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On The Brink: How ETC-1002 Could Still Change The CV Treatment Paradigm
Esperion Therapeutics, Inc. (*ESPR, $28.41*)

Despite perceived changes to the regulatory landscape that sent shares plummeting this summer, recent updates regarding the advancement of bempedoic acid (ETC-1002) as well as expert commentary offer additional insights into why we feel Esperion could still be on the brink of changing the CV treatment paradigm.

- Detailed presentation of mechanism and full dataset of 009 study at AHA provides mechanistic rationale for safety as well as efficacy of 1002

- FDA's contemporary view of the LDL hypothesis supports LDL-C lowering therapies whose mechanism is well-characterized, boding favorably for 1002

- December 14, 2015 AdCom for Vytorin/Zetia label expansion will provide additional insight into the FDA's new take on the LDL hypothesis, which could guide its approach to future labeling of other types of LDL-lowering agents such as PCSK9s and 1002

- Phase 2 study with high dose statins remains a likely positive catalyst since 1) observed increases in plasma concentration have been "transient," do not fluctuate, and are well-below increases with other drugs 2) 1002 is not metabolized through cytochrome enzymes as with most statins and 3) no change in efficacy from low to moderate statin intensities suggests equivalent efficacy in higher doses

- AMGN, SNY/REGN's conservative clinical development strategies that focused on high-risk patients open up the market opportunity for 1002 to capture a differentiated label inclusive of a wider patient population in statin intolerance

- Statin intolerance occurs across statin intensities not just in patients who no longer tolerate maximal dose. Bempedoic acid's ability to lower LDL-C in combo with low-to-moderate intensities (80% of statin users) suggests it plays a paradigm-shifting role in potentially reducing statin doses (note Statin Rule of Six)

- Management's adjusted timeline maximizes current cash on hand - $302M as of 3Q15 – until pivotal Phase 3 readouts in 2017. While a partnership would signify a validation of the science as well as a source of non-dilutive capital, it would also considerably cap potential upside

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Immediately following the announcement of the End-of-Phase 2 meeting with the FDA on September 28, 2015, shares of Esperion sank to their lowest level last seen fifty-two weeks earlier prior to release of proof-of-concept data from the Phase 2b ETC-1002-008 study. Reasons for the heavy selloff included the unexpected change in management's tone from an August press release that suggested the possibility of a need to complete a cardiovascular outcomes trial (CVOT) prior to approval which allowed opportunistic short-sellers to insinuate that management had not disclosed to investors the entire safety dataset that the FDA had seen; notably, the Chardan analyst's deceptive claims were never substantiated and were understood to have been fomented in order to profit from additional uncertainty. While the irrational selling has since weighed heavily on investors, the still deep discount at which shares of Esperion trade has created one of the more compelling risk-rewards in biotech with the company trading at an enterprise value of just roughly $300M.

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AHA Updates On Mechanism Support Positive Safety And Efficacy Data

On November 10, 2015, Esperion presented two oral presentations at the American Heart Association (AHA) Sessions highlighting additional details on bempedoic acid's (ETC-1002) mechanism of action as well as full results from ETC-1002-009 study in combination with low-to-moderate statins. While yet to be fully appreciated by the investing community, these updates from AHA underscore 1002's position within the competitive landscape as a safe and efficacious once-daily oral therapy for statin intolerant patients. The full dataset from the 009 study reiterated statistically and clinically significant LDL-C reductions of up to 24% in combination with statins along with other atherogenic lipoproteins such as total cholesterol, non-HDL-C, ApoB, LDL(p) as well as hsCRP. It confirmed, more importantly, the entire clinical safety dataset for 1002 from 134 patients that has been consistent with previously reported results.

In addition to the confirmation of the entire safety database, Esperion identified the specific isoform of Acyl-CoA Synthetase (ACS), ACSVL1, which activates prodrug ETC-1002 (Figure 1). The fact that ACSVL1 is largely expressed in the liver (some expression in the kidney) and not in skeletal muscle cells (Figure 2) provides mechanistic rationale for the lack of muscle-related adverse events thus far demonstrated by 1002.

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Figure 1

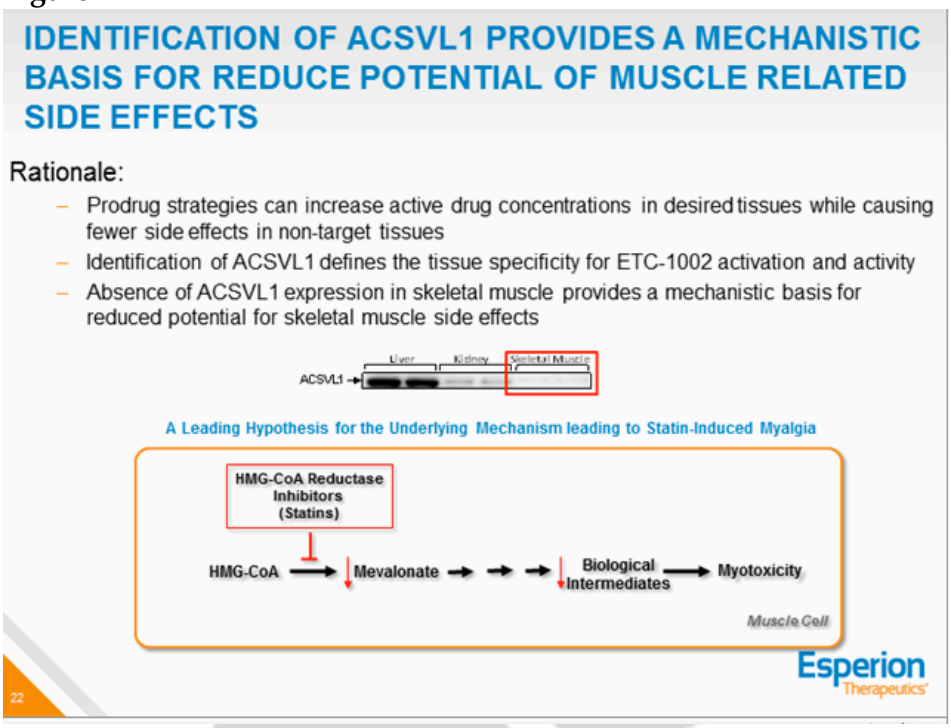
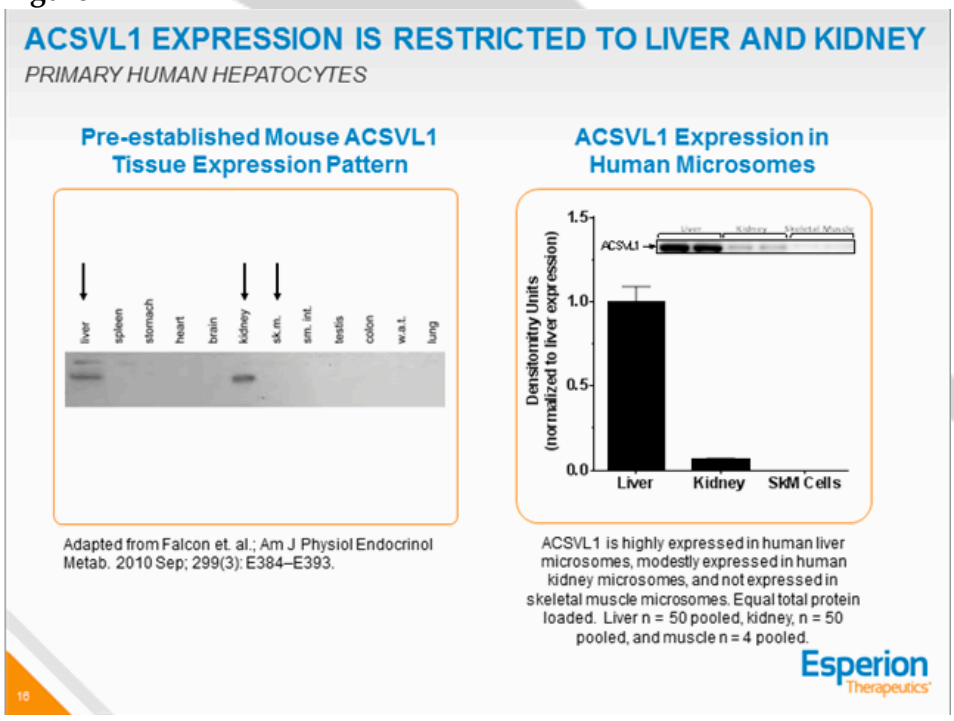


Figure 2



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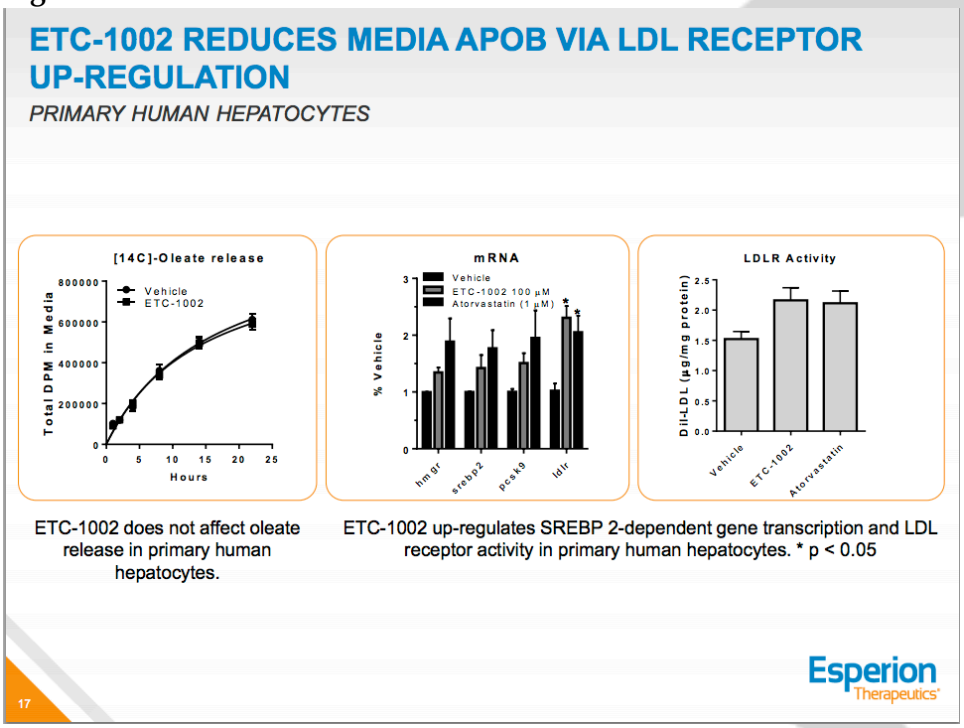
Moreover, the company demonstrated 1002's ability to increase activity at the LDL receptor (LDL-R) in human cells, a mechanistic result directly similar to that of statins and PCSK9s (Figure 3). The significance of this update while seemingly overlooked by investors fundamentally supports reasons why the FDA has not and will likely not require a CVOT prior to initial approval. Despite the FDA's newfound contemporary view that draws into question aspects of the LDL hypothesis (Reducing LDL with PCSK9 Inhibitors — The Clinical Benefit of Lipid Drugs), the PCSK9 AdCom panels as well as FDA voting members supported approval of these novel drugs on the basis of their known mechanism on LDL-R.

Figure 3



Dr. William Hiatt, who presided as a voting member of the Advisory Committee meeting on evolocumab, has championed the contemporary perspective that emphasizes the mechanism by which LDL-C is lowered. On the virtues of PCSK9s, he writes:

> *"That inactivation results in decreased LDL-receptor degradation, increased recirculation of the receptor to the surface of hepatocytes, and consequent lowering of LDL cholesterol levels in the bloodstream. Statins, by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, similarly act by increasing LDL-receptor expression. This shared LDL cholesterol–lowering*

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> *mechanism…has led to optimism regarding the potential — but as yet unproven — cardiovascular benefits of these agents."*

Had there been a concern from the agency on 1002's known ability to lower LDL-C, it is likely they would have been explicitly instructed to conduct a CVOT prior to approval as in the case of CETP inhibitors whose mechanism of lowering LDL-C remains unknown. The FDA rather guided Esperion to walk a similar approval path to that of PCSK9s:

> *"Both [PCSK9s] were submitted through the traditional FDA approval pathway, with LDL cholesterol reduction as the surrogate measure of clinical benefit. No efficacy data on cardiovascular outcomes were provided to the advisory committee, except for encouraging but preliminary analyses of cardiovascular adverse events with evolocumab."*

Those preliminary analyses (Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events) provide early evidence of a reduction in the risk of cardiovascular events:

> *"The rate of cardiovascular events at 1 year was reduced from 2.18% in the standard-therapy group to 0.95% in the evolocumab group (hazard ratio in the evolocumab group, 0.47; 95% confidence interval, 0.28 to 0.78; P=0.003)."*

An overview of the post hoc analyses of ODYSSEY LONG TERM and OSLER trials at 12 to 18 months in the New England Journal of Medicine (Lowering LDL Cholesterol Is Good, but How and in Whom?) further underscores the regulatory precedent set by the approval of Praluent and Repatha.

> *"All these results, including the current ones, fit well into the framework established by the 2013 cholesterol guidelines of the American College of Cardiology and the American Heart Association, which recommended that nonstatins could be used in higher-risk patients in whom statin therapy did not lower LDL cholesterol levels sufficiently or in patients with unacceptable side effects from statin therapy, with a strong preference for use of non-statins that have been determined to be safe and effective in randomized, controlled trials. The evidence-driven cholesterol guidelines did not endorse the concept that lower LDL cholesterol levels are better at all costs. They emphasized that, while lower is better, it matters how you get there and whether the benefits outweigh the risks for that patient."*

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Despite an unforeseen change in tone in its last communication with the FDA following the End-of-Phase 2 meeting, Esperion management astutely assessed the FDA's pulse on the matter of the CVOT and plans to have it (with "preliminary analyses" available) well underway along with a completed long-term Phase 3 safety study by the time of the NDA submission for 1002.

IMPROVE-IT Could Still "PROVE-IT"

More details on the FDA's contemporary view of the LDL hypothesis will be elucidated at the December 14, 2015 AdCom meeting to discuss the label expansion of Vytorin and Zetia based on positive results from Merck's CVOT, IMPROVE-IT. In light of recent clinical failures for niacin, fenofibrate, and CETP inhibitors, the FDA has more recently drawn into question the virtues of approving new therapies on the sole virtue of their ability to lower LDL-C. Support of label expansion would seemingly confirm the hypothesis thereby boosting the prospects for positive CVOTs and commercial success for new classes of LDL-C lowering drugs including 1002.

While most have trumpeted IMPROVE-IT as the landmark study showing a benefit of adding a non-statin lipid-modifying agent to statin therapy (Proof That Lower Is Better — LDL Cholesterol and IMPROVE-IT), others have been more skeptical the results to suggest the FDA consider a label applicable to only certain subgroups based on vulnerabilities within the dataset that suggest greater benefit in diabetics (Merck's IMPROVE-IT: FDA Panel Review Has Implications Beyond Zetia, Vytorin).

Nevertheless, the FDA is unlikely to completely forsake the long-standing hypothesis, but rather stress the importance of understanding the mechanism by which a drug lowers LDL-C. Approving drugs based on LDL as a surrogate endpoint will likely be considered within this context. It is possible the FDA amend its guidelines to use LDL as an approvable endpoint through an accelerated approval pathway as it had essentially when approving PCSK9s. As such, 1002 with its clear-cut mechanism, safety and efficacy dataset to date along with additionally planned studies prior to NDA would likely qualify for an accelerated path to market.

AMGN, SNY/REGN's Conservatism Is ESPR's Opportunity

The FDA approved both Praluent and Repatha without requiring a completed CVOT in a more restrictive patient population based on Phase 3 programs that included a majority of high-risk patients. Their narrower-than-expected labels led consensus opinion to insinuate that other non-statin LDL-lowering therapies such as 1002 would be limited to the same HeFH and ASCVD patient populations (~8M-11M patients US) prior to completing a CVOT. Comments from the End-of-Phase 2 meeting, however, have guided Esperion to propose conducting a two-pronged Phase 3 program focused on

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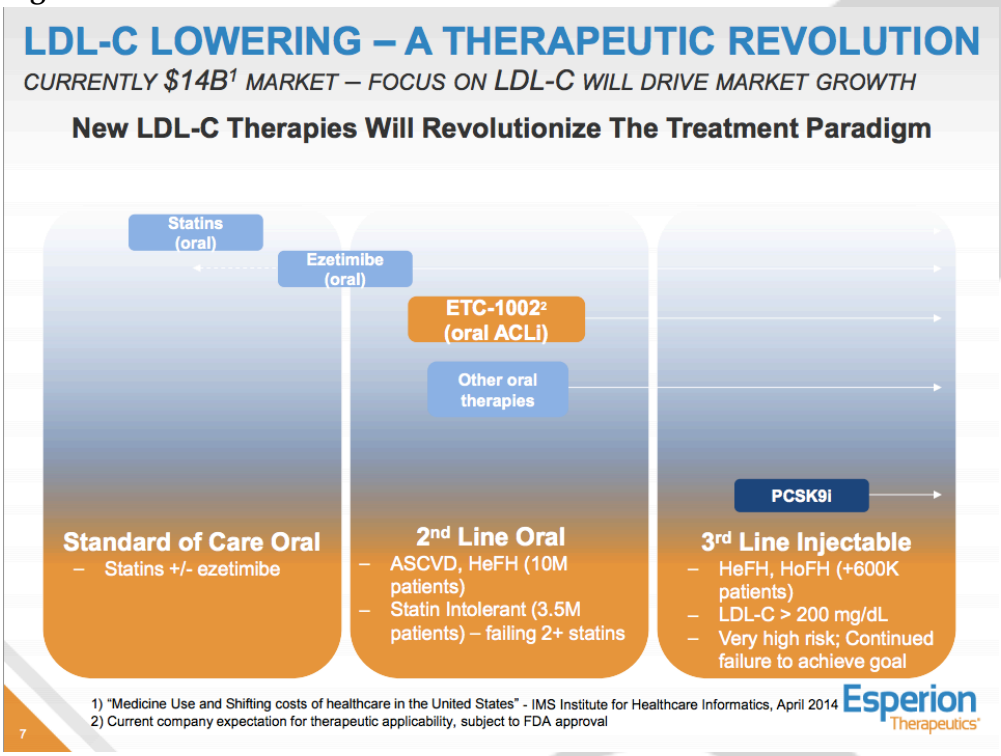
patients who had a CV event or genetically high cholesterol as well as those who cannot tolerate statins based on the high unmet medical need in the latter population. Esperion envisions 1002 serving a key role in the evolving treatment paradigm as a 2nd Line Oral therapy (Figure 4). Given a compelling "risk/benefit profile" for 1002 to date, the FDA is more likely to agree to a Phase 3 protocol that includes statin intolerant patients, which would expand the initial market opportunity for 1002 by an additional 30-50% (~12M-15M patients in the US) to include the 10% of the 35 million patients that cannot tolerate statins.

Figure 4



Statin Intolerance Made Equal

According to a June 2014 NLA expert panel, statin intolerance is presumably equally prevalent across statin intensities (see definition below). Given the fact that eighty percent of patients taking statins are on low-to-moderate dose should give the FDA comfort in accepting this patient population as part of a Phase 3 program based on the totality of safety and efficacy datasets from Esperion's Phase 2 studies to date.

> *Statin intolerance is a clinical syndrome characterized by the inability to tolerate at least 2 statins: one statin at the lowest starting daily dose (rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg,*

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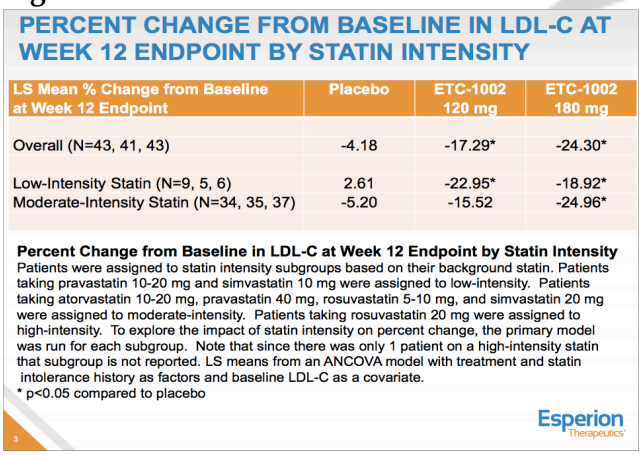
pravastatin 40 mg, fluvastatin 40 mg, and pitavastatin 2 mg) AND another statin at any daily dose, due to either objectionable symptoms (real or perceived) or abnormal lab determinations, which are temporally related to statin treatment and reversible upon statin discontinuation, but reproducible by rechallenge with other known determinants being excluded (such as hypothyroidism, interacting drugs, concurrent illnesses, significant changes in physical activity or exercise, and underlying muscle disease)

It is worth noting that 1002's opportunity within the statin intolerant treatment paradigm includes the possibility of even reducing statin doses. Given the dose-adjusting nature of physicians' practices as well as the polypharmacy approach to tackling other indications such as diabetes and hypertension, 1002 could very well play a pivotal role in reshaping the way statins have been commonly used over the past several decades; not to mention, the Statin Rule of Six which supports a significant safety benefit on top of LDL-C lowering.

Drug-drug interaction is not uncommon among drugs for cardiovascular patients. The Phase 2 study in combination with high dose statins set to start by year-end and report topline results in mid-2016 will be important in reaffirming 1002's safety as well as efficacy profile. The concern of an increase in plasma concentration of statins, however, ought to consider the effect's "transient" nature and its modest increase compared to other drugs as well as its lack of fluctuation. Bempedoic acid is also not metabolized by cytochrome enzymes (as in the case of most statins) that are well known to cause statin intolerance. Any questions around waning efficacy also ought to take comfort in the lack of change from baseline in LDL-C between low and moderate statin patients (Figure 5). Therefore, a successful readout would likely further convince the FDA of the "risk/benefit" proposition regarding 1002 based on positive results.

Figure 5



PERCENT CHANGE FROM BASELINE IN LDL-C AT WEEK 12 ENDPOINT BY STATIN INTENSITY

LS Mean % Change from Baseline at Week 12 Endpoint	Placebo	ETC-1002 120 mg	ETC-1002 180 mg
Overall (N=43, 41, 43)	-4.18	-17.29*	-24.30*
Low-Intensity Statin (N=9, 5, 6)	2.61	-22.95*	-18.92*
Moderate-Intensity Statin (N=34, 35, 37)	-5.20	-15.52	-24.96*

Percent Change from Baseline in LDL-C at Week 12 Endpoint by Statin Intensity
Patients were assigned to statin intensity subgroups based on their background statin. Patients taking pravastatin 10-20 mg and simvastatin 10 mg were assigned to low-intensity. Patients taking atorvastatin 10-20 mg, pravastatin 40 mg, rosuvastatin 5-10 mg, and simvastatin 20 mg were assigned to moderate-intensity. Patients taking rosuvastatin 20 mg were assigned to high-intensity. To explore the impact of statin intensity on percent change, the primary model was run for each subgroup. Note that since there was only 1 patient on a high-intensity statin that subgroup is not reported. LS means from an ANCOVA model with treatment and statin intolerance history as factors and baseline LDL-C as a covariate.
* p<0.05 compared to placebo

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Why Regulatory Uncertainty Shouldn't Impact Its Value Proposition

While the current overhang on the stock comes from greater regulatory rather than clinical uncertainty, the looming December AdCom as well as the agreed upon design of the Phase 3 program should be viewed with additional comfort given referenced comments from industry experts. Dr. Hiatt's Perspectives piece along with additional analyses from the NEJM strongly suggest an accelerated regulatory pathway and a potential initial label as a 2nd Line Oral therapy for 1002 in patients with HeFH and ASCVD as well as patients with statin intolerance.

- Bempedoic acid's well-elucidated statin-like mechanism, which up-regulates LDL-R (as well as down-regulates hsCRP), seemingly satisfies the FDA reviewers' contemporary view of the LDL hypothesis; they also approved PCSK9s without a completed CVOT on similar mechanistic merits

- A clean safety profile from a comprehensive Phase 2 dataset that is explained mechanistically by its specificity in the liver and kidney and not skeletal muscle as well as statistically significant efficacy looks to fulfill the FDA's criteria of a "risk/benefit" proposition in addressing a high unmet medical need

Expert commentary, therefore, suggests that 1002 finds itself in a competitively advantageous position heading into upcoming regulatory events. The AdCom will readdress the FDA's contemporary view of the LDL hypothesis while agreed upon design of the Phase 3 program will do much in determining the company's initial labeling fate. These regulatory outcomes could also influence ongoing partnership discussions with potential suitors. Though an expanded Phase 3 would likely require a larger trial (and possibly more money), the company's development strategy over the coming year allows for significant value-creation that would better prepare the company to leverage itself in partnership talks or to go-it alone.

The next six to twelve months offer an exciting chapter within the evolving cardiovascular space that will likely see Esperion flourish amidst regulatory support as well as confirming safety and efficacy data rather than languish amidst a puddle of ambiguous data and/or a more stringent regulatory pathway.

In light of the aforementioned clarifications, a quick-handed, risk-adjusted fair value assessment of $82 per share per our last note (Clarifying The Conversation Part II – Esperion Therapeutics) seems ever more modest. With a catalyst-rich calendar in 2016, we continue to view Esperion at current levels as one of the more attractive risk-reward opportunities in biotech today.

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APPENDIX

Event Catalysts & Share-price Inflection Points For Esperion

Product	Indication	Timing	Milestone	Significance
Bempedoic Acid (ETC-1002)	LDL-C Lowering	~~First half of August 2015~~	~~End of Phase 2 Meeting with FDA~~	~~High~~
		~~Mid/Late September 2015~~	~~FDA minutes on Phase 3 design~~	~~High~~
		~~November 7-11 2015~~	~~Publication on Phase 2 studies, MOA at AHA Sessions~~	~~Medium~~
		YE 2015	Initiation of Phase 2 study with high-dose statins (ETC-1002-035)	Medium
		YE 2015	Initiation of Phase 3 Long-term safety study (ETC-1002-040)	Medium
		1H 2016	File IND for FDC of ETC-1002+ezetimibe	Low-Medium
		Mid-2016	Topline data readout from Phase 2 '035 study	High
		Mid-2016	Initiation of Phase 3 programs in statin intolerant patients	Medium
		2H 2016	Initiation of CVOT study	Medium
		1H 2017	Topline Phase 3 Long-term safety data readout	High
~~Anacetrapib (Merck's CETP inhibitor)~~	~~HDL-C Raising~~	~~4Q 2015~~	~~Interim futility analysis of CVOT study~~	~~Low-Medium~~
Zetia (Merck)	LDL-C Lowering	December 14, 2015	AdComm meeting for IMPROVE-IT CVOT study	Medium-High
Repatha (Amgen's PCSK9)	LDL-C Lowering	2H 2016	Topline data from CVOT study	High
Praluent (REGN/SNY's PCSK9)	LDL-C Lowering	YE 2017	Topline data from CVOT study	High

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