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BME 340

BME 340 Final Report: An Analysis of Mevacor (Lovastatin)

Predecessors

Mevacor, generically known as lovastatin, was the first statin approved and commercialized by Merck in 1987 for treatment of hypercholesterolemia and prevention of cardiac events [1]. Hypercholesterolemia is characterized as having high levels of low-density lipoprotein (LDL), or bad cholesterol, which is associated with the development of different heart diseases such as atherosclerosis and cardiac events such as heart attacks [2]. In 1959, Triparanol was introduced for clinical use in the United States as the first drug to inhibit cholesterol synthesis, however, it was quickly removed from the market due to serious side effects such as cataracts [2]. Following this, the top cholesterol lowering drugs on the market were gemfibrozil and cholestyramine [3]. Cholestyramine is an anion-exchange resin that binds with bile acid in the intestinal lumen preventing reabsorption and promoting excretion [2]. This forces the body to use more of its LDL cholesterol stores to make more bile acids [3]. Additional options for treating high cholesterol were nicotinic acid and other fibrates like gemfibrozil [2]. The main effects of fibrates include reduced triglyceride (TG) levels and increased high-density lipoprotein (HDL), or good cholesterol, levels [4]. Fibrates lower TG levels by triggering increased uptake of fatty acids in the liver leaving fewer fatty acids available for TG synthesis [5]. They also upregulate the production of Apo-AI and Apo-AII in the liver which contributes to increased HDL levels [6]. Nicotinic acid's main effects also include lower TG levels, lower LDL levels, and increased HDL levels [7]. Nicotinic acid lowers TG levels in the same way that fibrates do, however, the mechanism for increased HDL levels is not totally clear [8]. The reduction of TG molecules also leads to a reduction of very-low-density lipoproteins (VLDL) since TG molecules are used to synthesize VLDL molecules. VLDL molecules eventually turn into LDL molecules [7]. Due to the reduction of VLDL molecules, nicotinic acid is able to lower LDL levels. Fibrates can also lower LDL levels from this mechanism, however, it only has a modest effect [6].

Improvement

While cholestyramine, nicotinic acid, and fibrates were all used to treat hypercholesterolemia, each had their drawbacks. Cholestyramine caused unpleasant side effects such as constipation and was not tolerated well by all patients making it a less optimal choice for treatment [2], [3]. While fibrates have a clear effect on TG and HDL levels, there is little evidence to show that fibrates lower the chances of mortality due to cardiac events [9]. Mortality due to cardiac events such as heart attacks, or strokes is the main concern with many heart diseases such as hypercholesterolemia. Thus, there is not enough evidence showing that fibrates

will change the outcome for someone at high risk of a cardiac event. Meanwhile, lovastatin was found to generally reduce the risk of mortality by around 30% offering clear advantages that fibrates could not [10]. Early studies of nicotinic acid done by the Coronary Drug Project found that TG levels were lowered by 26.1%, total cholesterol was lowered by 9.9%, and nonfatal myocardial infarctions (MI) were lowered by 27% [11]. These early results were promising enough that nicotinic acid was often used in combination with statins like lovastatin. However, two recent large randomized clinical studies found that nicotinic acid does not offer any increased benefit when used in combination with statins [11]. Additionally, these studies saw a significant increase in adverse effects such as diabetic complications and development of diabetes, increased risks of infection and bleeding, and increased risk of myopathy [11]. While nicotinic acid showed promise of being an effective treatment on its own early on, with the development of lovastatin nicotinic acid has become unnecessary. Not only does nicotinic acid bring more negative effects than positive effects when combined with statins, it also does not have as great of cardiovascular effects as lovastatin, as the early studies of nicotinic acid alone only found a decrease in MI which is just one cardiovascular event [11]. The clear advantages made lovastatin the preferred option for treatment of hypercholesterolemia. Lovastatin does not have the share the same unpleasant side effects of cholestyramine and offers a greater reduction in mortality than fibrates or nicotinic acid, making it the clear winner between the various options.

Mechanism of Action

Lovastatin differs from its predecessors in its mechanism of action. The mechanisms of cholestyramine, fibrates, and nicotinic acid all directly affect various processes in the liver that have further effects of lowering cholesterol. However, none of them directly target the biosynthesis pathway of cholesterol. In the 1950s, there was a large effort to understand how cholesterol is synthesized in the body [2]. Konrad E. Bloch, Feodor Lynen, John Cornforth, and George Popják discovered the complex pathway consisting of 30 enzymatic reactions and broke it down to four main stages:

1. Combination of three acetate units to produce mevalonate, a six-carbon intermediate.
2. The transformation of mevalonate into activated isoprene units.
3. The polymerization of isoprene units to create a 30-carbon linear squalene.
4. Formation of the steroid nucleus through cyclization of the squalene and further changes to create cholesterol [2].

During the first stage of the pathway the HMG-CoA reductase reaction occurs in which HMG-CoA is reduced to mevalonate (Figure 1).

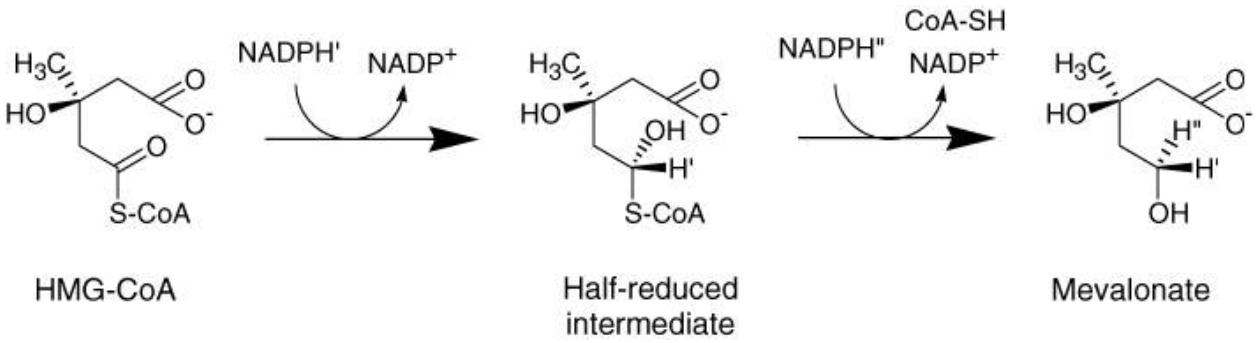

Figure 1: HMG-CoA reduction to mevalonate [2].

This reaction became critically important because this is the rate-limiting step of the pathway making it a target for regulation of cholesterol [2]. Lovastatin is a competitive inhibitor of the HMG-CoA reductase enzyme that blocks the enzyme's ability to convert HMG-CoA to mevalonate [2], [12]. Because this blocks the rate limiting step of the biosynthesis pathway, there is not an alternative path to continue synthesis and production of cholesterol is stopped. This leads to decreased intracellular cholesterol levels in hepatocytes which then causes increased expression of the LDL receptor gene. The LDL receptor facilitates the clearance of LDL and VLDL from the bloodstream and into the cells where they are broken down releasing the cholesterol that is then used up or stored by the cell [12]. There are two main effects from this mechanism: a decreased amount of cholesterol carried by each LDL molecule and less LDL molecules in blood circulation [12], [13]. By inhibiting production of cholesterol there are less cholesterol molecules available to be incorporated into newly synthesized LDL molecules. This lowers the amount of cholesterol carried by each LDL molecule and then the increase in clearance of LDL molecules lowers the amount of LDL in blood circulation.

Additionally, lovastatin has a modest effect on increasing HDL levels which is thought to be through the activation of PPARα, a key receptor in lipid metabolism regulation. Activation of PPARα causes an increase in Apo-AI expression and a decrease in CETP activity [12]. Since Apo-AI is one of the main components of HDL, increased levels of Apo-AI promote the synthesis of more HDL molecules. CETP is an enzyme that transfers cholesterol esters from HDL molecules to LDL and VLDL molecules resulting in a lower concentration of HDL in the blood [14]. Decreasing CETP activity allows for maintenance of HDL levels in the blood. The combination of increased Apo-AI expression and decreased CETP activity leads to the mild effect lovastatin has on increasing HDL levels. Overall, the inhibition of HMG-CoA reductase leads to significant reduction in LDL and a modest increase in HDL blood plasma concentration.

Target Engagement

The primary target of lovastatin is the liver, where most of the body's cholesterol is produced [20]. More specifically, lovastatin's mechanism of action reveals that the drug targets the HMG-CoA reductase enzyme as a competitive inhibitor. The results of this mechanism are less cholesterol in each LDL molecule and fewer LDL molecules in circulation in the blood [12]. Evidence of these two results imply correct target engagement and can be seen through biomarkers. Two biomarkers were used to evaluate lovastatin: LDL-C and apolipoprotein B (ApoB) concentration in the blood [13]. LDL-C measurements determine the cholesterol content carried by the LDL molecules [15]. Lovastatin was found to reduce normal and elevated levels of LDL-C suggesting that the drug successfully lowers the amount of cholesterol carried by each LDL [13].

The ApoB biomarker was used to evaluate if lovastatin successfully lowered the amount of LDL molecules in circulation. Every LDL molecule, regardless of its size or cholesterol content, contains one ApoB molecule, whereas ApoB is found on very few other lipoproteins [13]. Because ApoB is almost exclusively found on LDL molecules, measurements of ApoB levels in the blood provide insight into the number of LDL particles in circulation. Treatment with lovastatin found a substantial decrease in ApoB levels [13]. This was a key indicator that lovastatin lowered the number of LDL molecules in circulation. Together these two biomarkers are evidence of successful target engagement.

PK Data

As an oral drug, Mevacor is absorbed in the small intestine — with 30% uptake of the dosage [13]. Similar to 50% of medicines, lovastatin absorption is regulated by the CYP3A4 enzyme, mostly located in the small intestine and liver [13], [16]. The CYP3A4 enzyme is crucial for limiting the amount of absorption of lovastatin into the bloodstream by metabolism, which will be further discussed.

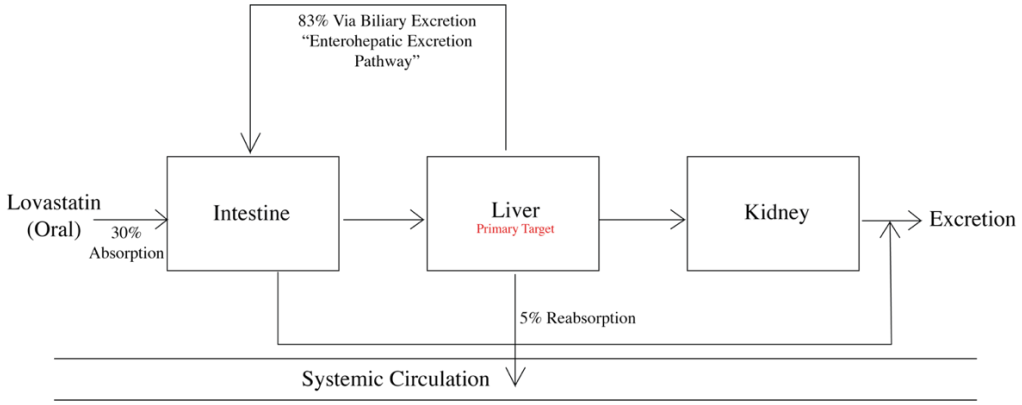

Figure 2: Schematic compartment model.

As seen in Figure 2 (Schematic Model) after absorption, the primary target of lovastatin is the liver [13], [17]. After the drug performs its inhibitory action on HMG-CoA reductase outlined in previous sections, the statin is sent out for excretion in via two pathways:

1) Renal Excretion Pathway
2) Enterohepatic Excretion Pathway

Approximately 10% of the drug is filtered by the renal system and excreted via urea. Whereas the majority follows the enterohepatic pathway being secreted from the liver via biliary excretion into the intestinal lumen, resulting in approximately 83% of the drug being disposed as feces [13]. Eventually, 5% of the biliary excreted drug is reabsorbed in the intestine by the enterohepatic recirculation [13], [18].

As aforementioned, the CYP3A4 enzyme determines the plasma concentration of lovastatin by regulation of intestinal absorption. An important class of CYP3A4 inhibitory agents are the furanocoumarins, commonly found in grapefruit juice [19]. The New Drug Application (NDA) for Mevacor conducted 2 experiments that consider the effects of coadministered lovastatin and different strength grapefruit juice in relation to the pharmacokinetics of the drug:

Grapefruit Juice (GJ) Experiment	**Number of Subjects**	**Dosage of GJ**	**Dosage of Lovastatin**	**AUC Ratio (with/without coadministered grapefruit)** ***No Effect = 1.00***	
				Lovastatin	**Lovastatin Acid**
1) High Dose	10	200 mL (Double Strength TID 3 days)	80 mg (single dose on 3rd day)	15.3	5.0
2) Low Dose	16	8 oz ~250 mL (Single Strength 3 days)	40 mg (single dose on 3rd day)	1.94	1.57

Table 2: Pharmacokinetic Effect of Coadministered Grapefruit Juice on Lovastatin [13].

As seen in Table 1, the high dose experiment uses 200 mL of double strength grapefruit juice (*1 can concentrate:1 can water)* 3 times a day with a single dose of 80 mg lovastatin administered the 3rd day. The low dose experiment uses 250 mL of single strength grapefruit juice (*1 can concentrate:3 cans water*) with breakfast, where 40 mg was lovastatin administered the evening of the 3rd day [13]. Looking at the AUC ratio for the high dose, it is evident that the sum of lovastatin plasma concentration over time (AUC) when the double strength grapefruit juice is administered is about 15 times that of when not coadministered. Similarly, for the low dosage coadministration, grapefruit juice seems to increase the plasma concentration of lovastatin by a factor of 2. From this information, the physiological phenomenon of grapefruit juice inhibiting the CYP3A4 enzyme metabolizing lovastatin and therefore increasing its overall plasma concentration is demonstrated. However, the NDA fails to cover the statistical significance of this increase by not providing information on the lower limit of the harmful range, and the C_{max} (maximum lovastatin plasma concentration) of a safe and effective dosage. This lack of information makes it difficult to determine the pharmacodynamic and toxicologic effects of the drug with respect to the pharmacokinetic response of different grapefruit juice concentrations.

Toxicology

Toxicology studies are used to establish the safety of a drug and determine at what levels a drug becomes seriously harmful. In order to evaluate the toxicology results, it is important to first consider the intended dosage of lovastatin. The recommended starting dose of Mevacor for adults is 20 mg/day taken with an evening meal and the recommended dosage range is 10-80 mg/day taken in 1 or 2 doses [13]. There are variations in administrative advice for adolescents or if taken with other drugs as there are warnings for different drug interactions. While the complications of drug interactions are important, the main toxicology studies focus on the potential for adverse effects in larger populations. These studies look for major adverse events to the vital organ systems which are the central nervous system (CNS), cardiovascular system, and respiratory system. Additionally, they investigate effects on the reproductive system and risks of cancer.

Results of the reproductive toxicity testing revealed skeletal malformations in mice dosed such that their total plasma drug exposure was 40 times the human exposure level and in rats dosed at 80 times the human exposure level [13]. These results suggest a small risk of negative outcomes as the instances only occurred at dosage levels much higher than should be expected in humans. However, it is still unknown whether lovastatin is excreted in human breast milk. Additionally, small traces of another drug in the same class have been found in human milk. Risks of adverse events to the fetus are unknown for this class of drugs and further investigation is needed to establish the safety of lovastatin for nursing or pregnant women. However, because hypercholesterolemia is an ongoing condition, it was argued that discontinuation of lipid-

lowering drugs during pregnancy and nursing shouldn't have a large impact in the long-term outcome of treatment. As a result, no further studies were done, rather, Merck recommended that pregnant and nursing women be taken off lovastatin until after pregnancy.

Reproductive studies investigating the effects of lovastatin on male fertility saw decreased spermatogenesis, testicular atrophy, and spermatocytic degeneration in male dogs dosed at 20 mg/kg/day [13]. This aligned with findings seen in a different drug in the same class, but the drug it was compared to is not mentioned. Studies of lovastatin in rats found no drug-related effects on fertility, however, studies of a similar drug in the same class found decreased fertility in rats dosed at 25 mg/kg/day for 34 weeks and seminiferous tubule degeneration in rats does at 180 mg/kg/day [13]. These fertility results were considered to have inconclusive clinical significance as they didn't show a clear trend between animal models or the drug comparisons. However, it is interesting to note that the maximum dosage recommended for humans of 80 mg/day would be about 1.14 mg/kg/day for an average 70kg human. This is much smaller than the 20 mg/kg/day given to dogs that resulted in these adverse effects.

Oncology studies investigating cancerous outcomes in mice dosed at 500 mg/kg/day found a statistically significant increase in both cancerous and non-cancerous liver tumors. This dosage resulted in a total plasma drug exposure of 3 to 4 times the exposure seen in humans given the maximum dosage of 80 mg/day [13]. These results were not seen in mice when given dosages of 20 and 100 mg/kg/day that resulted in 0.3 to 2 times the drug exposure seen in humans. Increases in liver cancer were also seen in rats when given dosages between 5 and 180 mg/kg/day of lovastatin that resulted in 2 to 7 times the drug exposure in humans [13]. The results of these rodent studies indicate that high dosages of lovastatin pose a risk of developing liver cancer, however, the dosages that resulted in adverse effects were all higher than the maximum recommended dosage of 1.14 mg/kg/day for an average human. Though, the lowest dosage in rats that saw adverse effects, 5 mg/kg/day, is much closer to 1.14 mg/kg/day.

Further toxicology studies found optic nerve degeneration in dogs dosed with 60 mg/kg/day, and vestibulocochlear nerve degeneration, retinal lesions, and CNS vascular legions in dogs dosed with 180 mg/kg/day. Both dosages of lovastatin were found to have a total plasma drug exposure of 30 times the mean drug exposure level in humans and CNS lesions have also been seen with usage of other drugs in this class [13]. Any adverse effect to the CNS is considered worrisome as it is one of the vital body systems. However, both dosages from this trial are much higher than the recommended 1.14 mg/kg/day dosage in humans, suggesting that the risk to humans when taken correctly is small. It is interesting to note that both dosages in dogs resulted in a drug exposure of 30 times the mean drug exposure level in humans suggesting

that the maximum plasma concentration was met for both doses. This ensures that the highest level of drug concentration where toxicity could occur was met for the study.

One final concern investigated to establish the safety of lovastatin is the possibility of overdosage. The median lethal dosage that killed 50% of mice was found to be greater than 15 g/m^2. Based on this, 200 mg/day was the maximum dose given to humans with no adverse effects during clinical trials [13]. This is equivalent to 2.86 mg/kg/day in a 70kg human. This is much lower than any of the dosages that saw adverse effects in animals in the trials mentioned previously. Testing a dosage at about triple the maximum recommended dose is another necessary safety measure as the bioavailability of a drug can vary greatly from person to person. The average bioavailability of lovastatin is reported to be 30%, but in the case that it was much higher in an individual, these results suggest some level of safety.

There were also a few accidental overdoses, with the highest dose taken at about 5-6g, however, no symptoms were experienced, and each person made a full recovery [13]. A 6g dosage in a 70 kg human is equivalent to 85.7 mg/kg/day. This dosage is higher than dosages that saw adverse effects in some of the animal studies mentioned previously. It is above the 20 mg/kg/day given to dogs in the male fertility study that saw negative effects on the male reproductive system. It is also in the range of dosages that saw increased liver cancer in rats and above the 60 mg/kg/day dose that saw optic nerve damage in dogs. This implies some safety concerns if overdosage were to happen, however, there was not enough research done to suggest a treatment for overdosage. Additionally, it is unknown whether lovastatin and its metabolites are able to be removed from the body through dialysis [13].

It is also interesting to note that many of the toxicology studies mentioned that a specific dosage in an animal model resulted in a plasma drug exposure several times the plasma drug exposure seen in the maximum 80 mg/day dose in humans. In many of these cases the dosage given was tens to hundreds of times larger than the 1.14 mg/kg/day dose recommended for humans. It would be expected that the drug exposure in the animal should also be tens to hundreds of times larger than in humans, however, the numbers were much lower than this. This could be due to differences in how animals metabolize the drug as compared to humans. Thus, while the toxicity results seem to show some level of safety in lovastatin, there are still some unknowns about how the drug is metabolized.

Clinical Trials

The 10 Mevacor adult clinical trials presented in the NDA assess the main target problems of hypercholesteremia and hyperlipidemia, in addition to trials for atherosclerosis and coronary heart disease conducted by collaboratory institutions. The trials presented are mostly fitting of Phase 2b, Phase 3, and some Phase 4, albeit no specific categorization within the NDA.

The first presented clinical trial model is suggestive of a Phase 2b study, particularly due to the focus on refining dose and dose intervals. The multicenter, double-blind, parallel study on familial or non-familial hypercholesterolemia, consists of comparisons of a placebo group between permutations of 10, 20, and 40 mg dosages being administered in different conditions: specifically, q.p.m. (once a day in the evening) and b.i.d. (two dosages daily) [13]. As seen in Table 2, the primary chemical mechanism of lowering LDL via increasing HDL explored in previous sections has been achieved, quantified in mean percentage change from baseline in a 6-week timeline:

TABLE II
MEVACOR vs. Placebo
(Mean Percent Change from Baseline After 6 Weeks)

DOSAGE	N	TOTAL-C	LDL-C	HDL-C	LDL-C/ HDL-C	TOTAL-C/ HDL-C	TG.
Placebo	33	–2	–1	–1	0	+1	+9
MEVACOR							
10 mg q.p.m.	33	–16	–21	+5	–24	–19	–10
20 mg q.p.m.	33	–19	–27	+6	–30	–23	+9
10 mg b.i.d.	32	–19	–28	+8	–33	–25	–7
40 mg q.p.m.	33	–22	–31	+5	–33	–25	–8
20 mg b.i.d.	36	–24	–32	+2	–32	–24	–6

Table 2: Multiple Dosage and Interval Mevacor Administration vs. Placebo [13].

The beginning of the “Clinical Studies in Adults” section in the NDA suggests a theory based on presumably earlier trials, where single daily doses administered in the evening were more effective than the same dosage given in the morning — and that this phenomenon can be explained by the synthesis of cholesterol primarily being during the night [13]. However, there doesn’t seem to be a quantitative representation of such trial. Looking at Table 2 through this lens, there isn’t a benefit of taking the same dosage q.p.m. relative to b.i.d. This is probably due to the pharmacokinetic effect of the drug being extended by second dose: making a 20 mg q.p.m. dose essentially have the same pharmacokinetic response as a 10 mg b.i.d. — and similarly for the 40 mg q.p.m. and 20 mg b.i.d. Therefore, even if this experiment demonstrates the successful chemical mechanism of lovastatin in comparison to placebo, it fails to expand on the theory made in the introduction.

The next two studies detailed can still be classified within a Phase 2b category; however, are special in nature, as they can be further classified as special population studies since there is a focus on patients with heart disease risk and insulin dependent diabetes mellitus. The second experiment — randomized open parallel study in hypercholesterolemic patients in high risk of myocardial infarction (heart attack) — is a superiority trial, where two Mevacor dosage groups are compared to a cholestyramine group. Even though superiority trials aren't determining factors of drug approval in the US nowadays, having such a trial comparing the newly discovered statin technology to previous methods of treatment may have been considered as an important argument in the 1980's. From the data provided in Table 3 the 20 and 40 mg b.i.d. Mevacor have approximately 1.5 to 2 times the effect across almost all parameters compared to the 12 g b.i.d cholestyramine dose, clearly demonstrating the significance of the newer technology:

TABLE III
MEVACOR vs. Cholestyramine
(Percent Change from Baseline After 12 Weeks)

TREATMENT	N	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	VLDL-C (median)	TG. (mean)
MEVACOR								
20 mg b.i.d.	85	–27	–32	+9	–36	–31	–34	–21
40 mg b.i.d.	88	–34	–42	+8	–44	–37	–31	–27
Cholestyramine								
12 g b.i.d.	88	–17	–23	+8	–27	–21	+2	+11

Table 3: 20-40 mg Mevacor Administration vs. 12 g Cholestyramine [13].

The third study within the Phase 2b trials is the controlled trials in hypercholesterolemic patients with insulin dependent diabetes mellitus and normal renal function [13]. Even though there is no quantitative information on the special population study, there is mention of the safety and efficacy profile being similar to nondiabetic patients. Furthermore, the NDA suggests no 'clinically significant' effect of Mevacor on glycemic control or coadministered hypoglycemic agents, even though there isn't any insight on which agents were considered. Nevertheless, consideration of diabetic patients is a notable inclusion into the NDA, particularly for observing any unexpected events that may happen in the complex and interrelated energy metabolism pathways such as the Citric Acid Cycle, where both glucose and fatty acids (from triglycerides) have a crucial impact on.

The fourth study detailed is the main trial that can be classified as Phase 3. The *"Expanded Clinical Evaluation of Lovastatin (EXCEL) Study"* was an 8245 hypercholesteremic patient, randomized, double blind, parallel, and 48-week (~ 1 year) study [13]. As seen in Table 4, the experiment is almost identical in terms of Mevacor dosages and intervals in comparison to the first trial presented (Table 2).

TABLE ~~III~~IV
MEVACOR vs. Placebo
(Percent Change from Baseline —
Average Values Between Weeks 12 and 48)

DOSAGE	N**	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	TG. (median)
Placebo	1663	+0.7	+0.4	+2.0	+0.2	+0.6	+4
MEVACOR							
20 mg q.p.m.	1642	–17	–24	+6.6	–27	–21	–10
40 mg q.p.m.	1645	–22	–30	+7.2	–34	–26	–14
20 mg b.i.d.	1646	–24	–34	+8.6	–38	–29	–16
40 mg b.i.d.	1649	–29	–40	+9.5	–44	–34	–19

**Patients enrolled

Table 4: Multiple Dosage and Interval Mevacor Administration vs. Placebo [13].

In comparison to the Phase 2b trial, the dosage and interval options for Mevacor have now been determined. The significance of the Phase 3 trial is that it validates the previously obtained information of efficacy and safety over a larger population. However, it is worth mentioning that in all the clinical trial data provided (Tables 2-4), the statistical significance of 1 unit of percentage change from baseline isn't mentioned — making it difficult to quantitatively determine what the exact comparative difference in efficacy is between the different dose and dose interval permutations.

Finally, the remainder of the adult clinical trials chapter consist of other institutions conducting studies, mainly in atherosclerosis. Since the main objective of lovastatin is to treat hypercholesterolemia, this report will not dive into each trial in detail. However, since hypercholesterolemia is considered as one of the precursor conditions to atherosclerosis and coronary artery disease, inclusion of such studies is of importance. All atherosclerosis trials share the common parameter of being long term studies, with a timeline of 2 to 5 years [13]. The extended timeline of the experiments in addition to institutions other than Merck (Mevacor's company) suggest that these trials are Phase 4 studies. Indeed, all studies yield the same result of regression of atherosclerosis progression, by considering different indicators of the disease, such as progression of lesions by measurement of lumen diameter change and angiographic change. This further supports the assumption of these being post-approval studies, as Phase 4 trials are typically performed to provide physicians real world experience.

Intellectual Property Generation

Even though the HMG CoA reductase enzyme was discovered in 1959 in the Max Planck Institute, it took more than a decade to isolate compounds that would effectively inhibit the enzyme [3]. These compounds called citrinin and compactin were found in the early 1970s from mold samples [2].

In February 1979, Merck isolated a similar statin to compactin from the fungus *Aspergillus terreus* — named mevinolin [2]. Along with the discovery of another statin named monacolin K in the same year, it was determined that both mevinolin and monacolin K were the same substance, eventually named lovastatin. This technological breakthrough was immediately filed for a patent by Merck on June 15th, 1979 [20]. This first patent named "Hypercholesteremic Fermentation Products and Process of Preparation" has only one claim, which is the MSD803 (lovastatin acid) product isolated from the genus Aspergillus:

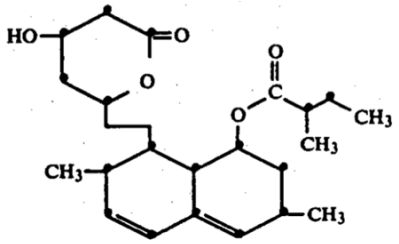

Figure 3: Claimed MSD803 Molecule, Lovastatin [20].

Interestingly, this patent frequently referring to the product as "the compounds of this invention" along with the title implies that the process of generating the lovastatin compound is also claimed [20]. The entire patent demonstrates that the invention claimed is, indeed, produced — with experimental proof from NMR and IR spectra, in addition to elucidating 9 experiments that form MSD803 [20]. It is noteworthy that there is only a brief explanation of the possible applications of the substance, with some mention of the connections between high cholesterol and atherosclerosis.

The next patent of the compound was filed on January 7th, 1988 — after Mevacor was FDA approved on August 31st, 1987 [21], [22]. This document is the first patent to include the Mevacor name [21]. Contrary to the first patent of the technology, the 1989 approved patent has 19 claims in which the majority covers functional group variations in the main carbon skeleton [21]. Some of the other claims, for instance 17 and 18, are specific to the applicational use of the product — highlighting the clinical use of compound 1 (finalized lovastatin), and its mechanism of action regarding hypocholesterolemic and hypolipidemic conditions [21].

Business Aspects

While Mevacor was in its clinical trial stages in the 1980's, the Merck company was aware of similar research into the HMG CoA reductase enzyme by its competitor, Bristol-Myers Squibb, and their pravastatin drug: Pravachol [3]. Like Mevacor, Pravachol was also based on Akira Endo's compactin discoveries — which was a more potent and efficacious statin [2], [3]. While conducting the clinical trials for Mevacor's approval, Merck was also developing a second statin to compete with the semi-synthetic drug Pravachol (FDA approved in 1991) [2], [23]. The semi-synthetic competitor Merck released was the simvastatin compound, named Zocor (approved in early 1998) [24].

Comparing Merck's two technologies, simvastatin (Zocor), was determined to be twice as potent as lovastatin (Mevacor): where a daily 10 mg dose of simvastatin reduced cholesterol 25-30% as opposed to 20 mg lovastatin [25]. Similarly comparing the two semi-synthetic competitors, simvastatin exceeded pravastatin in a randomized open parallel comparative study, which demonstrated simvastatin reducing total cholesterol levels by 24% versus pravastatin reducing levels by 15% [26].

In addition to these 2 semi-synthetic statins following Mevacor, 4 other synthetic statins where approved — with Pfizer's atorvastatin (Lipitor) being the most popular (approved late 1999) [2], [27]. In a one-year multicenter double-blind comparative safety and efficacy trial, performed in 31 community and university research centers, the difference between lovastatin and atorvastatin treatments in hypercholesteremic patients was considered [28]. Amongst 3 groups — 10 mg atorvastatin, 20 mg lovastatin, and placebo — it was determined that the atorvastatin group saw a greater percent reduction in LDL (-37% vs -29%) and total cholesterol (-27% vs -21%) [28].

In the year 2000, Merck got denied by the FDA the right to sell an over-the-counter version of Mevacor [29]. As a business decision, getting such an approval might have allowed Merck to remain as the dominant company within the hypercholesteremia market for a variety of reasons:

1) Getting the edge over the newly approved atorvastatin, Lipitor.
2) Having an opportunity to also bring simvastatin, Zocor, to the over-the-counter market.
3) Being able to file patents for the over-the-counter drugs they produce, which would extend their revenue by eliminating competitors since their previous patents for Mevacor and Zocor were near the end of their life.

However, the denial by the FDA appeared to be the first hit to Merck. Lipitor's higher efficacy solidified the decline of Merck's dominance in the field of statins [30].

What's Next

According to the Mayo Clinic, of the most common complaints in patients taking statins are muscle pain, or in severe cases, myopathy [31]. Even though some of the reported pain has been associated with the 'nocebo' effect — where placebo-controlled trials have determined that people negatively expecting side effects report higher pain rates than the drug can be responsible for. However, the greater issue related to taking statin medications is that they must be taken for life; it is especially important to maintain this as years progress, since risk of heart diseases increase with age [32]. Considering information from the toxicology lectures, it might be noteworthy that taking statins for a lifetime may have toxic effects on the liver and metabolism.

Even though statins remain to be the main treatment option for hypercholesteremia and associated heart diseases, newer non-statin alternatives are currently being produced and developed, aiming to increase positive clinical outcomes by minimizing the aforementioned, negative effects of statins. One of the newer non-statin LDL lowering technologies is bempedoic acid. Bempedoic acid acts by antagonizing the enzyme ATP citrate-lyase upstream of the HMG CoA reductase enzyme statins act upon [33]. Furthermore, the compound being a pro-drug (inactive upon administration) enables it to be converted into an active metabolite endogenously, via a series of naturally occurring reactions within the liver alone and not the skeletal system, preventing the drug from causing musculoskeletal symptoms like myopathy [33]. In a 12-week placebo-controlled study on hypercholesteremic patients with a history of statin intolerance, a single daily 180 mg dose of bempedoic acid reduced percent LDL change up to 28.5 % in comparison to placebo. Assuming similar trial parameters, this value it within the ranges of percent LDL reduction values seen in the Mevacor clinical trials, Tables 2-4.

Another technology with promise is the PCSK9 gene inhibitors, with two FDA approved medications already in the market [34]. The PCSK9 gene, found in the first chromosome, when mutated causes familial hypercholesteremia by reducing the number of LDL receptors in hepatocytes — which decreases plasma LDL clearance [34], [35]. Even though PCSK9 gene inhibitors cut cholesterol levels by approximately 50-60%, they are expensive: costing anywhere up to about $15,000 annually, with some newer ones being available for $6,000 [36], [37]. Furthermore, this gene inhibitor must be administered as shots, every 2-4 weeks. Also, statins can still be used to supplement PCSK9 treatments.

Identifying this gap in new PCSK9 gene inhibitor treatments, as of 2023, Merck is in phase 3 clinical trials for developing an oral PCSK9 inhibitor called MK-0616 [38]. A successful oral PCSK9 treatment option will allow Merck to reestablish market dominance in the field of LDL lowering drugs. The ability to supplement PCSK9 treatments along with statins without side effects may also be an avenue for Merck to explore in the future.

It is an indisputable fact that the discovery of lovastatin has been a major steppingstone in the history of cardiovascular disease science. Statins still maintaining their status as the gold standard in the field of hypercholesteremia and having the ability to be coadministered with new non-statin technologies to further decrease plasma LDL makes them a strong candidate worth using in clinical applications — even after 4 decades of lovastatin being approved.

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Note: Knowledge gained from in-class lectures in BME 340 was referenced in some of the statements made in the target engagement, PK data, toxicology, and clinical trials sections. The lectures were "Target Engagement" by Dr. John Donello, "Pharmacokinetics and Pharmacodynamics" by Professor Robert Linsenmeier, "Toxicology" by Professor Andy Dahlem, and "Clinical Trials" by Dr. Ron Burch.

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Alyssa Eckels and Kaan Börekçi
BME 340

BME 340 Final Report Response

Q1) Please give some detail and context of what has happened to Lovastatin in the last 20 years

Q2) Please contextualize this against the rest of the statin field.

Mevacor's first patent as a company was approved in 1988, right after its 1987 FDA approval [1], [2]. During its initial release, Mevacor was highly successful as it captured 42% of the market for cholesterol lowering drugs in less than 18 months [3]. However, whilst in the clinical trial stages for Mevacor (lovastatin), Merck, aware of its competitor Bristol Myers Squibb's near-approval semi-synthetic Pravachol (pravastatin) drug, decided to simultaneously work on their own more potent statin [4]. Pravachol was FDA approved in 1991 [5]. Merck's second statin Zocor (simvastatin), FDA approved 1998, was an attempt to maintain market dominance [6]. Indeed, Merck's simvastatin did exceed pravastatin in a randomized open parallel comparative study — where simvastatin reduced total cholesterol levels by 24%, whereas pravastatin reduced levels by 15% [7]. Zocor was also proven to be twice as potent as Mevacor, with a daily 10 mg dose of simvastatin reducing cholesterol 25-30%, similar to a 20 mg dosage of lovastatin [8]. As a business move, releasing Zocor was one of the last resorts of Merck, as the patent for Mevacor was nearing its end in 2001 [3]. However, this also meant that Zocor would be a self-competitor to Mevacor in its last years of IP.

Another significant development in the statin industry that severed the market dominance of Merck was the 1996 FDA approval of Warner-Lampert/Pfizer's Lipitor (atorvastatin) [9], [10]. Lipitor was proven to be more effective in lowering LDL and total cholesterol, as seen in a one-year multicenter double-blind comparative safety and efficacy trial amongst 3 groups — 10 mg atorvastatin, 20 mg lovastatin, and placebo [11]. Here, it was determined that the atorvastatin group saw a greater percent reduction in LDL (-37% vs -29%) and total cholesterol (-27% vs -21%) [11]. Not only was Lipitor more effective, but it was nicknamed "turbostatin" as it provided over 20% of Pfizer's annual revenue for years, as it turned into the world's best-selling drug with more than $125 billion in sales over 14 years [10]. It should be noted that Pfizer acquired Warner-

Lampert to eliminate Merck and Bristol-Myers competition [10]. The only downside to Lipitor was its price. Lipitor was sold at $3 per pill, or $3 per day since it was only taken once per day even at its highest doses, whereas Mevacor was sold at $2 a pill, making Mevacor the cheaper option at lower doses that were only taken once a day [3], [12]. Although Lipitor was found to be more effective at lowering LDL levels, many doctors would still prescribe Mevacor if the patient agreed to diet and exercise changes [12]. These changes also lowered LDL levels and allowed for the patient to save on costs. However, in the end, Mevacor's lower cost was not beneficial enough to beat out Lipitor.

With Mevacor's patent life nearing its end, and Merck's other drug Zocor being outcompeted in efficacy by Lipitor, the company's last resort was to apply for over-the-counter FDA approval for Mevacor. Getting an approval for an over-the-counter version of their drug would allow for them to continue their statin dominance by allowing for a newer market to provide revenue. Furthermore, an approval would have provided an avenue for Zocor to also eventually be available as an over-the-counter. Overall, this would have bought Merck time, while generating profit, to overcome Lipitor's success trend. Unfortunately for Merck, the FDA rejection of over-the-counter statins solidified the defeat of lovastatin, and eventually of Merck within the cholesterol lowering field — for the time being… [13]

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