mutations have been defined as follows:

- Class 1 includes null alleles that result in complete absence of the LDL receptor.
- Class 2 includes defective transport alleles, which disrupt normal folding of the receptor and cause either failure in transport to the cell surface or successful transport of truncated, mutated receptors.

- Class 2a mutations completely block the transport of the receptor from the endoplasmic reticulum to the Golgi apparatus.
- Class 2b mutations result in a partial blockade of transport of the receptor from the endoplasmic reticulum to the Golgi apparatus.
- Class 3 includes defective binding alleles that affect binding of LDL and, in some cases, binding of VLDL as well.
- Class 4 includes defective internalization alleles that affect the concentration of normal receptors in clathrin-coated pits for internalization by the hepatocyte.
- Class 5 includes defective recycling alleles that prevent dissociation of the receptor and the ligand and thereby interrupt recycling of the receptor.

FREQUENCY

United States: The prevalence of heterozygous FH in the US (where patients have only one faulty copy of the gene) is approximately 1 case per 500 persons. Importantly for lomitapide, conservative estimates on the prevalence of homozygous FH (where patients have two defective copies of the gene) in the US is 1 case per 1 million persons. This translates to a conservative estimate of approximately 350 HoFH patients in the US.

International: The prevalence of heterozygous FH patients in Europe is about the same of that in the United States, but certain regions, such as Iceland and Finland and certain areas in Russia and Greece, have a relatively higher incidence. The prevalence of heterozygous FH among French Canadians is 1 case per 270 persons, while the prevalence among Christian Lebanese is 1 case per 170 persons. Due to the founder effect and relatively isolated populations, three distinct populations within South Africa have an extremely high prevalence of FH: 1 case per 67 in Ashkenazi Jews and 1 case per 100 persons in both Afrikaners and South African Indians. Overall, experts whom we have spoken to have suggested to us that the overall ex-US population of HoFH is about 650 patients, bringing the worldwide population to about 1,000 total patients.

MORTALITY/MORBIDITY

Homozygous FH

Homozygous FH (when a patient has two copies of a defective LDL receptor gene) often results in LDL levels of 500 to 1,000 mg/dL. These very elevated cholesterol levels very quickly lead to the formation and buildup of cholesterol plaques, a condition called atherosclerosis. This severe and widespread atherosclerosis affects all major arterial beds, including the carotid, coronary, femoral, and iliac. HoFH atherosclerosis is so severe that even children are at risk for early coronary events. Sudden death or acute myocardial infarction may occur in patients as young as one or two years. Valve abnormalities are common, particularly aortic stenosis. Patients frequently develop angina, or chest pain, due to restricted blood flow to the heart muscles. Without heroic interventions to lower blood cholesterol levels, survival beyond young adulthood is unlikely for HoFH patients.

HoFH patients can also develop accumulations of cholesterol in nonvascular tissue, such as areas of the skin. These include fatty, cholesterol-rich skin deposits called xanthomas around the elbows, knees, buttocks, tendons, and cornea of the eye. Corneal arcus and

plantar, tendon, and tuberous xanthomas are present early in childhood and sometimes at birth. Patients can also develop these deposits in the eyelids where they are called xanthelasmas. Tendon xanthomas can cause Achilles tendonitis and articular symptoms, particularly of the hands, wrists, knees, and ankles.

Figure 13: Xanthomas of the hand in an HoFH patient

Figure 1 The hands of a patient with homozygous familial hypercholesterolemia. This 16-year-old girl had interdigital web planar xanthomata, tendinous xanthomata, and subcutaneous xanthomata. Regression following plasmapheresis allowed the wearing of rings.

Source: Company reports

HoFH is highly correlated with and thought to contribute to obesity. Recognition of the skin manifestations of FH are important as they can lead to early diagnosis and treatment to prevent the otherwise severe and inevitable cardiovascular complications associated with the disease.

Heterozygous FH

Similar to HoFH patients, premature CAD is the most serious and preventable disease complication for heterozygous FH (or HeFH) patients. HeFH patients often have LDL levels of 200 mg/dL or more. Left untreated, men are likely to develop cardiovascular disease in their 40s. The onset of heart disease in female HeFH patients lags behind men by about 10-15 years. Xanthomas, most commonly of the Achilles tendon and extensor tendons of the hands, are rare in HeFH children but common in untreated adults.

Figure 14: Typical LDL blood lipid levels seen with types of familial hypercholesterolemia

Genotype	Age, yrs	Total Cholesterol (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	Triglycerides (mg/dL)
Normal	1-19	175 ± 30	110 ± 25	55 ± 15	60 ± 25
Heterozygotes	1-19	300 ± 60	240 ± 60	45 ± 10	80 ± 50
Homozygotes	1-19	680 ± 170	625 ± 160	35 ± 10	100 ± 50
Normal	>20	200 ± 40	125 ± 30	55 ± 15	80 ± 30
Heterozygotes	>20	380 ± 80	300 ± 80	45 ± 15	150 ± 75

Source: Michael W. King, Ph.D / IU School of Medicine / miking at iupui.edu

DIAGNOSIS AND TREATMENT

Clinical diagnosis of HoFH is usually made in childhood when cutaneous and tendinous xanthomatas appear and total cholesterol, consisting almost entirely of LDL cholesterol, is over 600 mg/dL. Usually, both parents will have very high cholesterol levels (>300 mg/dL total cholesterol) and tendon xanthomatas, and family history will show a pattern of premature ischemic heart disease.

Because of the severity of CHD and lack of response to standard drugs and lifestyle modifications, HoFH patients require heroic intervention to treat their disease. Dietary changes have negligible effect on LDL levels in HoFH patients, although these changes are still almost always included in front-line therapy. Since lifestyle changes have other cardiovascular benefits, they are still strongly encouraged for HoFH patients.

In some patients with certain mutations, LDL receptors retain some degree of function. In these cases, diet control and high doses of statins (HMG-CoA reductase inhibitors), combined with bile acid sequestrants, ezetimibe and niacin, can be effective. Statins essentially work by increasing the number of LDL receptors on liver cells. However, if a patient has defective genes and is unable to produce functional LDL receptors, these drugs will have little to no effect, as there is either little to no upregulation, or upregulation of only faulty receptors. While statins can typically reduce LDL levels by 30%-50% in normal patients, with the degree of benefit greatest in those patients with higher baseline LDL levels, they have a significantly more modest effect in HoFH or severe HeFH patients.

High doses of the two strongest statins, Lipitor (atorvastatin) at 80mg daily or Crestor (rsouvastatin) at 20mg daily, can result in meaningful LDL lowering. However, in HoFH patients, these types of treatment rarely result in LDL goal attainment.

Estrogen replacement therapy in postmenopausal women is also effective, but this therapy is not recommended due to its adverse effects in older women. However, in some women the benefits may outweigh the risks.

Apheresis and plasmapheresis

The most effective therapies for lowering LDL cholesterol in HoFH are currently apheresis or plasmapheresis.

LDL apheresis for HoFH resembles dialysis and involves selective removal of lipoproteins that contain apo-B by heparin precipitation, dextran sulfate cellulose columns, or immunoadsorption columns. All methods reduce LDL-C levels by more than 50% and also lower lipoprotein (a), VLDL, and triglyceride levels. HDL is spared. Apheresis usually takes around four hours.

LDL apheresis is FDA approved for severe hypercholesterolemia in patients with CHD or vascular disease who have LDL-C >200 mg/dL on maximally tolerated lipid drug therapy, or for primary prevention patients with LDL-C >300 mg/dL on maximally tolerated drug treatment. The two techniques, dextran sulfate (liposorber) and heparin extracorporeal lipoprotein precipitation (HELP), can produce time-averaged LDL-C reductions of 50% when performed biweekly.

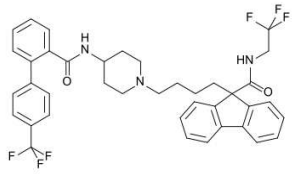
Plasma exchange plasmapheresis is the removal, treatment, and replacement of blood plasma. It is a lower-tech method for HoFH and is typically used because of its lower cost or due to lack of access to apheresis equipment. During plasmapheresis, blood is initially taken out of the body through a needle or previously implanted catheter. Plasma is then removed from the blood by a cell separator and the blood cells returned to the patient. The removed plasma is discarded and the patient receives replacement donor plasma, albumin, or a combination of albumin and saline (usually 70% albumin and 30% saline). Rarely, other replacement fluids, such as hydroxyethyl starch, may be used in individuals who object to blood transfusion. The use of these other replacement fluids is rare due to severe side-effects. Medication to keep the blood from clotting (an anticoagulant) is given to the patient during the procedure. Plasmapheresis is an uncommon treatment in the United States, but is more common in Europe and particularly Japan.

LDL apheresis is a considerably more expensive and time consuming therapy. Each session costs about $2,500, bringing annual treatment cost to ~$130,000. Additionally, access is limited, as few centers are set up to perform the procedure. The procedure takes about four hours and uses a 17-gauge needle, which severely comprises patient tolerability. Few serious adverse events are experienced, most of which are noncritical episodes of hypotension. Ideally the procedure should be performed weekly, but due to cost and tolerability factors, most HoFH patients receive apheresis biweekly.

LOMITAPIDE

OVERVIEW

Figure 15: Lomitapide



Source: Company reports

Aegerion's lead product compound, lomitapide, is a small molecule microsomal triglyceride transfer protein inhibitor, or MTP-I, in trials as an oral daily treatment for patients with severe lipid disorders. Lomitapide is currently in a pivotal Phase 3 trial for the treatment of patients with HoFH. Additionally, Aegerion plans to submit to each the FDA and EMA a protocol for a Phase 2/3 clinical trial of lomitapide for the treatment of patients with familial chylomicronemia (FC).

Researchers from the University of Pennsylvania, or UPenn, completed a Phase 2 clinical trial of lomitapide for the treatment of patients with HoFH in 2004. In addition to the UPenn trial, lomitapide has been evaluated in seven Phase 1 and five Phase 2 clinical trials. A total of 703 patients were treated with lomitapide in these Phase 1 and Phase 2 trials, including the patients in the UPenn trial.

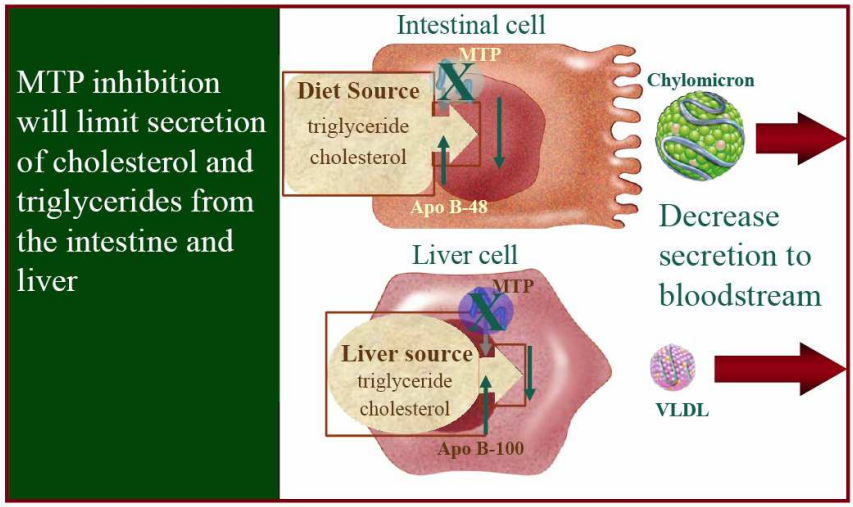
In October 2007, the FDA granted lomitapide orphan drug designation for the treatment of HoFH. In July 2010, Aegerion submitted an application to the EMA for orphan drug designation for lomitapide for the same indication. However, the company has indicated that the EMA is unlikely to grant lomitapide orphan designation for HoFH. In July 2010, Aegerion submitted an application to the EMA for orphan drug designation for lomitapide for the treatment of FC, and plans to make a similar request with the FDA in the next few months.

Aegerion believes that lomitapide may also be effective as a treatment for elevated lipid levels in broader patient populations, such as those suffering from heterozygous familial hypercholesterolemia (HeFH), patients who are statin intolerant, and patients with severe hypertriglyceridemia brought on by factors other than FC. FC is a rare genetic disorder where patients have extremely high levels of blood triglycerides, or TGs, generally greater than 2,000 mg/dL. These patients are at an increased risk of developing acute pancreatitis, a significant and sometimes life-threatening inflammation of the pancreas.

MECHANISM

As mentioned in the section on cholesterol synthesis and metabolism, microsomal triglyceride transfer protein exists in both the liver and intestines where it plays a role in the formation and transfer of cholesterol and TGs. The two main sources of lipids in the body are the liver and the intestines, which synthesize cholesterol (including LDL). These two organs provide a patient's intrinsic supply of lipids using MTP as part of the synthesis pathway.

Figure 16: Lomitapide MTP inhibitor mechanism



Source: Company reports

By inhibiting the MTP-1 protein, lomitapide effectively inhibits transport of triglycerides from the intestines into the hepatic portal circulation as well the processing of triglycerides into cholesterol particles inside hepatic cells. This mechanism directly contributes to the side effect profile of the drug. As higher amounts of triglycerides would remain in the lumen of the gut, diarrhea would be expected. Similarly, as transport of triglycerides out of hepatic cells is slowed, fat may accumulate inside hepatocytes, thereby elevating hepatic fat levels.

ONGOING PHASE 3 CLINICAL TRIALS

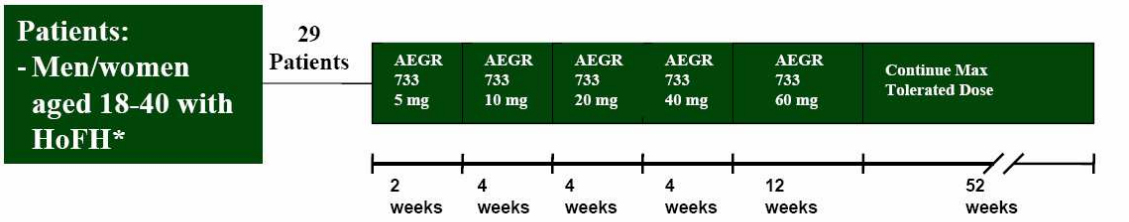
Lomitapide is currently in a pivotal Phase 3 clinical trial to evaluate efficacy and long-term safety for HoFH at the maximum tolerated dose of up to 60 mg. The trial is a single-arm, open-label clinical trial involving 29 patients with HoFH and is fully enrolled. The trial is being conducted at 11 sites in four countries. Mean patient age is 31 with no children allowed per protocol. Average baseline LDL is 354 mg/dL despite all patients being on background combinations of lipid-lowering therapies.

Diagnostic entry criteria were genotyping, fibroblast activity tests and clinical/familial history, which are the three major methods for formal diagnosis of HoFH . The genotyping method is based on a genetic test for mutations of the patient's two LDL-receptor genes. However, in clinical practice, it is often difficult to discern which patients have HoFH based solely upon a genetic test because there are more than 900 known mutations of these genes. Additionally, rare cases of HoFH have also been attributed to defects in genes other than those of the LDL receptor. For this reason, clinicians also identify patients as having HoFH through a test of LDL-receptor activity on skin fibroblast cells. LDL-receptor activity of less than 20% is typically considered to be indicative of HoFH. Alternatively, physicians can utilize a clinical assessment of the patient's symptoms and history, including documented hypercholesterolemia in both parents.

Patients went through a six-week run-in period on current lipid-lowering therapy, including apheresis if applicable. Patients were then started on ascending doses of lomitapide beginning at 5 mg/day and then titrated to as much as 60 mg/day over the first 26 weeks of the clinical trial. Background therapies were maintained during the 26-week efficacy phase of the trial, but may be modified during the safety phase of the trial at the investigator's discretion. Patients will then be maintained on the highest tolerated dose of lomitapide for an additional 52-week safety phase. The total efficacy and safety phases combined will last 78 weeks. LDL-C levels are measured at weeks 0, 2, 6, 10, 14, 18, 22, 26, 36, 46, 56, 66 and 78.

After these 78 weeks, eligible patients may enroll in a long-term, open-label extension trial protocol to evaluate the long-term efficacy and safety of lomitapide at the maximum tolerated dose beyond 78 weeks. Patients who do not roll over to the extension trial will have a six-week wash-out period during which lomitapide will be discontinued and patients will remain on concomitant lipid-lowering therapy. Aegerion expects to complete this trial in the second half of 2011 concomitant to additional required preclinical work described at length in a later section of this report.

Figure 17: Lomitapide pivotal trial design

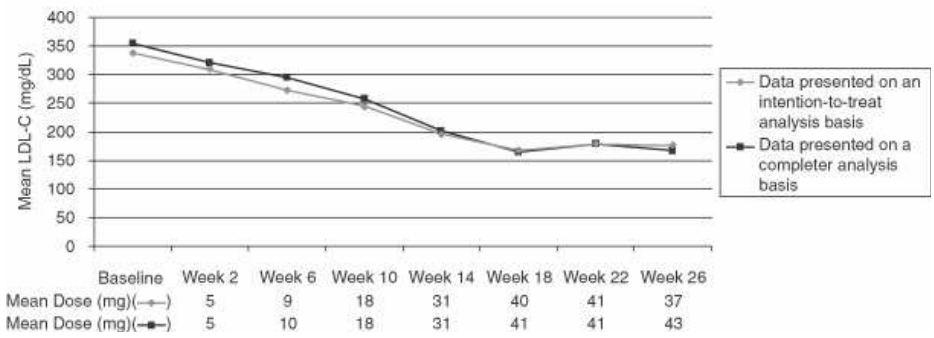


- **Primary Efficacy Endpoint**: % Reduction in LDL-C at Week 26
  - Hepatic fat measured at weeks 0, 26, 56, 78
  - Background therapies allowed, can be modified after week 26

Source: Company reports

The primary efficacy endpoint of the lomitapide pivotal trial is percent change in LDL-C at the maximum tolerated dose compared to baseline after 26 weeks of treatment in combination with other lipid-lowering therapies. The secondary endpoints of this trial include the evaluation of other lipid parameters, including percent change in TG levels from baseline, long-term safety, percent change in hepatic fat as measured by magnetic resonance spectroscopy, or MRS, and pharmacokinetics in combination with other lipid-lowering agents.

Figure 18: Mean change in LDL in lomitapide pivotal trial



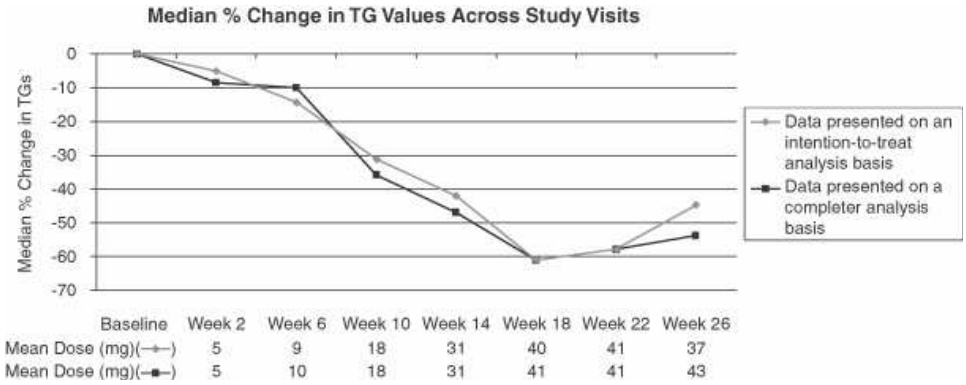
Source: Company reports

Aegerion completed enrollment in the pivotal trial in March 2010 with a total of 29 patients. Of the 29 patients originally enrolled, as of September 30, 2010, three patients have withdrawn their consent to participate in the trial and three other patients have discontinued treatment due to gastrointestinal adverse events. All of the remaining 23 patients in the trial have completed the 26-week period of therapy, at the end of which the primary efficacy endpoint is measured. The 23 trial patients are now in the 52-week safety monitoring period. As of September 30, 2010, 12 patients have already completed the full 78 weeks of the trial and Aegerion expects all trial patients to reach the end of the full 78 week in the second half of 2011.

Pivotal efficacy data

Primary endpoint: ITT LOCF 26-week primary endpoint data showed a mean LDL reduction of 45% from baseline (from 337 mg/dL to 176mg/dL). We note that since baseline LDL measurement were with maximum-tolerated background therapy, these data represent additional benefit to the best possible current patient care. The 26-week primary endpoint completer analysis (n=23) showed a very similar mean LDL reduction of 50% from baseline (from 354 mg/dL to 167mg/dL).

Figure 19: Median percentage change in TG values in lomitapide pivotal trial



Source: Company reports

Eight of the 23 patients (35%) who completed the 26-week efficacy phase of the trial achieved an LDL level below 100 mg/dL at week 26, which represents AHA target LDL

levels for those with high cardiovascular risk. Fifteen of 23 patients (65%) achieved an LDL-C level below 175 mg/dL at week 26, a threshold that represents seriously elevated LDL . The mean daily dose of lomitapide for the 23 patients who completed the 26-week efficacy phase of the trial was 43 mg at week 26 of the trial. The mean daily dose of lomitapide for the full 29 patients who began treatment in the trial was 37 mg at week 26 of the trial.

Secondary endpoints: ITT LOCF 26-week secondary endpoint triglyceride data showed a mean TG reduction in LDL of 45% from baseline (from 82 mg/dL to 42mg/dL). The 26-week secondary TG M endpoint completer analysis (n=23) showed a very similar mean TG reduction of 54% from baseline (from 97 mg/dL to 43mg/dL).

Safety and tolerability

Hepatic fat: Previous clinical trials have shown MTP inhibitors such as lomitapide can raise liver fat levels. Elevated liver fat can result in overall abnormal liver function as well as abnormal systemic glucose metabolism, resulting in elevated blood sugar levels similar to those seen in Type 2 diabetes. In this pivotal trial, Aegerion is measuring hepatic fat levels and pulmonary function at weeks zero, 26, 56 and 78. Hepatic fat levels will also be measured after the six-week wash-out period for patients who do not enter the extension phase.

As of September 30, 2010, 22 patients have had consistent evaluable hepatic fat measurements. These patients have had modest increases in hepatic fat from a mean of 1.2% at baseline to 8.7% at 26 weeks of treatment. Of these, 16 patients had completed 56 weeks of treatment as of September 30, 2010, and 14 of these patients had hepatic fat measurements available; these 14 patients had a mean hepatic fat level of 5.1% at this measurement time. In addition, the median change in hepatic fat from baseline in these patients was 5.48% at 26 weeks of treatment and 2.14% at 56 weeks of treatment.

Figure 20: Lomitapide pivotal trials

	Baseline	26 weeks Tx (n=22)	56 weeks Tx (n=14)
Mean hepatic fat level	1.2%	8.7%	5.1%
Median change in hepatic fat	n/a	5.48%	2.14%

Source: Canaccord Genuity, company reports

Significant elevation and accumulation of fat in the liver is called hepatic steatosis and can result from lifestyle factors, such as obesity and type 2 diabetes. Some studies suggest that patients with hepatic steatosis may be at an increased risk for more severe long-term liver consequences, such as hepatic inflammation and fibrosis. However, the consequences of hepatic steatosis that results from factors other than obesity and diabetes are unclear. Additionally, the % levels of liver fat needed to increase risk of altered glucose metabolism, inflammation and/or fibrosis are also very unclear. For example, in recent observational study published in the *Journal of Lipid Research*, patients who suffer from a genetic deficiency of microsomal triglyceride transfer protein have been shown to have some degree of hepatic steatosis, with average hepatic fat levels of 14.8%, without long-term liver complications. Lipid experts that we have spoken

to indicated to us that the level of liver fat that results in increased risk of altered glucose metabolism or inflammation varies greatly between individuals and is likely dependent on a number of factors in addition to liver fat levels. Multiple lipid specialists have indicated to us that while there are no guidelines for a hepatic level threshold that is clinically meaningful, they themselves generally regard levels of 15% or above as cause for additional liver safety and function scrutiny.

Liver enzymes: Previous clinical trials have shown that MTP inhibitors such as lomitapide have the potential to elevate liver enzymes, which can be sign of serious liver toxicity and organ damage. These effects are thought to be directly related to the drug's impact on MTP-mediated hepatocyte lipid metabolism and processing. As part of the pivotal trial, Aegerion is tracking ALT (alanine transaminase) or AST (aspartate transaminase) liver enzyme levels. As of September 30, 2010, four patients had ALT elevations >5x but <11x the upper limit of normal (ULN). Of these four patients, three underwent a temporary dose reduction and have since been re-challenged at higher doses. One patient discontinued treatment for seven weeks, and then safely restarted lomitapide therapy. Importantly, no patient has discontinued treatment due to liver enzyme changes, which we think bodes very well for the safety profile of lomitapide.

GI side effects and tolerability: As mentioned before, as of September 30, 2010, three trial patients had discontinued treatment due to gastrointestinal adverse events and three patients had withdrawn consent. All patients had been titrated to the maximum tolerated dose at the time of trial discontinuation. As per previous lomitapide trial experience, mild to moderate gastrointestinal adverse events have been the most commonly reported side effect in this trial. The majority of these gastrointestinal adverse events occurred during the first days following the introduction of a higher dose during the titration phase. Aegerion noted that in patients treated to week 56, there has been a noticeable reduction in gastrointestinal adverse effects after the 26-week efficacy phase. Clinicians we have spoken to who have had patient treatment experience with lomitapide have indicated to us that they believe they see a clear tolerance to or attenuation of lomitapide-associated diarrhea in patients who continue treatment with the drug. They believe that once patients experience this lessening of GI symptoms, the tolerability profile of the drug is very manageable.

ADDITIONAL PRE-NDA LOMITAPIDE STUDIES

We note that Aegerion will need to complete several additional small-scale clinical and preclinical studies, as well as certain specified additional analyses of previous Phase 2 trials. Aegerion must complete a thorough QT study of lomitapide in healthy volunteers. Aegerion also intends to complete additional drug-drug interaction studies investigating the impact of lomitapide with drugs that might be commonly used in patients with HoFH, such as the anti-clotting drug warfarin and the LDL-lowering statin Zocor (simvastatin). Aegerion also plans to conduct a pharmacokinetic study that investigates the impact of lomitapide in combination with a drug that could inhibit lomitapide's metabolism.

Figure 21: Additional lomitapide studies planned

Study type	Details
Phase 1 safety	Thorough QT study
Drug-drug interaction PK study	With warfarin
Drug-drug interaction PK study	With simvastatin
Drug-drug interaction PK study	With drug that is metabolized through same pathway as lomitapide
Preclinical PK study	To characterize lomitapide metabolism pathways and active metabolites
Clinical PK study	To characterize lomitapide metabolism pathways and active metabolites
Biomarker analysis	Analysis of 6 hepatic inflammation/fibrosis biomarkers from a prior Phase 2 trial samples to investigate liver complication outcomes

Source: Canaccord Genuity, company reports

Another planned study is a metabolite isolation and identification study in animals and a similar clinical study in healthy volunteers to better understand lomitapide metabolization. Aegerion has also agreed with the FDA to perform an analysis of six biomarkers for hepatic inflammation and fibrosis using stored samples from a prior Phase 2 clinical trial, to determine if lomitapide is associated with more significant liver complications. Aegerion intends complete all of these studies prior to the submission of its NDA for HoFH.

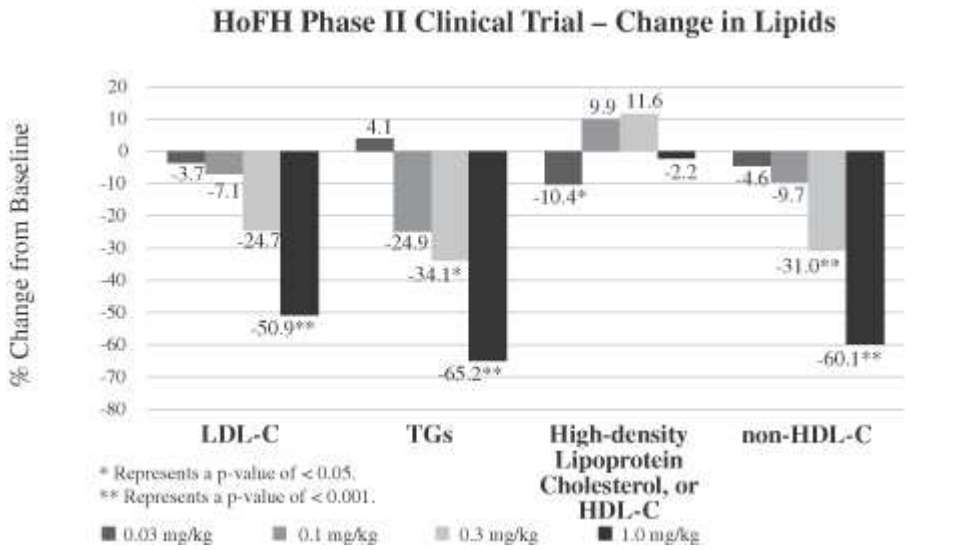
PHASE 2 LOMITAPIDE CLINICAL TRIALS

Phase 2 development in HoFH

In February 2004, UPenn completed a Phase 2 clinical trial of lomitapide for the treatment of patients with HoFH. In this single-arm, open-label clinical trial, six patients were given ascending daily doses, based upon body weight, of 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg and 1.0 mg/kg of lomitapide at four-week intervals for a total of 16 weeks. Given the weight-based dosing, the average dose at 1 mg/kg was 67 mg/day.

Data from this study showed a very clear dose-dependent and highly statistically significant reduction in LDL (51% from baseline), TG (65% from baseline) and total non-HDL cholesterol (60% reduction from baseline). In January 2007, the results of this trial were published in The New England Journal of Medicine and are summarized below. Percentage change represents the average percentage change from baseline in the four lipid parameters for the six-patient group. HDL levels appeared largely unchanged in four of the four, although appeared to decrease in the lowest lomitapide dose. In addition, patients treated with lomitapide experienced a mean reduction in body weight of 4.4% (2.8 kg) over the 16 weeks of therapy.

Figure 22: Change in lipids in lomitapide UPenn Phase 2 trial in HoFH



Source: Company reports

No patient withdrew from the trial and all patients were titrated to the maximum planned dose. Drug-related adverse events were primarily gastrointestinal in nature. These were largely transient episodes of increased stool frequency of mild or moderate severity but also included diarrhea, nausea and vomiting. Clinically significant elevations in the liver enzyme ALT were observed in three of the six patients. In one patient, lomitapide dose was temporarily reduced per protocol, after which ALT returned to lower levels. This patient subsequently was able to resume the earlier, higher dose and continue to be titrated to the maximum dose. In the other two patients, the transient elevations in ALT returned to lower levels with continued lomitapide treatment without dose reduction. Increases in hepatic fat levels were also seen in four patients. The remaining two patients had minimal changes in hepatic fat levels. All values for liver transaminases and hepatic fat returned to baseline levels upon cessation of therapy, other than for one patient, who consumed large quantities of alcohol (self-reported to be 6-7 oz. of ethanol per day) during the trial. Because this trial employed a forced-titration scheme of treating the patients at increasing doses at four-week intervals, we believe it is possible to infer that in those patients experiencing increases in hepatic fat, greater increases in hepatic fat are seen with the higher doses of lomitapide.

An increase in the international normalized ratio, which measures the blood's ability to form clots, was observed in the two patients receiving warfarin, an anti-coagulation therapy, which may be due to a drug-drug interaction. In addition, pulmonary function tests were conducted at baseline, at the end of each dose and four weeks after study treatment. Pulmonary function tests remained unchanged for the duration of treatment compared to baseline in all patients.

Historical development of lomitapide

Bristol-Myers Squibb and UPenn previously pursued extensive development of lomitapide for LDL and cholesterol lowering in broader patient populations, including patients at

moderately high risk of a cardiovascular event or statin-intolerant patients with high LDL levels.

In the mid-to-late 1990s, BMS developed lomitapide as a monotherapy treatment aimed at producing LDL-lowering efficacy equal to or greater than statins. Early clinical trials produced meaningful percent reductions in LDL, but participants discontinued at a high rate due to gastrointestinal adverse effects.

Aegerion and lipid specialists believe this effect could have been greatly improved with dose titration. In 2003, BMS donated certain patent rights and other rights related to lomitapide to The Trustees of the University of Pennsylvania and in May 2006, Aegerion licensed certain of these rights from UPenn.

BMS' previous clinical program for lomitapide consisted of seven Phase 1 clinical trials involving 251 patients who received single or multiple doses of lomitapide of between 1 mg/day and 200 mg/day. Lomitapide was also studied in six Phase 2 clinical trials, including the UPenn-sponsored Phase 2 clinical trial in patients with HoFH (discussed in the previous section) and another BMS-sponsored Phase 2 clinical trial in 452 patients with hypercholesterolemia who received lomitapide. Patients in five Phase 2 trials received daily doses of lomitapide of between 2.5 mg/day and 67 mg/day over four and 12 weeks, while the patients in the HoFH Phase 2 trial sponsored by UPenn received weight-based dosing with mean doses of 2 mg/day to 67 mg/day during the 16-week trial.

Figure 23: Lomitapide clinical development history

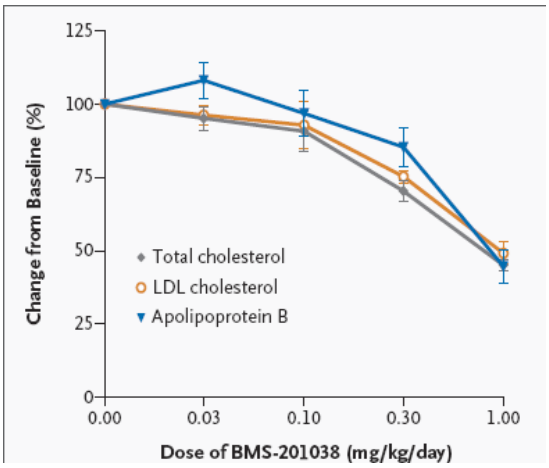
Trial Description	Dose Range and Concomitant Drugs	Duration of Trial	Number of Patients Dosed with Lomitapide
Combination use of lomitapide with ezetimibe	Lomitapide, 5 mg to 10 mg with or without ezetimibe, 10 mg	12 weeks	56
Combination use of lomitapide with atorvastatin	Lomitapide, 5 mg to 10 mg with or without atorvastatin, 20 mg	8 weeks	104
Combination use of lomitapide and other lipid-lowering therapies	Lomitapide, 2.5 to 10 mg; Lomitapide, 5 mg with atorvastatin, 20 mg, fenofibrate, 145 mg, or ezetimibe, 10 mg	12 weeks	227
Impact of titration on efficacy, safety and tolerability of lomitapide in combination with atorvastatin	Lomitapide, 2.5 mg and 5 mg, with or without atorvastatin, 20 mg	8 weeks	21

Source: Company reports

In the Phase 2 clinical trials summarized in the table above, lomitapide at doses ranging from 2.5 mg/day to 10 mg/day reduced LDL from baseline in a dose-dependent manner by 9% to 37% when given as a monotherapy, by 35% to 46% when used with Merck's

Zetia (ezetimibe), a drug that inhibits intestinal absorption of cholesterol, and by 47% to 51% when used with Pfizer's Lipitor (atorvastatin). Modest reductions in TG levels and body weight were also observed in these patients. Most LDL reductions from baseline were statistically significant but many TG changes were not statistically significant due to the naturally high degree of variability in TG levels in the blood and the fact that the trials were designed and powered to evaluate effect on LDL levels and not TG levels.

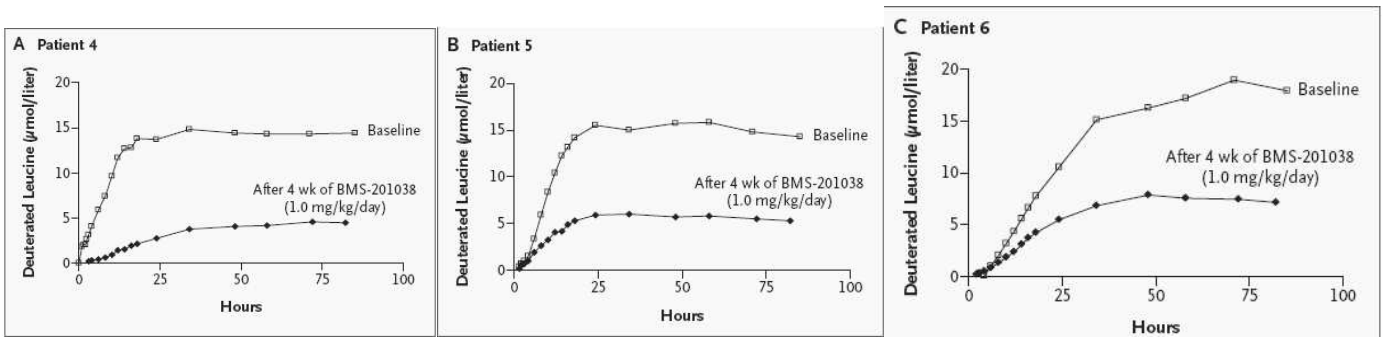
Figure 24: Lomitapide UPenn HoFH Phase 2 lipid efficacy data



Source: Rader et al. Inhibition of Microsomal Triglyceride Transfer Protein on Familial Hypercholesterolemia. N Engl J Med 2007;356:148-56.

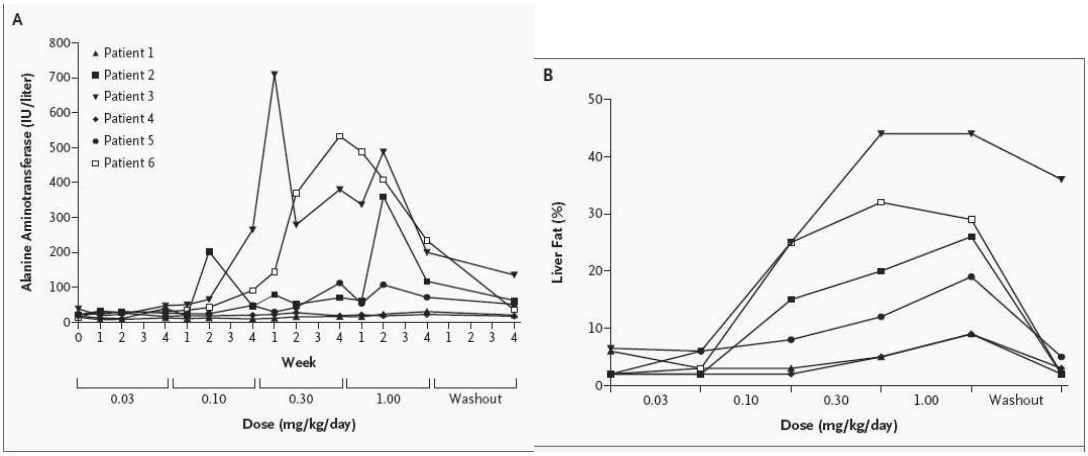
In all six Phase 2 clinical trials and the seven Phase 1 clinical trials, the most common adverse events reported were gastrointestinal, including diarrhea, nausea and vomiting, especially at the 25mg and 100mg doses. These adverse events were generally mild to moderate in nature. In addition, liver enzyme elevations occurred in a small proportion of patients and led to discontinuations from study drug. In the majority of patients who experienced liver enzyme elevations and remained on study drug, the levels returned to baseline while dosing continued. In these trials, patients with baseline hepatic fat concentrations of less than 6.2% showed increased mean hepatic fat at four weeks of treatment, which then plateaued at eight weeks and 12 weeks of dosing to levels of 6.2% to 9.7% respective (study doses of 2.5 mg/day to 10 mg/day). Higher levels of hepatic fat increases were occasionally observed at higher dose levels.

Figure 25: Lomitapide UPenn HoFH Phase 2 trial – impact on ApoB levels in select patients



Source: Rader et al. Inhibition of Microsomal Triglyceride Transfer Protein on Familial Hypercholesterolemia. N Engl J Med 2007;356:148-56.

Figure 26: Lomitapide UPenn HoFH Phase 2 trial – ALT And hepatic fat elevations



Source: Rader et al. Inhibition of Microsomal Triglyceride Transfer Protein on Familial Hypercholesterolemia. N Engl J Med 2007;356:148-56.

Phospholipidosis concerns around MTP inhibitors. In June 2007, Aegerion received notice from the FDA of a partial clinical hold with respect to clinical trials of longer than six months duration for lomitapide. The FDA issued such notices to all sponsors of MTP-Is. At that time, the FDA did not apply this partial clinical hold to the lomitapide pivotal Phase 3 HoFH clinical trial. In connection with the partial clinical hold, the FDA requested Aegerion collect additional preclinical data to assess the risk for pulmonary phospholipidosis with long-term use of MTP inhibitors. FDA has undertaken a broader initiative to understand phospholipidosis in those drugs commonly evidencing this phenomenon, typically characterized as cationic (positively charged) and lipophilic (soluble in lipids). MTP-Is are both cationic and lipophilic. In connection with the partial clinical hold, the FDA requested that Aegerion conduct a three-month, repeat-dose rat toxicology study that included a recovery group and a sufficient number of active doses to establish the level of exposure at which there is no biologically or statistically significant increase in the frequency or severity of pulmonary phospholipidosis, which is commonly referred to as the no observable adverse effect level (NOAEL). The FDA also requested an electron microscopy lung tissue analysis. Aegerion submitted the requested

preclinical data for lomitapide in December 2008, and the FDA removed the partial clinical hold with respect to this compound in February 2010.

REGULATORY STRATEGY AND PATHWAY

Aegerion has already secured orphan status from FDA for lomitapide for the treatment of HoFH. This fall, Aegerion held additional talks with FDA to reconfirm its regulatory strategy once the lomitapide data set included primary endpoint efficacy data for all trial patients. Aegerion indicated that FDA reiterated it would consider the lomitapide NDA with data from the single open-label, uncontrolled pivotal trial. Aegerion indicated it and FDA reviewed additional questions and points of scrutiny the agency had on the lomitapide profile, from which it compiled a list of additional preclinical, small-scale clinical and retrospective analyses (discussed previously in this report). Aegerion anticipates all of these trials to complete concurrently with final safety data from the current pivotal trial in H2/11 and intends to compile and submit the lomitapide NDA shortly thereafter. We believe that the drug will likely get fast-track status and priority review. We also believe that FDA will hold an advisory committee meeting to review the lomitapide approval application, likely in H1/12. We think that the proceedings of this meeting will be key for lomitapide's chances of approval, and that the committee will vote to recommend approval. We think that lomitapide will receive FDA approval in mid-2012.

Aegerion had filed in the EU for orphan status for lomitapide in the treatment of HoFH. In October 2010, Aegerion withdrew its EMEA HoFH orphan application based on guidance the company received from the EMA that lomitapide is not eligible for orphan drug designation for this indication since lomitapide has the potential to treat hypercholesterolemia in broader patient populations. Aegerion plans to file the EMEA approval application in 2012.

COMPETITIVE DEVELOPMENT-STAGE DRUGS FOR FH

Isis/Genzyme's mipomersen

The only other drug in late-stage clinical development for HoFH is Isis' mipomersen, partnered with Genzyme, which has a leading orphan drug franchise. Genzyme and Isis are developing mipomersen for patients whose LDL-C levels exceed recommendations despite taking maximally tolerated lipid-lowering treatments. The two companies intend to first secure approval for mipomersen in HoFH, and ultimately for HeFH other non-FH patient populations characterized by very high LDL levels and elevated CV risk. Mipomersen is in late Phase 3b development and has already successfully completed a pivotal trial in HoFH, showing a 25% ITT LDL reduction on top of optimized background therapy with acceptable safety and tolerability.

Mipomersen. Mipomersen is an antisense drug. Antisense drugs are made of RNA strands that work by binding to very select messenger RNA strands within cells, thereby preventing the production of the protein that the strands code for. Mipomersen is the most advanced systemic antisense drug currently in development. There is only one current approved antisense drug, Isis' Vitrovene, a locally injected drug for CMV infections of the eye.

Mipomersen is a first-in-class apolipoprotein B synthesis inhibitor (ABSI), currently in Phase 3 development. It acts by decreasing the production of apolipoprotein B, or apoB, which provides the structural core for all atherogenic lipids, including LDL. It is a second-generation antisense drug administered to patients through a once-weekly subcutaneous injection.

Mipomersen Phase 3 efficacy in HoFH. In November 2009, Isis/Genzyme reported positive data from their HoFH Phase 3 trial. The trial was a randomized, double-blind, placebo-controlled study that enrolled 51 homozygous FH patients who were randomized 2:1 to receive a 200 mg dose of mipomersen or placebo by weekly injections for 26 weeks. The trial was conducted at 10 sites in seven countries in North America, Europe, Asia, South America and Africa. Although the patients were on maximally tolerated statins and other lipid-lowering therapies, their average LDL-C at baseline was greater than 400 mg/dL. The reductions observed in the study were in addition to those achieved with the patients' existing therapeutic regimen.

Data showed that the trial met its primary endpoint in an intent-to-treat analysis with a 25% reduction in LDL after 26 weeks of treatment, vs. 3% for placebo ($p < 0.001$). This represented an average LDL reduction greater than 100mg/dL.

The study also met all of its secondary and tertiary endpoints to statistical significance, including a 27% reduction in apoB vs. 3% for placebo; a 21% reduction in total cholesterol vs. 2% for placebo; and a 25% reduction in non-HDL cholesterol vs. 3% for placebo (all $p<0.001$). Statistically significant reductions were observed in other atherogenic lipids, including Lp(a) (31%) and VLDL (7 percent (both $p<0.01$); and triglycerides by 18 percent ($p=0.013$). Mipomersen HDL levels increased 15 percent ($p=0.035$), which resulted in improved LDL/HDL ratios, an important measure of cardiovascular risk. Mipomersen LDL/HDL ratios decreased by 34 percent ($p<0.001$).

Mipomersen safety and tolerability. Six of the original 34 patients (18%) who started the trial discontinued, leaving 28 completing the 26-week course of mipomersen therapy. Of the six discontinuations, one patient discontinued due to non-Hy's law elevations in liver transaminases. This patient also did not show any other signs of liver toxicity. Of the remaining discontinuations, two patients stopped treatment due to injection site reactions, one patient stopped treatment due to a rash, one patient stopped treatment for personal reasons and one was discontinued due to patient non-compliance.

Consistent with previous studies evaluating mipomersen, the most commonly observed adverse events were injection site reactions (76%, versus 24% for placebo), flu-like symptoms and elevations in liver transaminases. Four mipomersen patients (12%, versus 0 in the placebo) had elevations in liver transaminases above 3x the upper limit of normal, three of whom reached between 5x and 8x ULN. None of these patients, including the patient who discontinued the study, had changes in other laboratory tests to indicate liver dysfunction. In all cases, transaminases returned to entry criteria by the end of planned clinical observations.

Mipomersen regulatory and commercialization strategy. Mipomersen has FDA orphan status for HoFH. Genzyme's initial US and EU regulatory filings for mipomersen will seek marketing approval for the treatment of patients with homozygous FH.

By mid-2011, Genzyme expects to have filed for approval in the US and EU and to have made progress toward filing in other major international markets. In addition, Isis and

Genzyme expect that data from all of the mipomersen trials described above will be available at the time of the initial submissions, and this data will continue to build the body of clinical evidence around mipomersen's value in managing high-risk, high-cholesterol patients.

Following a successful severe hypercholesterolemia submission in Europe, Genzyme plans to file a second submission in Europe for heterozygous FH patients. Genzyme and Isis are also planning an outcomes study that may support the potential expansion of mipomersen's indication to include a broader group of high-risk, high-cholesterol patients.

Comparison: We think that overall, lomitapide represents a superior treatment option for HoFH patients compared to mipomersen. Phase 3 data suggests that lomitapide reduces LDL 50% from baseline on top of optimized background therapy, whereas Phase 3 HoFH data shows mipomersen reduced LDL levels only about 25% comparatively. Other mipomersen Phase 3 trials show slightly improved LDL reductions (33-37%); however, none showed LDL lowering comparable to lomitapide. All of the lipid experts we have spoke to who treat HoFH patients have indicated to us that they see lomitapide as a stronger LDL-lowering drug than mipomersen. They also regard the mipomersen injection site reactions as a serious tolerability issue. Some experts see the seriousness of the mipomersen injection site reactions as equivalent to the lomitapide GI side effects. Other clinicians have indicated to us that they think lomitapide's side effects are less severe than those of mipomersen as they seem to improve with length of treatment.

FAMILIAL CHYLOMICRONEMIA (FC) STRATEGY

Aegerion also plans to develop lomitapide for patients with familial chylomicronemia (FC). In July 2010, Aegerion submitted an application to the EMA for orphan drug designation for lomitapide for the treatment of patients with this condition, and plans to submit an application for orphan designation to the FDA soon.

Aegerion is currently treating two patients with lomitapide for severe hypertriglyceridemia under the FDA's compassionate use program. Based on the TG reductions seen in these patients and the TG reductions seen in other clinical trials of lomitapide, Aegerion believes lomitapide has potential for treating patients suffering from extremely high levels of TGs, which can lead to life-threatening pancreatitis.

Aegerion recently initiated discussions with the EMA regarding a Phase 2/3 clinical trial for the treatment of patients with FC and is currently developing a protocol for such trial. Aegerion plans to submit this Phase 2/3 FC protocol shortly to the FDA and EMA. This protocol would allow FC patients to enter the trial on their existing treatment regimen and then be randomized to a lomitapide or placebo treatment arm for 12 weeks. Patients receiving lomitapide would start at 5 mg and be titrated to 10 mg and 20 mg at four week intervals. The primary efficacy endpoint would be the percent reduction in TG levels at week 12. After week 12, patients would remain on lomitapide as part of a long-term safety phase of the trial.

SALES AND MARKETING

Aegerion believes that it will be able to fully commercialize lomitapide for the orphan HoFH population itself in the US and EU. Orphan disease clinical and patient communities tend to be very organized, concentrated, well-informed and highly motivated, making commercial outreach very efficient.

Aegerion believes that targeting the HoFH-treating doctors and their HoFH patients will be straightforward and closely resemble other orphan disease commercialization efforts. Most patients with HoFH or FC are treated at a limited number of academic and apheresis centers or otherwise by physicians who specialize in the treatment of highly elevated lipid levels. For instance, there are only about 40 treatment centers in the entire US that are equipped to provide LDL apheresis. We believe that Aegerion is in the process of forging strong relationships with specialists who serve patients with HoFH and FC, and data from its ongoing Phase 3 development of lomitapide is being very well received both from these doctors and from patient advocacy groups. We believe Aegerion's ongoing activities and dialog will give it a strong knowledge of the target physicians as well as potential US and EU market dynamics.

Aegerion anticipates it can commercialize lomitapide for these indications with a relatively small specialty sales force that calls on a limited and focused group of physicians. The company plans to recruit a sales force and medical education specialists and take other steps to establish the necessary commercial infrastructure once lomitapide is approaching marketing approval. Aegerion plans to strike distribution or other collaboration arrangements for lomitapide commercialization outside the US and EU.

MANUFACTURING AND SUPPLY

Both lomitapide and implitapide are small molecule drugs that are synthesized with readily available raw materials using conventional chemical processes. Hard gelatin capsules are prepared at 2.5 mg, 5 mg and 20 mg strength by filling the capsule shell with formulated drug product.

Aegerion currently uses contract manufacturers to produce both drug substances and drug products required for its clinical trials. All lots of drug substance and drug products used in clinical trials are manufactured under current good manufacturing practices, with oversight by internal managers. Aegerion plans to continue to rely upon contract manufacturers and, potentially, collaboration partners to manufacture commercial quantities of lomitapide on approval. The company currently relies on a single manufacturer for the preclinical and clinical drug supply, purchases these supplies from this manufacturer on a purchase order basis and does not have a long-term supply arrangement in place. While Aegerion does not have redundant drug supply or a second supply source, it has identified a possible secondary supplier of drug substance. Aegerion believes that there are alternate sources of supply that can satisfy its clinical trial requirements without significant delay or material additional costs.

PIPELINE

Implitapide

Aegerion also has rights to implitapide, a second MTP-I, that could be developed for the same indications as lomitapide. Aegerion believes that implitapide could be a slightly different MTP-I than lomitapide. A lower concentration of implitapide was needed to inhibit the activity of MTP to 50% of its baseline activity in the intestines; Aegerion believe implitapide may be slightly more active in the intestines than the liver, perhaps positioning it as a preferable treatment of hypertriglyceridemia. Aegerion has focused on optimizing its implitapide manufacturing process.

As discussed previously, in June 2007, Aegerion received notice from the FDA of a partial clinical hold with respect to clinical trials of longer than six months duration for MTP-I drugs, including both lomitapide and implitapide. The FDA removed the partial clinical hold with respect to lomitapide in February 2010, but this partial clinical hold remains in effect with respect to implitapide.

INTELLECTUAL PROPERTY & LICENSES

Aegerion's lomitapide patent portfolio consists of five issued US patents and related issued patents in Europe, Canada, Israel and Japan, one pending US non-provisional patent application and related pending applications in Europe, Australia, Japan, Canada, Israel, South Korea and New Zealand, all of which have been licensed to the company in a specific field. The issued US patents are scheduled to expire between 2013 and 2019. The US patent covering the composition of matter of lomitapide is scheduled to expire in 2015.

The implitapide patent portfolio consists of four issued US patents, two pending US non-provisional applications, and related patents and pending applications in Europe, Australia, Asia, Africa, and South America. The issued US patents are scheduled to expire between 2015 and 2017. The US patent covering the composition of matter of implitapide is scheduled to expire in 2015.

Aegerion has also filed four non-provisional US patent applications and two international applications directed to pharmaceutical combinations of an MTP-I, such as lomitapide or implitapide, and other cholesterol-lowering drugs, and to methods of using such combinations in certain dosing regimens to reduce serum cholesterol or TG concentrations.

LICENSES

University of Pennsylvania

In May 2006, Aegerion entered into a license agreement with The Trustees of UPenn, pursuant to which the company obtained an exclusive, worldwide license from UPenn to certain know-how and a range of patent rights applicable to lomitapide. In particular, Aegerion obtained a license to certain UPenn patents and patent application relating to the dosing of MTP-Is, including lomitapide, and certain patents and patent applications

and know-how covering the composition of matter of lomitapide that were assigned to UPenn by BMS for monotherapy or in combination with other dyslipidemic therapies for treatment of patients with severe hypercholesterolemia unable to come within 15% of NCEP LDL-C goal on maximal tolerated oral therapy, or with severe combined hyperlipidemia unable to come within 15% of NCEP non-HDL-C goal on maximal tolerated oral therapy, with severe hypertriglyceridemia unable to reduce TG <1,000 on maximal tolerated therapy. Aegerion also licensed the right to use lomitapide either as a monotherapy or with other dyslipidemic therapies to treat patients with HoFH.

To the extent that rights under the BMS-UPenn assigned patents were not licensed to Aegerion or were retained by UPenn for non-commercial education and research purposes, those rights were licensed by UPenn back to BMS on an exclusive basis pursuant to a technology donation agreement between UPenn and BMS. In the technology donation agreement, BMS agreed not to develop or commercialize for any purpose any compound, including lomitapide, covered by the composition of matter patents included in the BMS-UPenn assigned patents in the field licensed to Aegerion by UPenn. Through Aegerion's license with UPenn, as provided in the technology donation agreement, the company has the exclusive right with respect to the BMS-UPenn patents regarding their enforcement and prosecution.

The UPenn license covers, among other things, the development and commercialization of lomitapide alone or in combination with other active ingredients in the licensed field. The license is subject to customary non-commercial rights retained by UPenn for non-commercial educational and research purposes.

Aegerion is obligated under this license agreement to use commercially reasonable efforts to develop, commercialize, market and sell at least one product covered by the licensed patent rights, such as lomitapide. Pursuant to this license agreement, Aegerion paid UPenn a one-time license initiation fee of $56,250. Aegerion is required to pay UPenn one additional development milestone payment of up to an aggregate of $150,000 when a licensed product's indication is limited to HoFH or severe refractory hypercholesterolemia, and an aggregate of $2.6 million for all other indications within the licensed field. All such development milestone payments for these other indications are payable only once, no matter how many licensed products for these other indications are developed. In addition, Aegerion will be required to make specified royalty payments on net sales of products covered by the license (subject to a variety of customary reductions), and share with UPenn specified percentages from any sublicensing royalties.

This license agreement will remain in effect on a country-by-country basis until the expiration of the last-to-expire licensed patent right in the applicable country. Aegerion has the right to terminate this license agreement for convenience upon 60 days prior written notice to UPenn or for UPenn's uncured material breach of the license agreement. The Trustees of UPenn may terminate this license agreement for Aegerion's uncured material breach of the license agreement, failure to make payments to UPenn or during specified bankruptcy or liquidation events.

FINANCIALS

Our forecast financial model is built on the assumption that lomitapide will be approved around early 2012 with a broad label encompassing HoFH patients who have been genotypically and phenotypically diagnosed. Our revenue model does not assume that lomitapide's label will include the group of patients we have referred to as "functional HoFH"; we do assume that the most severe of these patients will likely receive lomitapide treatment off-label.

We assume that lomitapide has standard small-molecule, single-digit percentage cost of goods and relatively simple manufacturing synthesis parameters. We also assume that Aegerion will choose to launch and market the drug itself in the US, Europe and possibly South Africa. We believe that the company will likely strike commercialization partnerships for other rest of world territories, but have not modeled any possible royalties as we think they would likely be immaterial to overall revenues.

We expect AMR101's launch to be successful and relatively rapid given HoFH's unmet medical need. We expect rapid sales growth in the 2012 and 2013 time frame. We think that lomitapide will generally be regarded as the best-in-class drug for HoFH treatment, and do not think that our revenue estimates will be greatly impacted by potential approval and launch of Isis/Genzyme's mipomersen. We think patients and clinicians will overwhelmingly prefer lomitapide due to its ease of use, stronger efficacy, and potentially better tolerability profile. We assume 95% peak market penetration of the genotypic HoFH market, 60% peak penetration of the phenotypic HoFH market and 30% peak penetration of the functional HoFH market

At the end of June 30, 2010, Amarin had $5 million in cash, but raised close to $45M in its October IPO. We think total cash on hand represents at least 18 months of operation, and we think it is likely that the current cash balance will last through the first lomitapide revenues in H1/12.

MANAGEMENT

Figure 27: Management team

Name	Title	Experience prior to Aegerion	At Aegerion since:
Marc D. Beer	CEO	Founding CEO of ViaCell; VP Global Marketing, Genzyme Abbott Labs	August 2010
Will H. Lewis	President	Director, BayStar Capital; Managing Director, Head of Capital Markets Investment Banking, Wells Fargo	2005
Christine A. Pellizzari	Executive Vice President and General Counsel	Pfizer Global Research and Development	2007

Source: Company reports

We believe that the Aegerion senior management has extensive experience in the biotechnology and pharmaceutical industry. Notably, CEO Marc Beer founded and led ViaCell through commercial development, its IPO process and ultimate acquisition by Perkins Elmer. Mr. Beer has also had extensive experience with the commercialization and marketing of orphan drugs from his experience at Genzyme, which is considered the flagship orphan disease-focused biotechnology firm. President Will Lewis has had extensive experience in the field of biotechnology finance and capital markets.

Figure 28: Aegerion P&L

	2009A	Q1/10A	Q2/10A	Q3/10A	Q4/10E	2010E	2011E	2012E	2013E
Lomitapide - US								98.5	169.7
Lomitapide - EU/SA				-		-	-	96.6	164.8
Total product revenues	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**195.1**	**334.5**
Revenue from royalties and royalty rights	-	-	-	-	-	-	-		3.0
Revenues from license agreements	-	-	-		-	-	-		0.5
Total revenues	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**195.1**	**338.0**
Cost of goods sold	-	-	-	-	-	-	-	9.7	16.5
Gross Profit	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**185.4**	**321.5**
R&D expense	7.0	1.1	1.1	1.3	1.5	5.1	20.0	20.0	20.0
SG&A expense	3.1	0.8	0.8	1.5	3.0	6.2	10.0	20.0	15.0
Other operating expense	-	-	-	-	-	-	-	-	-
Total operating expense	**10.1**	**2.0**	**2.0**	**2.9**	**4.5**	**11.3**	**30.0**	**40.0**	**35.0**
Operating income	**(10.1)**	**(2.0)**	**(2.0)**	**(2.9)**	**(4.5)**	**(11.3)**	**(30.0)**	**145.4**	**286.5**
(interest expense)	(2.1)	(0.6)	(0.6)	(0.6)	(0.6)	(2.4)	0.2	0.3	0.5
Interest income	0.2	0.0	0.0	0.0	0.0	0.1	(0.2)	(0.2)	(0.2)
Change in fair value warrant liability	(0.2)	0.2	0.2	(1.8)	(0.5)	(2.0)	(3.0)	-	
Other non-operating income (expense)	-	0.0	0.0	0.0	0.0	0.1	-	-	-
Pre-tax income	**(12.0)**	**(2.4)**	**(2.4)**	**(5.3)**	**(5.6)**	**(15.6)**	**(33.0)**	**145.5**	**286.8**
Income tax expense (benefit)	-	0.9	0.9	-	-	1.8	-	1.5	6.0
Accretion of Dividends	**(3.3)**	(0.9)	(0.9)	(0.9)	(0.9)	(3.5)			
Net income	**(15.3)**	**(2.3)**	**(2.3)**	**(6.2)**	**(6.5)**	**(17.4)**	**(33.0)**	**144.0**	**280.8**
Basic EPS	**(9.19)**	**(1.41)**	**(1.37)**	**(3.60)**	**(0.38)**	**(3.17)**	**(1.87)**	**7.40**	**13.12**
Diluted EPS	**(9.19)**	**(1.41)**	**(1.37)**	**(3.60)**	**(0.38)**	**(3.17)**	**(1.87)**	**7.40**	**13.12**
Basic shares outstanding	1.7	1.7	1.7	1.7	16.9	5.5	17.7	19.5	21.4
Diluted shares outstanding	1.7	1.7	1.7	1.7	16.9	5.5	17.7	19.5	21.4

Source: Canaccord Genuity estimates, company reports

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(as of 1 December 2010)

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Sell	20	2.8%	5.0%
	727	100.0%	

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Company	Disclosure
Aegerion Pharmaceuticals	1A, 2, 3, 5, 7

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