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Opportunities Beyond GLP-1s

It seems like study after study of GLP-1 receptor agonists—GLP-1s for short—has reported they help address some terrible chronic condition. Especially in cardiac conditions, GLP-1 use has shown a notable 20% reduction in major cardiovascular events.[1] Muscle wasting aside, one might start to think these drugs are a silver bullet to all cardiometabolic diseases. But are they? That's where we begin today: examining indications that are not solved by the widespread use of GLP-1s, and opportunities for investment in the innovations being developed in those areas.

While GLP-1s may be an excellent preventative step against the many potential comorbidities that come with obesity, the data are starting to show that some subsets of patients are not responding optimally. Whether that is due to a genetic condition, another medication they may be taking, or any number of other reasons, the medical community continues to search for solutions for those patients. Examples include individuals with certain types of obesity, uncontrolled high cholesterol, and genetically driven conditions.

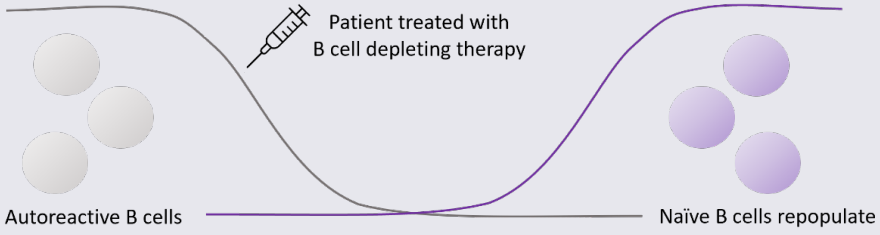
Obesity can be caused by medications intended to treat other conditions.

Wait, there are types of obesity that can't be addressed with a GLP-1?! Yes. One scenario is if a person is taking a medication that is weight-promoting, like steroids for the treatment of autoimmune disease. In the autoimmune disease lupus, which affects more than one million people in the US, the immune system begins attacking healthy tissues which can cause damage to the body over time. Corticosteroids are often used as a first-line treatment to quiet the immune system. This is because inflammation and pain are the primary symptoms and steroids are known to treat those conditions well. Well-known side effects of steroids are puffiness resulting from increased water retention and weight gain due to changes in metabolism. A study showed that 30% of women with lupus are obese,[2] highlighting the unmet need in medication-related obesity. Additionally, though GLP-1s might be effective for some patients, their use in lupus is limited by potential drug-drug interactions with lupus medications and the risk of side effects.

Innovation in the lupus space has been speeding up, with several targeted biologic medicines entering the clinic in the past year. Some of the most exciting data have been produced by cell products that deplete B cells, the immune cells thought to cause lupus in the first place.[3] Most impressively, patients participating in these clinical trials have been able to discontinue immunosuppressive therapies and there is early evidence that healthy B cells repopulate after the disease-causing cells are removed. This immune system reset could mean a potential cure for lupus patients, which would enable them to discontinue weight-gain-causing medications and regain a state of relative health.

From an investment standpoint, the opportunities in lupus have multiplied in the past two years with several smaller biotech companies initiating and collecting data in Phase 1 clinical trials.[4]

From an investment standpoint, the opportunities in lupus have multiplied in the past two years with several smaller biotech companies initiating and collecting data in Phase 1 clinical trials.[4] In addition to the cell product mentioned above, there are several earlier-stage candidates in development by other companies that deplete B cells via a different mechanism: using bispecific antibodies to signal T cells to munch up B cells to prevent them from wreaking havoc on the body. Other companies are taking yet another approach that seeks to quiet the immune system by reducing inflammatory signals before the B cells become overactivated in the first place. While these early-stage trials are tempting, with plenty of upside potential if successful, they are also the riskiest investments as there is little data available on which to base an investment thesis. Finding the eventual winners in this dense space will require patience, thoughtful scientific diligence, and a thorough understanding of what patients really need to improve the standard of care.

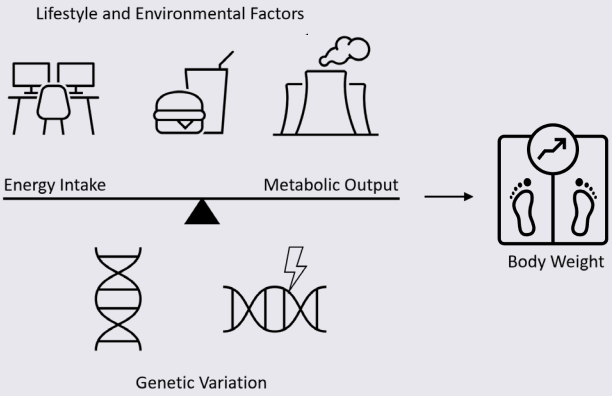


[3] See footnotes section for source information.

Genetic mutations can predispose someone to obesity via a pathway independent of GLP-1.

Over 500 obesity-related genes have been found in humans to date.[5] These genes can predispose someone to develop obesity by affecting appetite signaling and energy homeostasis. A person affected by genetic obesity might have one or several gene alterations and may manifest as obesity alone or obesity plus other conditions such as developmental delay or early onset of obesity. In addition to these genes, large genetic sequencing studies have identified genes that, if mutated, directly cause obesity.[5] While very rare, genetic obesity can be extremely difficult to treat, as these mutations inhibit the effectiveness of diet, exercise, medication (like GLP-1s), and even the long-term benefit of bariatric surgery. Because hyperphagia, more commonly known as overeating, is a key attribute of these genetic obesities, the most effective strategy historically has been food restriction. This tactic can be extremely taxing on both obese individuals and their caregivers.

For the most common genetic obesities, there is one medication available to help curb the urge to eat, thereby reducing weight. This drug approved for patients diagnosed with Bardet-Biedl syndrome or POMC, PCSK1, or LEPR mutations is setmelanotide. The molecule has some undesirable side effects. In particular, changes in skin pigmentation affect 78% of patients and are a major reason for patient discontinuation.[6] In another syndrome, Prader-Willi, which also features childhood obesity and hyperphagia, two medications are in late-stage development: pitolisant and diazoxide choline. Pitolisant is currently approved for excessive daytime sleepiness in narcolepsy and may cause insomnia, and the FDA approval date for diazoxide choline was recently delayed.

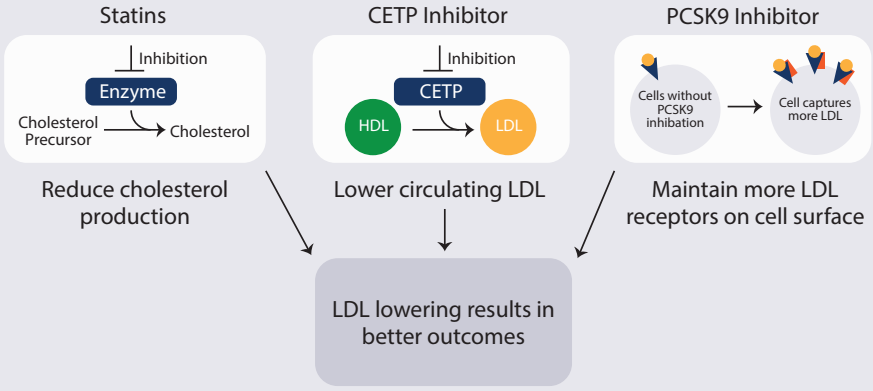


[7]See footnotes section for source information.

To evaluate investment opportunities in this space, it's critical to identify the pain points of current therapies: not only do GLP-1s have lower efficacy, but the one approved treatment for weight loss in the population can cause undesirable changes in skin pigmentation. Innovation in the space includes more specific molecules that avoid the off target binding that causes skin pigmentation changes and changes to formulation that allow for more convenient dosing (versus the current daily injection). In addition to these very targeted therapies, other molecules in development may have a pleiotropic effect, upregulating several gut peptides at once. Determining which of these approaches will provide the most benefit to patients and be used most broadly can help determine the best place to invest.

Uncontrolled high cholesterol requires more than high-dose statins and lifestyle changes.

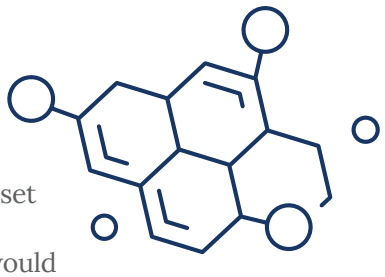
While there is certainly evidence that GLP-1s can normalize the lipid profile of the typical obese patient,[8] adding a GLP-1 may not help in patients whose lipids are off the charts despite maximally tolerated therapy. Chronically high cholesterol increases the risk of heart disease by causing fatty deposits to build in blood vessels, eventually constricting blood flow and forcing the heart to work harder to pump blood throughout the body. You might wonder how, in a space where there are so many good therapies, we don't have cholesterol under control at this point. One consideration is the number of people with high cholesterol (10% of adults in the US)[8] and while over half of the patients treated get their cholesterol under control, the other half need additional help. Some reasons for this are drug tolerability, compliance with dosing schedules, and genetic factors that lead to unusually stubborn high cholesterol. New drugs are being developed and combinations of new and old options are being tested for patients requiring extra help to lower cholesterol. Some of the most exciting innovations in this space are in oral drugs—oral PCSK9 and CETP inhibitors—that can be combined with the current standard of care.



[9] See footnotes section for source information.

PCSK9 is a protein that controls how cells bind to LDL, commonly known as bad cholesterol for its role in clogging arteries. By inhibiting PCSK9, the binding of LDL to cells in the liver to be degraded increases, lowering the amount of LDL in circulation. Existing PCSK9 inhibitors work very well to lower LDL cholesterol and prevent related cardiovascular events, but the therapy requires frequent injections; the drug needs refrigeration, making travel hard; and it can be prohibitively expensive. To solve this problem, a handful of companies are designing oral PCSK9 inhibitors that are stable at room temperature. While these early-stage molecules still need to generate more human data, early results look promising with an oral PCSK9 inhibitor showing 65% LDL reduction, comparable to injectable PCSK9 inhibitors.[10, 11] One oral PCSK9 asset is now in Phase 3 studies and should report data within the next year.

The second exciting mechanism of action in development, now in Phase 3 testing with additional data expected in 2026, is a cholesterylester transfer protein (CETP) inhibitor. CETP mediates the transfer of a

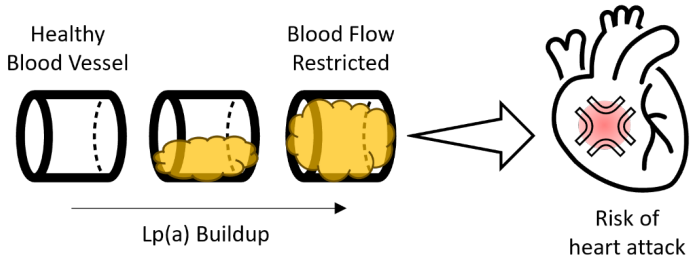


lipoprotein building block, cholesteryl esters, from HDL to make LDL, so inhibiting it increases the amount of HDL in circulation and decreases the amount of LDL. This asset is so interesting because it is the first in its class of drugs that has not had limiting toxicities.[12] Previous CETP inhibitors in development have shown some efficacy but would accumulate in fat tissue, leading to complicated food effects, or had off-target effects, such as elevating blood pressure. The most recent iteration of this approach seems to sidestep the previously observed safety signals while showing LDL lowering consistent with the class. As an oral molecule with no food effect or notable safety concerns, it could be added on top of the standard of care.

In an indication where patients have a high disease burden that requires numerous injections and daily pills, adding another high-maintenance (injections, refrigeration, food effects) drug is hard to justify. Further, with so many medications on board, the risk of drug-drug interactions increases. In this space, the form factor and safety of new medications is key, as doctors will seek to add to the standard of care versus transitioning patients off one drug and onto another, as might be done in other indications. Analyzing clinical trials for baseline patient severity is also crucial to contextualize results. If a more severe patient at baseline is harder to treat, for example, it's important to consider baseline characteristics when comparing across studies for drug efficacy. At the end of the day, such a large market as uncontrolled high cholesterol can likely support several late-line add-on therapies, but finding the handful of best options that will command the largest patient segments remains our goal as investors.

Elevated Lp(a) is a heritable type of dangerously high cholesterol that is difficult to treat.

L-P-little-A, say it with me. This is a type of lipoprotein, or small unit of LDL cholesterol, found in our blood. GLP-1s don't seem to affect it. In some with certain genetic differences (about 20% of people!),[13] Lp(a) is significantly higher than it needs to be. This elevation can lead to an increased risk of heart disease and stroke because Lp(a) is stickier than regular LDL and can cause clots more easily. Until recently, there were not many great therapies to treat elevated Lp(a) and it wasn't commonly tested for. That is now changing with several late-stage targeted therapies in development. Though PCSK9 inhibitors and CETP inhibitors, mentioned above, can reduce Lp(a) in addition to regular LDL, drugs specifically designed to target Lp(a) may be needed in patients with abnormally high levels. Several late-stage candidates are in development, showing varied reductions of Lp(a) across different modalities ranging from gene silencing to enzyme inhibition. It is interesting to note that candidates in development get as high as 97% reduction of Lp(a) while others are closer to 50%.[12, 13] You may wonder why all these competitors with less reduction don't just pack up and go home. While too much Lp(a) can increase the risk of heart attack or stroke, too little can increase the risk of diabetes. All that to say, some patients might need more Lp(a) reduction than others depending on their baseline levels, so several lowering strategies may have an eventual niche to fill in the market.



[14] See footnotes section for source information.

> When considering investing in this space, the educational component is just as important as the scientific one. While drug characteristics may determine how efficacious the drug is, education will be needed to convince doctors and patients to test for Lp(a) and then prescribe a treatment. Historically, testing has been uncommon due to the lack of Lp(a) lowering therapies. Educational efforts like this can require post-marketing studies, large advertising campaigns, and more time to get through to the patient population and their doctors. Therefore, the company that can develop the best molecule and launch the most effective educational campaign may be the likely leader in this space.

Our approach to investing in cardiometabolic indications in the face of GLP-1 therapies.

The impact of GLP-1 therapy is not yet fully understood by patients, doctors, or investors. In light of that, we believe there are opportunities to invest in areas of innovation where outflows resulting from GLP-1 news coverage may create value gaps. As each study of the already approved GLP-1s for weight loss (most widely used are Wegovy (semaglutide) and Zepbound (tirzepatide)) and the more recently developed next generation of GLP-1s and related molecules is reported, there will undoubtedly continue to be ripples in the market. By pursuing the fundamental research we've highlighted in this piece, we can tease apart indications where GLP-1s really do spell the end of a drug class versus where they may have a role to play as part of combination treatment therapy, and even where incretin therapies may be wholly ineffective. It's in these spaces, some of which are highlighted above, that we believe there will be opportunities to invest at valuations that do not reflect the value of the drug or cell candidate in development. In the past two years, it's been difficult to identify these indications because there was a lack of comprehensive data on how GLP-1s would be utilized. While that is still taking form, we have a better idea now than we did a year ago as to how this class of medications fits into modern medicine. Furthermore, companies working in this space range in market capitalizations, opening the door to acquisitions of smaller biotech companies by large pharma. In particular, larger players who are not investing in GLP-1s may look to bulk up their offerings in indications where they won't face GLP-1 competition. We're mindful that this landscape is always evolving and look forward to future studies that may reveal many more conditions that do not benefit from GLP-1 therapy than we realize today.

At Kennedy Capital Management, we approach investment outside of GLP-1s by identifying and investing in:

1 Differentiated assets:

We use scientific literature and company publications to compare various drugs that differ in their activity profiles and form factors. This allows us to target those that may be differentiated in safety, efficacy, or route of administration.

2 Potential acquisition targets:

Through our small-cap focus, we can evaluate and invest in the next generation of weight loss and lipid normalizing assets—potential acquisition targets for large pharmaceutical companies.

3 Logical development pipelines:

We assess all the assets in a company's pipeline to understand where synergies may be realized, with the goal of maximizing return on investment.

Please see footnotes on page 8 of this document.

In conclusion

While it would be wonderful for the world if a single pill could solve all medical concerns, it doesn't seem we've discovered the silver bullet just yet. We believe investigation into novel mechanisms to complement GLP-1s and to work where GLP-1s fail is likely to continue to present interesting investment opportunities going forward.

1. Source: Novo Integrated Sciences, Inc., *"8-K SEC Filing"*: https://www.sec.gov/ix?doc=/Archives/edgar/data/1138978/000149315225005923/form8-k.htm
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5. Source: International Journal of Molecular Sciences, *"Genetics of Obesity in Humans: A Clinical Review"* https://www.mdpi.com/1422-0067/23/19/11005
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10. Source: Journal of the American Health Association (AHA|ASA Journals), *"Relationship Between Low-Density Lipoprotein Cholesterol and Lipoprotein(a) Lowering in Response to PCSK9 Inhibition With Evolocumab"* https://www.ahajournals.org/doi/10.1161/JAHA.118.010932
11. Source: *"Oral PCSK9 inhibitor found to be safe, effective to lower cholesterol, in first human trial"* https://newsroom.heart.org/news/oral-pcsk9-inhibitor-found-to-be-safe-effective-to-lower-cholesterol-in-first-human-trial
12. Source: NewAmersterdam Pharma, *"January 2025 Corporate Presentation"* https://ir.newamsterdampharma.com/static-files/e391b584-1a46-45f2-9af8-dbd415d71516
13. Source: Harvard Health Publishing (Harvard Medical School), *"The latest on lipoprotein(a), an inherited cause of early heart disease"* https://www.health.harvard.edu/heart-health/the-latest-on-lipoprotein-a-an-inherited-cause-of-early-heart-disease
14. Source: FH Australasia Network, *"Lipoprotein(a)"* https://www.athero.org.au/fh/lipoproteina/

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