# Altimmune Inc. (ALT)

## *Fat Chance*

We are short shares of Altimmune Inc, a pharmaceutical company developing a GLP-1 agonist, hoping to field a drug that might grab a slice of the booming weight-loss market. In December, Altimmune reported that patients on 2.4mg/week of its pemvidutide lost 15.6% of their weight at the end of 48 weeks. Since that release, Altimmune's stock has more than tripled on the hopes that a big-pharma partnership, or even acquisition, will follow. But investors are in for a rude awakening: a deeper examination of Altimmune's data reveals a drug with little chance of competing against either the approved incumbents or the other GLP-1 agonists progressing through clinical trials. We don't think legitimate prospective partners want to spend hundreds of millions of dollars and years of trials pursuing an obvious dead end.

Even if pemvidutide *did* result in 15.6% weight-loss, that's not good enough. Both semaglutide and tirzepatide (Ozempic and Mounjaro) have demonstrated superior weight-loss on a comparable basis, with the added benefit of controlling blood-sugar (which pemvidutide does not). Given the mountain of clinical studies and physician experience with these two drugs, that alone would be enough to dash the pemvidutide hope. But it gets worse: pemvidutide's tolerability is atrocious. Despite conducting a trial that offered free and unfettered weight-loss medication amidst the Ozempic social frenzy, a third of pemvidutide trial participants – and 42% of patients taking the 2.4mg dose – discontinued treatment. That bodes ill for the drug's commercial prospects, but it also has dire implications for the drug's looming phase-3 trial. The FDA requires phase-3 weight-loss results to *include patients who discontinue treatment*. For semaglutide and tirzepatide, the 15% of patients who stopped the drug in phase-3 impacted the headline weight-loss result by about 2%. If pemvidutide trial participants discontinue at the rate they did in phase-2 – and we see no reason why they won't – that 15.6% will end up closer to a 10% headline weight-loss number. At that level of effectiveness, the drug is toast.

Meanwhile, the pharmaceutical industry has dramatically geared up its R&D effort. Over two dozen weight-loss drugs are in the pipeline, including oral formulations of the currently approved drugs as well as novel multi-mechanism compounds that have demonstrated unique characteristics such as better tolerability, improved weight-loss durability, and substantially greater weight-loss. The drugs are being developed by large pharmaceuticals with the vision and capital necessary to secure a piece of the highly competitive market. Against them, Altimmune's inferior compound stands no chance.

The company is headed by CEO Vipin Garg, who spent two decades raising $500 million for two small-cap biotech companies that ran into the ground under his watch before coming to Altimmune and exploiting the COVID pandemic to raise $200 million in equity under the guise of a vaccine program that never made it out of phase-1. Joining him in the C-suite are CFO Rich Eisenstadt, who's been with Garg at his two prior failures, and CMO Scott Harris, who has an entertainingly checkered past raising capital for drugs that already failed. The odds of this crew getting an edge over Novo Nordisk or Eli Lilly – with an inferior and intolerable drug – are slim.

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# I. Investment Highlights

**Pemvidutide is less effective than current GLP-1 drugs and its headline weight-loss figure is suspect.** On the metric that everyone really cares about – weight-loss – pemvidutide is inferior to semaglutide and tirzepatide, the two approved weight-loss drugs known as Wegovy and Zepbound (or Ozempic and Mounjaro when used for diabetes). In the phase-2 data that provoked the recent tripling of Altimmune's stock price, patients on pemvidutide's highest dose lost 15.6% of their bodyweight, or 13.4% more than placebo, at the 48-week mark. That's about the same as semaglutide-2.4mg and much less than the 17-18% weight-loss induced by the 10mg and 15mg doses of tirzepatide, also at 48 weeks. That comparison actually understates the superiority of semaglutide and tirzepatide, which had patients slowly titrate up to the treatment dose over 3-4 months instead of the 4 weeks in the pemvidutide trial. Further, those already-approved drugs also control blood-sugar (which pemvidutide does not) and have massive libraries of clinical studies as well as countless physician experiences that support their everyday use. Pemvidutide has no chance of competing with them if the best it could do is equal their weight-loss result.

We also think that weight-loss result is questionable and won't hold up in a large phase-3 trial. Over the course of 4 trials and 6 data readouts, the 48-week 15.6% result is *the only time* that pemvidutide's 2.4mg dose demonstrated any statistical superiority to its 1.8mg dose, and even in this phase-2 trial, that superiority only crystallized at the 32-week mark. That fact pattern is strange in light of what we know about the dose-response curves of other GLP-1 drugs and how they evolve over time. We believe that the 15.6% result was partly a statistical fluke and that in a large phase-3 trial, the weight-loss effectiveness of pemvidutide-2.4mg will be much closer to the 1.8mg experience and lower than 15.6%.

**Pemvidutide's phase-2 tolerability profile was graded on a curve and it was still awful.** Altimmune ran its pemvidutide phase-2 trial from mid-2022 to late-2023. By this time, Ozempic and Mounjaro had become household names, Hollywood stars were rumored to be using the drugs for weight-loss, and social media influencers were flaunting weight-loss results. At the same time, manufacturing issues at Novo Nordisk created a shortage of semaglutide, and neither semaglutide nor tirzepatide – which cost over $1000/month out-of-pocket – were covered by insurers or Medicare for weight loss (coverage is still spotty as of this writing). In that context, the pemvidutide trial was an opportunity for interested patients to get unfettered access to perhaps the hottest pharmaceutical product in history for free. Participants *knew* that there were likely to be GI side-effects like nausea, diarrhea, and vomiting, because these side-effects were well-known. And yet, across the different pemvidutide dose-arms *36% of trial participants discontinued their use of the drug*. In the 2.4mg cohort, the one that resulted in 15.6% weight-loss at 48 weeks, *42% of participants discontinued the drug* (which makes that statistical fluke more likely). The equivalent numbers for semaglutide and tirzepatide are in the 15-17% range. It's hard not to conclude that pemvidutide is uniquely intolerable.

Altimmune's management has tried to frame this intolerability in as pleasant a light as possible, even claiming that similar levels of trial discontinuation were seen in the semaglutide and

tirzepatide phase-2s. We review these claims at great length in this report and completely dismantle them, showing how patient compliance rates in every relevant semaglutide and tirzepatide trial – both those from phase-2 and phase-3 – refute Altimmune's claims. At best, Altimmune's management is cherry-picking statistics. Other times, they're simply making claims that are factually untrue. A drug with the compliance rate that pemvidutide displayed in its phase-2 trial – especially given the insatiable and pervasive demand for weight-loss drugs during the trial period – has *zero* chance of physician or patient buy-in.

**The awful tolerability profile of pemvidutide will make headline weight-loss results of a phase-3 trial look like a disaster.** The FDA requires headline phase-3 weight-loss results to be reported in the form of a "treatment effect," i.e., *inclusive of patients who discontinued treatment during the trial*. This is how both Novo and Lilly reported their phase-2 and phase-3 results for semaglutide and tirzepatide, respectively. Altimmune…did not do that. Instead, the only result reported for pemvidutide was the "hypothetical effect," which uses statistical techniques to estimate hypothetical trial results had no patients discontinued treatment. This is allowed for phase-2, but a) it's aggressive not to report the treatment effect and b) they won't be able to pull that off for their phase-3 trial, because it goes against the FDA's guidance.

The FDA does allow for reporting both sets of results – the treatment effect *and* the hypothetical effect. Both Novo and Lilly did this for the phase-3 results of semaglutide and tirzepatide, and the difference between the two reporting methodologies was about 2% (e.g., semaglutide would have resulted in a *hypothetical* 16.9% weight loss if all participants remained on the drug the entire trial, but actual headline weight-loss was 14.9% because in reality about 17% of participants discontinued and they didn't lose as much weight). Why didn't Altimmune also report both sets of results? Well, a 42% discontinuation rate will result in a *massive* gap between the real-world treatment effect (which Altimmune will have to report for phase-3) and the hypothetical effect. We estimate that a discontinuation rate of about 40% would result in a gap of 4.5-5.5% between the two results, which means that the "real" headline weight-loss result in Altimmune's pemvidutide phase-2 was probably in the 10-11% range rather than the 15.6% reported. That kind of result in a phase-3 is likely to completely tank the company.

**The GLP-1 space is currently undergoing a Cambrian explosion of new drugs, and pemvidutide has no chance of competing successfully.** There are close to two dozen GLP-1 drugs currently being studied by a host of different pharmaceutical companies in various stages of development. Novo and Lilly are advancing oral formulations of semaglutide and tirzepatide. Both Novo and Lilly are also advancing new next-generation injectable compounds – CagriSema and retatrutide, respectively – that further target additional metabolic hormones and that have already been shown to result in more weight loss and better glycemic control than their current offering. There are also new mechanisms from Roche, Amgen, and Boehringer-Ingelheim as well as new takes on basic GLP-1 agonism from Sciwind and Sun Pharma. We discuss many of these molecules in greater detail, but it's notable that every single one results in more weight loss than pemvidutide, most of them also control blood-sugar well, and the majority of them are ahead of pemvidutide in their development trajectory as pemvidutide hasn't even begun a phase-3 yet. They're also all sponsored by serious pharmaceutical companies

with the financial capital and clinical talent needed to bring these programs past the finish line. Altimmune? Not so much.

**Altimmune's management team has a long history of raising capital for pharmaceutical train wrecks.** Prior to Vipin Garg's appointment as Altimmune's CEO, he had two stints as a pharmaceutical CEO. At Tranzyme, Garg successfully took the company public and raised over $200 million in capital over more than a decade, including well-timed offerings that were rapidly followed by trial failures. His tenure there ended with Tranzyme sold into a reverse merger at a valuation of $3 million. Then at Neos, Garg also took the company public and raised over $250 million in capital only to fail at commercializing the drug he was brought in to shepherd. After rejecting a generous unsolicited takeover offer and overseeing a 60% decline in the company's stock price after its IPO, Garg was forced to resign. Now at Altimmune, Garg is joined by CFO Rich Eisenstadt, who accompanied Garg in both of those previous busts, and CMO Scott Harris, who also oversaw the clinical trials that hit the wall at Tranzyme. Harris also has the notorious distinction of having cheaply acquired the rights to the drug whose clinical trial failure he helped oversee and then raise $20 million for a "stealth" biotech startup that spent 5 years re-studying it before quietly shutting down. Not everyone can claim they pulled one over on Dan Loeb's venture firm, but Harris can.

The gang has already comported itself disgracefully at Altimmune in an episode that may be forgotten but telling. Garg and company exploited the pandemic and Altimmune's failed track record in vaccinology to loudly tout the development of a COVID-19 intranasal vaccine that never got past a phase-1 trial. The program was shut down by mid-2021, but not before Altimmune took advantage of the continuous vaccine press releases and raised about $225 million in multiple offerings during the pandemic's peak period. Altimmune has about $135 million left on a shelf registration from last year that current shareholders should keep in mind. If this management team's track record is any indication, a successful equity offering and the failure of pemvidutide will look uncomfortably familiar.

## II. The Pemvidutide Context

**Altimmune Inc: Capitalization and Financial Results**

| Capitalization | |
|---|---|
| Share price ($) | $ 10.40 |
| Fully diluted shares (mm): | |
| Shares outstanding | 52.9 |
| Dilutive impact of Warrants | 1.0 |
| Dilutive impact of Options | 0.5 |
| Restricted Stock | 0.6 |
| Total | 55.0 |
| Fully diluted market cap (mm) | $ 572 |
| Less: net cash | 87 |
| Enterprise value | $ 485 |

| Financial Results | 2021 | 2022 | TTM |
|---|---|---|---|
| Revenue | 4 | (0) | 0 |
| Operating Income | **$ (97)** | **$ (88)** | **$ (85)** |
| Free Cash Flow | **$ (90)** | **$ (63)** | **$ (77)** |

*Source: company filings, Kerrisdale analysis*

If you haven't been living under a rock over the last 18 months, then you're at least mildly familiar with the brand names of GLP-1 receptor agonists – Ozempic, Wegovy, Mounjaro, and most recently Zepbound. You may even remember the earlier generation of these drugs, which included Victoza, Saxenda, and Trulicity among others. Altimmune's pemvidutide also belongs to this general class of drugs, so a little background is in order.

GLP-1 is short for glucagon-like-peptide-1, which confusingly does not have much to do with glucagon.[1] GLP-1 is secreted in the intestines upon the ingestion of food, and its job is primarily to signal for an increase in insulin secretion, thereby reducing blood-sugar. It also slows down secretion of glucagon by the pancreas (we'll get to glucagon in a bit) and, interestingly enough, is active in the brain promoting satiety and affecting the brain-cell lifecycle. In its natural form, GLP-1 breaks down rapidly, with a half-life of 2 minutes. It's really important to note upfront that while we know it decreases blood sugar and makes you feel full in response to eating, *the extent of GLP-1's activity and effects are not completely understood*.

Enter "GLP-1 receptor agonists," (or "GLP-1s" for the sake of brevity) which is a fancy name for manufactured molecules that activate the same receptors as GLP-1, with the same effect. The first of these to be used as medication was injectable exenatide – brand name Byetta – which was approved by the FDA in 2005 for use in patients with type-2 diabetes (T2D) that wasn't being sufficiently controlled through other oral medications typically taken by diabetics. The primary mechanism of action being stressed was the multiple effects on blood sugar (more insulin, less glucagon, slower stomach emptying), which is a major aim in treating diabetics.

[1] GLP-1's predecessor molecule – proglucagon – can be broken down into both GLP-1 and glucagon, as well as several other hormones.

The next major advance in GLP-1s was liraglutide (brand name Victoza and Saxenda), a daily injectable manufactured by Novo Nordisk, which was approved for diabetes in 2010 and, after studies elucidating the effect on weight-loss clarified the potential of the drug to ameliorate obesity, for weight-loss in 2014. Just to put some numbers around the efficacy of liraglutide, the LEAD series of clinical trials showed that the drug reduced hemoglobin A1C – a measure of average blood sugar level over the prior 3 months – by 1-1.5% in diabetics (over 6.5% is a fairly standard criterion of a diabetes diagnosis). The SCALE series of clinical trials showed that at a dose higher than that given to diabetics, liraglutide resulted in about 8% weight loss in obese non-diabetics and a bit less than that in obese diabetics.

Liraglutide had a half life of 13 hours – much longer than the 2 minutes of endogenously produced GLP-1 – but still required to inject daily. Novo improved on the liraglutide formulation with semaglutide – brand name Ozempic – which was first approved for treatment of diabetes in December of 2017. Semaglutide was a more potent GLP-1 agonist and resulted in greater decreases in HbA1C and more weight-loss than liraglutide. It was also designed to have a longer half-life – 7 days – and would only have to be injected weekly. As with liraglutide, a phase-2 trial was run to study the effect of semaglutide on obese non-diabetic patients (including prediabetics, commonly defined as those with an HbA1C of 5.7-6.4%) and the results were alluring: over about a year, the higher doses of semaglutide (0.3mg and 0.4mg daily, or the equivalent of 2.1mg and 2.8mg weekly, respectively) led to weight-loss of 12.5-17.5%.

In June of 2020, Novo Nordisk announced the results of its massive phase-3 STEP-1 trial, in which a 2.4mg weekly dose of semaglutide was administered to non-diabetic patients with the express purpose of treating obesity. People treated with semaglutide lost an average of 14.9% of their bodyweight, 12.5% more than placebo. In retrospect, the STEP-1 trial ushered in the era of GLP-1 agonists as drugs aimed mainly at obesity/weight-loss rather than merely diabetes drugs with a weight-loss component. In December of 2020, Novo filed with the FDA for approval of semaglutide for weight loss management, and the FDA approved the application in June of 2021 under the brand name Wegovy.

Contemporaneous with the GLP-1 agonist programs at Novo Nordisk, Eli Lilly was working on a GLP-1 agonist with a twist. Its lead drug, tirzepatide, didn't just target GLP-1 receptors but *also* GIP receptors. Like GLP-1, GIP – glucose-dependent insulinotropic polypeptide – is a hormone that stimulates insulin secretion and interacts with the nervous system and brain, regulating hunger and satiety. Unlike GLP-1, it stimulates glucagon secretion rather than inhibiting it. A phase-2 trial of tirzepatide showed that it was more potent than the other GLP-1s commonly used at the time (mid-2017), and seemingly even more effective than semaglutide at both glycemic control and weight-loss. Tirzepatide was approved by the FDA for treatment of diabetes in May of 2022 under the brand name Mounjaro, and for the treatment of obesity this past November under the brand name Zepbound.

Both semaglutide and tirzepatide have now undergone an enormous amount of clinical testing and rigorous study. Semaglutide underwent both the SUSTAIN and STEP series of trials, studying semaglutide in the treatment of diabetes and obesity, respectively. The equivalent pair

of series for tirzepatide is the SURPASS and SURMOUNT trials. In all, there have been dozens of trials studying the effects of these drugs in tens of thousands of patients.

As a result, the drawbacks and side-effects of GLP-1s are well-documented: gastrointestinal discomfort, including nausea, diarrhea, vomiting, and constipation are extremely common, and often debilitating enough to the point of inducing discontinuation (attrition in liraglutide clinical trials was 20-25% and for semaglutide and tirzepatide a lower but still notable 10-15%). There are also rarer but more severe side effects including gallbladder disorders, pancreatitis, and – extremely rarely – cancerous neoplasms. To minimize the GI side effects, the common practice has been that for higher doses of the GLP-1s, patients are usually titrated up to the target dose over the course of a few months, and if a patient can't tolerate the target dose, the dose is reduced to the point it's tolerated. While several phase-2 trials seem to suggest that the pace of dose escalation doesn't have much of an impact on tolerability, the practice has continued regardless, and almost all phase-3 trials in the space use a dose-escalation period to get patients to the targeted dose, believing this will reduce patient attrition.

A positive surprise in the course of all the clinical testing has been that both semaglutide and tirzepatide improve cardiovascular (CV) health by controlling blood sugar (obviously), reducing cholesterol and triglycerides, and lowering blood pressure. *These benefits have not been tightly correlated with the weight-loss effect*, and the CV benefits of tirzepatide seem to be just a tad more impressive than semaglutide. Novo has in fact been studying the CV effects of semaglutide and recently published a study that showed that semaglutide reduced the incidence of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke in trial participants. Why exactly these effects materialize somewhat independently of weight-loss is, like many other facets of the GLP-1 drugs, not very well-understood. There are many cellular pathways in different organ systems that are affected by these drugs, and empirically proven results speak much louder than theorized effects.

According to the dozens of physicians with whom we spoke, that's partly why the existence of a copious and robust clinical-research foundation delineating the real-life statistically validated experience of tens of thousands of patients is a major factor in the readiness to prescribe these drugs. This is especially the case considering that physicians almost unanimously expect these drugs to be taken *forever* by their patients. It's also why semaglutide retains an advantage over tirzepatide despite the latter's seeming superiority – semaglutide's longer track record and more robust and rigorously-investigated positive CV impact play a significant role in physician preference (of course, payor contracts and formularies also play a role, but those too are often a function of both clinical track record and price).

These advantages – physician experience and the breadth and depth of supportive clinical studies – are important because they set a high bar for prescribing anything other than semaglutide and tirzepatide. The skyrocketing popularity of these drugs – propelled by celebrity use, social media buzz, and the cumulative impact of hard-to-dismiss physical transformations – has led to almost a tripling of weekly semaglutide prescriptions since early 2002, and a rapid ramp of tirzepatide's sales since its mid-2022 approval. These drugs' success has fired up the R&D machine of the entire pharmaceutical sector and at this moment there are over two dozen

next-generation weight-loss drugs with a GLP-1 backbone in the clinical trial pipeline in various phases. Altimmune's pemvidutide is one of them.

## III. The promotional clown car that thinks it's in a gold mine

Altimmune finds itself in the hottest pharmaceutical arena in recent history by accident. The current public configuration of the company is the result of a reverse merger in May of 2017 with publicly traded PharmAthene. The latter had just successfully concluded a decade-long $200 million intellectual property battle, and after remitting the winnings to shareholders, what remained was a publicly traded shell (technically a money-losing former SPAC aimed at exploiting the post-9/11 obsession with anthrax vaccination which by 2017 was no longer a viable "business model"). The shell merged with privately held Altimmune resulting in a public company that was then focused on developing a nasal flu-vaccine and a Hepatitis B vaccine (the latter of which is still theoretically in the pipeline 7 years later).

This was 20 years after Altimmune was initially founded, in December of 1997, as Vaxin Pharmaceuticals, one of two companies started by Birmingham, Alabama-based Emerging Technology Partners (ETP). ETP was a public-private partnership designed to invest in commercially viable ideas coming out of the University of Alabama. Vaxin was developing "DNA-based vaccines which would dispense with hypodermic needles" while Tranzyme, the other company started by ETP, was commercializing "discoveries that will enhance the diagnosis and treatment of HIV patients." The boards of Vaxin and Tranzyme were naturally similar, and the C-suite at Altimmune today is filled with former Tranzyme executives, recruited by board members with whom they once worked, so their experience at Tranzyme is worth recounting.

ETP's investments were eventually moved into a VC fund managed by Redmont Venture Partners, who recruited David Drutz as Tranzyme's chairman in 1999 and Vipin Garg as its CEO in late 2000. For 5 years Tranzyme staggered from one futuristic concept to another (including "gene delivery," "cellomics," HIV vaccines, and "neurosensory system diseases"). By 2005, it was "developing GI-focused products in various stages of development" including a ghrelin agonist that would eventually be named ulimorelin. Tranzyme reported positive phase-2 results for the drug in 2007 and then raised a $20 million investment round for the purpose of running a phase-3 trial that simply never happened. 4 years later, Garg successfully took Tranzyme public, raising $55 million, again for the purpose of running that phase-3 trial, two of which were actually conducted this time. In early 2012, with multiple trial readouts looming and "expecting to file the NDA for our IV drug, ulimorelin, during Q4 2012" Tranzyme raised $9 million in debt to "extend our cash runway into Q4 2013." A month later Tranzyme announced the failure of ulimorelin in one phase-3 trial, followed by another phase-3 failure a few months after that. That didn't stop Garg from raising more capital on the prospects of the same drug successfully being approved in its oral form for a similar indication. After saying it didn't need any money through the end of 2013, Tranzyme raised $11 million in a registered direct offering

in September of 2012. Two months later, the oral formulation failed a preliminary phase-2 trial, and a month after that Tranzyme terminated the final phase-2 trial as interim results bombed.

By the end of 2012, Tranzyme's stock price had fallen to $0.54 from an IPO price of $4.00 and a high of $5.50 earlier in the year. In April of 2013, Tranzyme was acquired by Ocera Theraputics in a reverse merger struck at $0.12/share, with Tranzyme shareholders retaining about a quarter ownership in the combined company. Garg resigned with the merger's completion.

We bring up the Tranzyme story because if you look at the way Garg's bio is presented (either by Altimmune on its webpage or proxy, or on LinkedIn), you would never know he spent 5 years at Tranzyme jumping between failing projects before investing 7 years on an indication that spectacularly crashed and burned. Garg's LinkedIn profile brags that he secured over $200 million in financing including venture equity, venture debt, the IPO, and the $20 million in financing obtained post-IPO. He talks about negotiating a $50 million upfront deal with BMY and $500 million in potential milestone payments when the press release from Tranzyme indicate that he's inflating those numbers by 5x. Finally, Garg boasts that he "led a strategic review process that resulted in a successful merger with Ocera," which you'd never know came at a valuation of about $3 million *after* a stock price decline of 97% from the IPO and 4 failed clinical trials over the span of a few months. That's "over $200 million in financing" incinerated.

The salience of the Tranzyme story is that in the world of biotech corporate finance, Garg's tenure at Tranzyme was a *success*, which is measured in investment rounds and capital raised, not in treating disease. A few months after his resignation from Tranzyme, Garg was hired as CEO of Neos Therapeutics. Here too, Garg raised over $250 million, including a successful $72 million 2015 IPO. His time at Neos was marked by an FDA deficiency letter that came just a few months after the IPO, a rejection of an unsolicited takeover offer at a 40% premium to Neos's $7 stock price at the time, a failure to generate any sales momentum on the drug Neos was able to get approved, and an ignominious resignation in mid-2018, at which point the stock price was $6.20, down 60% in less than 3 years from the $15 IPO. Neos's corpse was eventually sold to Aytu for $1.15/share. Garg again floundered operationally, but he did successfully raise capital.

All of which explains why Garg was tapped by Altimmune's board at the end of 2018 to take the CEO position. Altimmune's board was controlled by the same directors that had founded Altimmune and Tranzyme 20 years earlier. The board was even chaired by the same David Drutz who had recruited Garg to be the CEO of Tranzyme in 2000. They had worked with Garg earlier and Garg was good at raising capital. Indeed, Altimmune has sold over 20 million shares and raised over $300 million since Garg took the reigns as CEO. How was such a successful capital-raising streak achieved? In a word, COVID.

On February 28, 2020, with a market cap of $26 million, Altimmune announced "the advancement of a novel single-dose, intranasal vaccine using Altimmune's proprietary technology to protect against COVID-19." Up to that point, Altimmune had a failing intranasal vaccine program, which suddenly became incredibly convenient in the context of the pandemic. The stock rose over 100% on that news, which Altimmune exploited in the next month by registering its 2020 ATM under which it sold close to $50 million in stock. The rest of 2020 was

filled with Covid press releases including the launch of a clinical trial for an intranasal "early COVID-19" therapy, the commencement of preclinical testing for a COVID-19 vaccine, and on July 13th, "Positive Preclinical Results for Intranasal COVID-19 Vaccine Candidate." With its stock closing at $25 – up from $1.76 on February 27th – Altimmune announced a secondary offering, selling $132 million of stock. On the day before Christmas Eve, after the market-close, Altimmune announced that its vaccine application was subject to a clinical hold by the FDA. By then, Altimmune had already taken advantage of the COVID hype to raise about $180 million, or close to seven times what the entire company was worth before the pandemic hit. In February of 2021, Altimmune announced FDA clearance for its application for a COVID vaccine, upon which Altimmune registered another ATM equity offering just a week later, raising another $35 million through the end of the quarter, and $18 million in the quarter after that. On June 29th, Altimmune announced that its vaccine did not stimulate an adequate immune response in the phase-1 trial and the clinical program would be discontinued. Disappointing perhaps, but after $225 million in capital raised, it wasn't completely unproductive. Notably, Altimmune registered another $150 million ATM offering in February of 2023 under which only $15 million of stock has been sold so far.

That Garg has a long and successful track record of raising almost $750 million in equity capital for a long line of clinical and commercial failures should concern current shareholders. That the current CFO, Rich Eisenstadt, worked with Garg at Tranzyme and Neos, should heighten that concern. If that weren't enough, Altimmune's Chief Medical Officer, Scott Harris, was also present at the Tranzyme bust as interim CMO running the failed clinical trials. Harris actually deserves special mention for his escapade after Tranzyme's ulimorelin failed multiple trials. In 2014, after Tranzyme had already been subsumed by Ocera in a merger that Harris claims he facilitated, he co-founded Lyric Pharmaceuticals and raised $20 million in funding. Lyric "in-licensed its initial development candidate in September of 2014" but was kept in stealth mode, only revealing that its development candidate was for a gastrointestinal indication. After almost 3 years in stealth mode, Lyric announced in early 2018 that the FDA granted it fast-track status for its lead product…ulimorelin! The same compound that failed at Tranzyme. Unbelievably, the trial was being run for almost the same indication for which Tranzyme had run the trial. Not shockingly, the Lyric trial went nowhere and Lyric ceased to exist by the end of 2018. But not before Harris raised $20 million from prominent investors like Dan Loeb's Third Point for a secret project that turned out to be a drug that had already failed spectacularly *in a clinical trial that he helped run as CMO at Tranzyme*![2] A funny footnote to this episode is that Ocera actually disclosed in its 2014 third quarter 10-Q that it sold the rights to ulimorelin to Lyric for $200 thousand plus potential milestone payments of up to $25 million. So Harris was running a stealth-mode biotech startup whose drug candidate could easily be discovered with a quick search on the SEC's EDGAR database.

[2] We suppose it's possible that Harris thought the trial run by Tranzyme was flawed and that he'd be able to get the drug across the finish line himself, but that would raise questions about breaching fiduciary duty while an officer at Tranzyme.

The management trio at Altimmune has a 20-year track record of very successfully selling stock while very unsuccessfully running actual pharmaceutical businesses. We expect the pemvidutide saga will end the same way.

That saga begins with the July 2019 acquisition of Spitfire Pharma, a privately held preclinical pharmaceutical company with a single drug in its pipeline – a dual GLP-1/glucagon agonist "designed to treat the metabolic dysfunction that causes non-alcoholic steatohepatitis [NASH]." The GLP-1 class of drugs, with its positive effects on blood sugar and weight, had by then been well-established as a treatment modality for type-2 diabetes. Liraglutide was also approved to treat obesity qua obesity, but it wasn't commonly used for that indication. The Spitfire drug was a dual-agonist like tirzepatide but combined GLP-1 agonism with glucagon agonism rather than GIP. The theory for adding glucagon to GLP-1 was that it would help target liver fat more specifically (through lipolysis) than the indirect effect from GLP-1 agonism, making it a natural choice for targeting NASH. At the same time, the tendency for glucagon to increase blood-sugar would be softened by the GLP-1 effect.

Just as GLP-1 drugs were targeting type-2 diabetes through weight loss and glycemic control, Altimmune was hoping to target NASH through weight loss and a glucagon boost that would target the liver. This was articulated in the presentation that accompanied the acquisition, in which Altimmune explained that "substantial weight loss can reverse NASH progression." The word "obesity" wasn't mentioned a single time in either the acquisition presentation or in the conference call discussing the acquisition. The goal was to treat NASH, and weight loss was the most effective way to do it. Altimmune boasted that in studies done on mice, the drug it was acquiring led to more weight loss and more liver fat reduction than semaglutide, which was then the most potent GLP-1 and also being studied as a NASH treatment. Altimmune clearly thought the drug it acquired could be uniquely effective in enabling patients to lose enough weight to make a material dent in their advanced fatty liver disease.

By the time Altimmune's phase-1 trial for pemvidutide for the treatment of NASH was under way, Novo Nordisk had announced its STEP 1 results and filed with the FDA for approval of semaglutide for weight loss management. Interim results of the pemvidutide phase-1 were announced by Altimmune just two weeks after the semaglutide approval, and they *seemed* tantalizing: in just six weeks on 1.8mg/week of pemvidutide, study participants achieved 5.4% weight loss compared to a weight *gain* of 0.9% in the placebo group, for a **net difference of 6.3% from placebo**. By comparison, participants in the STEP 1 semaglutide trial lost just 2% more weight than placebo at the same 6-week interval[3] and 12.4% more than placebo after *68 weeks*. Moreover, Altimmune reported that the drug was "well-tolerated without dose titration" in contrast to semaglutide and every other GLP-1 agonist, which all came with GI side-effects even *with* titration. Participants on pemvidutide meanwhile had "no reports of vomiting, diarrhea or constipation."

There were *some* hints that maybe the data wasn't as good as it looked – the average age of trial participants was under 30 (much lower than either the likely target patient or the STEP 1

[3] Not exactly comparable due to lower doses being used in the first 16 weeks of the trial.

average participant age of 46) and there was no readout of liver fat reduction because there weren't enough participants with fatty liver recruited (in opposition to the initial trial protocol). But a drug that a) resulted in more weight loss than semaglutide, b) had no tolerability issues, and c) didn't need titration was a potential breakthrough in the GLP-1 space. An excited sell side note instantly labeled pemvidutide the "best-in-class GLP1/Glucagon agonist of all," and Altimmune announced it would file an investigational new drug (IND) application for pemvidutide in obesity in addition to the IND already filed in NASH. The data was also seen by some on the sell side as opening the door to a partnership with a tier-1 pharmaceutical company, or even an acquisition.

What began as a long shot attempt at treating NASH through weight loss had morphed into a drug aimed mainly at just weight loss. And while pemvidutide was never going to challenge the GLP-1s in diabetes (given the glucagon impact on blood sugar), the idea was that it could potentially lead the market as an obesity medication given both its efficacy and seemingly clean side-effect profile (though in mid-2021 it wasn't yet known that obesity-related GLP-1 usage would soon take off explosively). Unfortunately for Altimmune shareholders, it turns out that the phase-1 results in 9 participants just didn't hold up. A close look at the data Altimmune has released since June of 2021 reveals that pemvidutide is not remotely the best way to treat obesity, that its tolerability profile is horrible, and that a treatment protocol with no titration is a pipe dream.

## IV. Pemvidutide is just a poor GLP-1 agonist that, if approved, will bomb massively

If there's one takeaway from the pemvidutide saga, it's this: pemvidutide began its life as *a drug to treat NASH* in non-diabetic overweight patients, morphed into a drug that would *treat obesity* in those patients, but will end up being useless in both. To understand how Altimmune got here, we look at the pemvidutide data on weight loss and tolerability in comparison to other established GLP-1s, and then sketch out the landscapes in both the GLP-1 space and NASH.

### *Pemvidutide is an inferior weight-loss drug*

Even taking Altimmune's highly illusory data at face value, pemvidutide is just not as good as semaglutide or tirzepatide in doing what these drugs are famously supposed to do: getting patients to lose weight. The headline phase-2 result from pemvidutide that kicked off the recent 230% increase in Altimmune's stock was that patients on the highest dose of pemvidutide (2.4mg) lost **15.6% of their bodyweight** after being on the drug for 48 weeks, **or 13.4% more than placebo**. On a like-for-like basis, that's **about the same** as was achieved by semaglutide-2.4mg at 48 weeks, and **substantially less than the approximate 17% placebo-adjusted weight loss** achieved by tirzepatide-10mg (the middle dose of the 3 tested by Lilly in the SURPASS-1 trial).

In actuality, this comparison significantly understates the superiority of semaglutide and tirzepatide over pemvidutide. In both the semaglutide and tirzepatide obesity trials, patients underwent 16- and 12-week titration regimens until they reached the 2.4mg and 10mg dose, respectively. At the 48-week mark, patients in those trials were on the relevant doses for a period much shorter than 48 weeks (32 for semaglutide and 36 for tirzepatide).[4] By contrast, the pemvidutide phase-2 had a short 4-week dose titration regimen, so patients at the 48-week mark had 44 weeks of exposure to the 2.4mg dose, and that was still not enough to beat semaglutide or even come close to tirzepatide.

It's also worth noting here that merely equaling the weight-loss efficacy of the two established incumbents, as pemvidutide superficially *seems* to do with semaglutide, is not going to cut it for commercial success. For one thing, both semaglutide and tirzepatide serve the critical function of glycemic control, bringing down a patient's blood sugar, while pemvidutide does absolutely nothing on that front. For another, semaglutide has almost a decade's worth of efficacy, tolerability, and safety data backing its use, including a robust set of studies demonstrating its role in improving cardiovascular health. This solid clinical foundation, as well as plain old inertia and physician conservatism, has made semaglutide a formidable incumbent even against tirzepatide, which has demonstrated undeniable superiority on patient weight loss. Pemvidutide really doesn't stand a chance in that context.

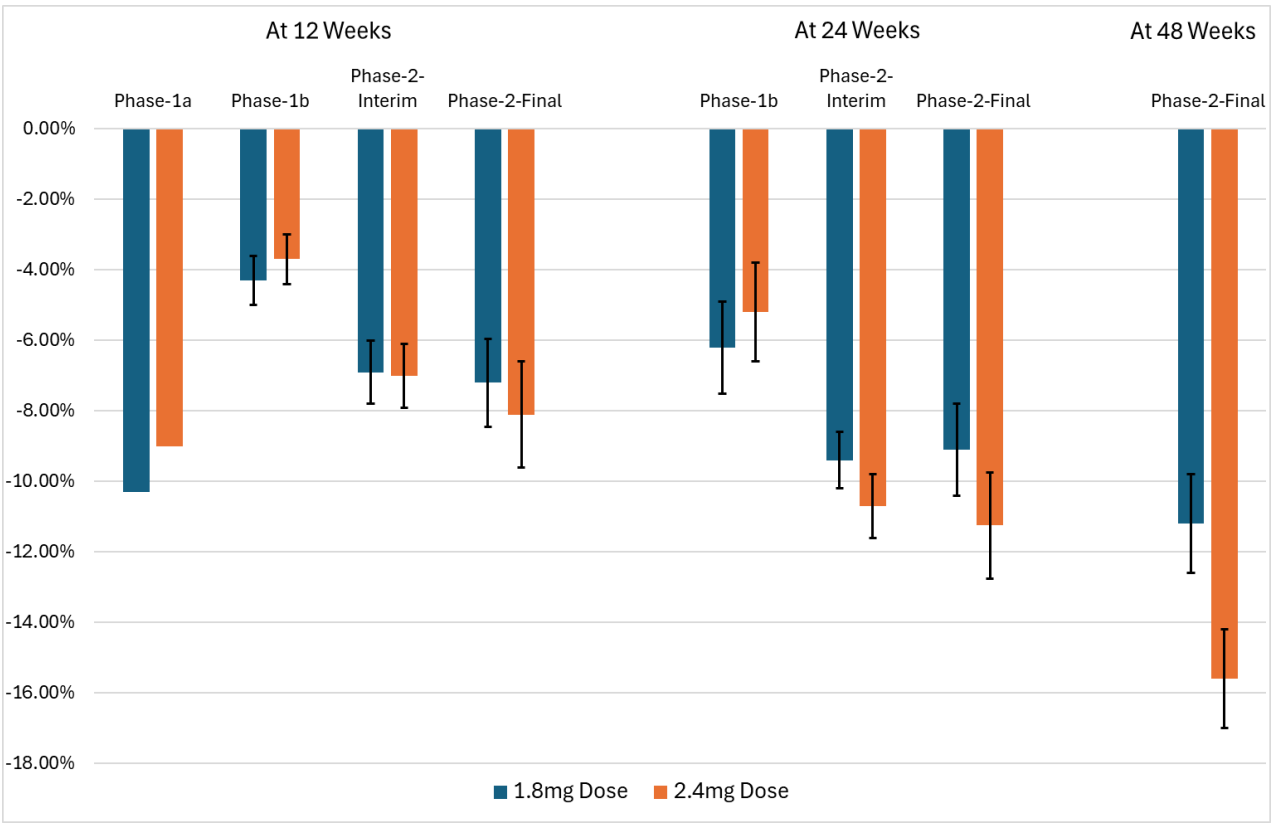
To make matters worse for Altimmune, *we don't think that the headline 15.6% weight-loss result will hold up in a phase-3 trial.* To understand why, consider that result in the context of the six different trial readouts Altimmune has announced over the last 2 years:

- Phase-1a interim (6-week) weight loss and tolerability data for the 1.2mg and 1.8mg doses
- Phase-1a final (12-week) weight-loss and tolerability data for 1.2mg, 1.8mg, and 2.4mg doses
- Phase-1b final (12-week) weight-loss, tolerability, and liver fat data for the 3 doses
- Phase-1b extension (24-week) data for all 3 doses on a variety of end-points including liver fat reduction, weight-loss, tolerability, glycemic control, and select cardiovascular markers
- Phase-2 interim (24-week) data for all 3 doses on a wide gamut of end points related to weight-loss, tolerability, glycemic control, and CV markers
- Phase-2 final (48-week) data for all 3 doses on mostly the same end points as were reported for the interim data release

In the chart on the next page, we show the absolute weight loss reported by Altimmune at each of the above readouts for subjects on pemvidutide 1.8mg and 2.4mg at 12 weeks, 24 weeks, and 48 weeks.

[4] Semaglutide phase-2 Trial 4153 (NCT02453711) for semaglutide showed that the difference between a fast dose-escalation and a slow dose-escalation persists even at week 52, and is statistically significant at about 2.5%, which means that the approximately equivalent levels of weight loss at week 48 in the STEP-1 trial and in pemvidutide's phase-2 are not really comparable given the slow dose escalation in STEP-1. This may be why Altimmune's management seems adamant that there will be no dose-escalating titration in their planned phase-3 trial.

**Pemvidutide Weight Loss Across 4 Data Readouts**



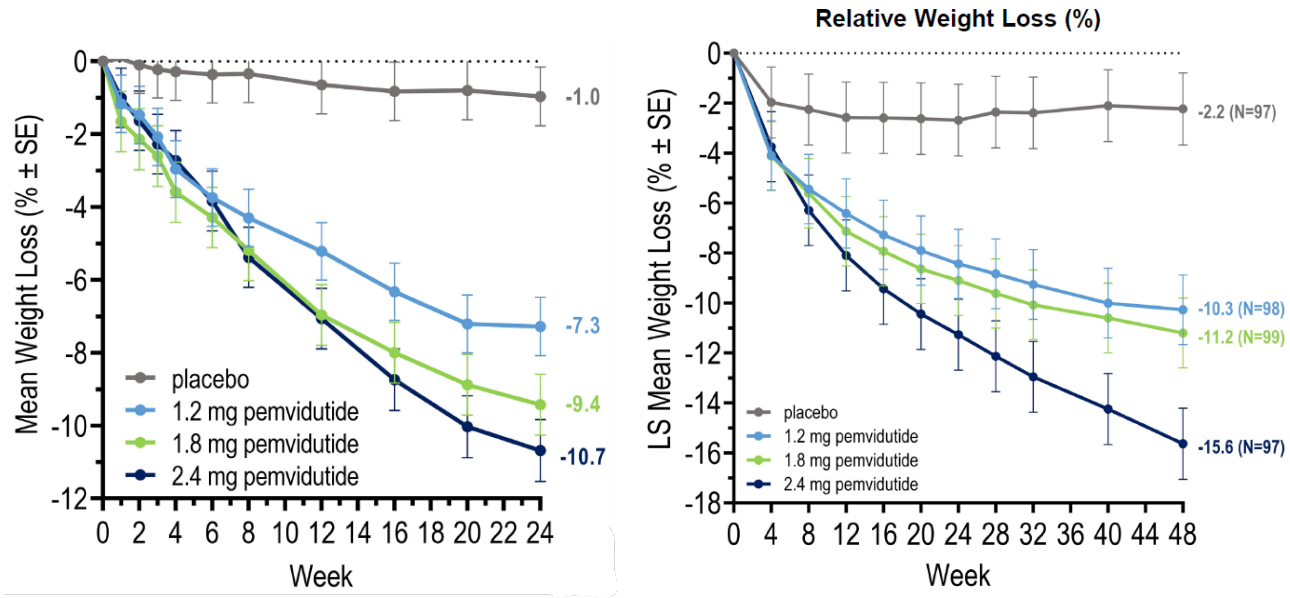

*Source: company filings and press releases, Kerrisdale analysis*

The 15.6% weight loss at 48 weeks for patients in the phase-2 on 2.4mg pemvidutide – that last orange bar, the result hailed as "best-in-class" – stands out as a fluke in two important respects:

- It's the only result that demonstrates a statistically superior response at a dose of 2.4mg vs 1.8mg. Aside from the phase-2 result at 48 weeks, across all the trials and all the data readouts, there's no statistical difference between the weight loss induced by 1.8mg vs. 2.4mg (note the error bars on the chart, which we obtained directly from Altimmune's data). At 48 weeks though, miraculously, the 2.4mg dose induces a significant 4.4% more weight loss.
- One way to rationalize a dose-dependent response suddenly appearing as statistically significant at 48 weeks (actually beginning at 32 weeks, see the graph on the next page) is to argue that it takes a while for the difference between the two doses to crystalize. But if that were the case, the same kind of separation would happen between the 1.2mg and 1.8mg dose-arms, and as the chart below shows, those two dose-arms remain statistically indistinguishable from each other over the course of the entire trial. Additionally, such a phenomenon – in which it takes over 6 months for a higher dose to yield materially different results than a lower one – is absent in any of the other GLP-1s. In the phase-2 trial testing tirzepatide's efficacy in diabetic patients, a statistically material difference in weight loss between different dose-arms of the trial appeared at the 12-week mark, and that was with a smaller number of participants in each arm than pemvidutide's phase-2, and a similar

percentage weight-loss number. In the retatrutide phase-2, all statistically distinct dose arms are apparent by week 16 (even with titration). In the semaglutide obesity phase-2 trial, the distinctions appear even earlier at 8 weeks, and any dose-arms that are statistically inseparable by week-16 remain that way at week-48. It's just very peculiar for it to take so long for a higher dose to "work," so it's plausible that the result is a statistical fluke.

**Pemvidutide phase-2 Weight-loss Curves: Interim 24-week vs Final 48-week results**




*Source: company filings*

We don't mean to imply that the dose-response curve for pemvidutide is completely flat (i.e., that an increased dose has *no impact at all* on incremental weight loss) or that time doesn't play any role at all in allowing for the effect of the increased dose to come into view. But most of the data suggest that the incremental dose-response beyond 1.8mg is negligible and that incremental weight-loss at that dose beyond week-30 is marginal. In other words, *the combination of more drug and more time aren't very effective for that much more weight-loss*. That leads us to believe that, even without the tolerability and resulting data-sampling issues we highlight below, investors should take pemvidutide's headline 15.6% 48-week weight-loss result with a massive grain of salt. That blue line at 48 weeks (right-hand chart above) should probably be a lot closer to the green one, just as it is at 24 weeks in the chart on the left. As a corollary, real-life weight-loss on 2.4mg at 48 weeks is probably closer to 10% than 15%.

## *The tolerability profile of pemvidutide is awful*

The most obvious drawback of the GLP-1s (aside from price) is tolerability. Given their mechanism of action, every drug in the category causes gastrointestinal discomfort ranging from mild nausea to some combination of nausea, diarrhea, constipation, and vomiting. Pemvidutide

is *much worse* in this respect than already-approved semaglutide and tirzepatide. How much worse? Well, Altimmune recruited 391 trial participants for the phase-2, 97 of which were in the placebo group and the rest split between the 3 different doses studied – 1.2mg (98 participants), 1.8mg (99 participants), and 2.4mg (97 participants). Of the 294 participants taking any dose of pemvidutide, *36% discontinued their use of the drug*. In the 2.4mg cohort, *42% of participants discontinued the drug*.

To put that number in context, in the semaglutide STEP-1 trial, just 17% of participants on 2.4mg discontinued their use of the drug and in tirzepatide's SURMOUNT-1 trial just 15% of participants across the 3 different dosage arms discontinued the drug (with no material difference between the different arms). That *chasm* between the discontinuation rates of pemvidutide and the other GLP-1s actually *understates* how bad the pemvidutide numbers are. Consider that the STEP-1 and SURMOUNT-1 trials were both run before Ozempic and Mounjaro were household terms. STEP-1 studied semaglutide in 2018-2019 and SURMOUNT-1 studied tirzepatide in 2020-2021. By this time, Ozempic and Mounjaro were being touted by social media influencers and rumored to be used by Hollywood stars. They were also in short supply given both the spike in demand and manufacturing issues on the part of Novo Nordisk, and even those who could get a hold of them for the purpose of weight-loss had to pay $1500 a month out of pocket because they weren't covered by insurance.[5] In that setting, pemvidutide trial participants were essentially being offered a year of *free* access to the hottest trend in weight-loss medication and they *still* quit the drug at unprecedented rates! Not exactly a ringing endorsement of tolerability.

Altimmune's management and its stock-market cheerleaders have a lot of excuses for this dismal level of patient compliance, insisting that it's not really indicative of pemvidutide's tolerability, which they claim isn't that different from semaglutide or tirzepatide. Their argument goes something like this:

- The actual proportion of pemvidutide trial participants who *formally discontinued the drug due to drug-related adverse events* (AEs) was "only" 16% in the 1.8mg and 2.4mg arms (20% including all-AEs, which includes additional adverse events that weren't ascribed to the drug).[6]
- That's much higher than the 5-7% comparable rates in STEP-1 and SURMOUNT-1, but those trials allowed for dose reduction, which the pemvidutide trial did not.
- To quote Scott Harris, "The semaglutide program…**had towards 30% adverse discontinuation rates in phase-2** and [tirzepatide]...**had about 25% in phase-2** and got them down to single digits in phase-3… by extending the dose titration" and allowing for dose reduction. "In fact, if you look at the phase-3 tirzepatide and semaglutide programs, 30% of patients had either dose-reduced or never got up to the upper dose. So you can see the power of what would happen if we introduce [dose reduction] in a phase-3 program…by

[5] As of this writing, payor coverage for GLP-1s for the obesity indication is still very spotty.

[6] The correct "adverse discontinuation" metric to use in comparison with semaglutide and tirzepatide is *all* adverse events leading to discontinuation rather than "drug-related adverse events." The former is what's used in the semaglutide and tirzepatide trials.

allowing dose reduction in the phase-3 program, we expect the discontinuation rates to drop down to single digits as they have in other phase-3 programs."

Basically, the argument is that semaglutide and tirzepatide demonstrated *even worse tolerability than pemvidutide* in their respective phase-2 trials, and they "fixed" it through extending the dose-escalation period and allowing for dose reduction. All Altimmune needs to do is allow for dose reduction, and voila, tolerability will look just as good as the other GLP-1s.

But Altimmune's argument is misleading and flat out dishonest, not to mention delusional:

- The framing of the tolerability issue exclusively around the 16% "drug-related adverse-event discontinuation" rate is wildly misleading. The proportion of study participants who *explicitly* quit the drug or the trial because they can't tolerate the side effects is one measure of tolerability. But so are those who quit the trial without giving any reasons, like those who are lost to follow-up because they just don't show up for appointments or those who withdraw without explicitly providing a reason. Particularly in the context of a highly desirable and expensive class of medication subject to shortages, the all-in discontinuation rate – 36% for pemvidutide's 1.8mg dose and 42% for its 2.4mg dose – is highly indicative of tolerability, or in pemvidutide's case, lack thereof.

- Did the phase-2 programs of the other GLP-1s have 25-30% discontinuation rates as Harris claims? Not exactly. We've looked through every single completed semaglutide phase-2 study, and two of them are most relevant. In a 26-week trial in patients with type-2 diabetes, there were 5 different semaglutide dosage arms with all-inclusive discontinuation rates of 9-20% and official AE-driven discontinuation rates of 4.7-9.2% (details in the study appendix). 4 of the arms did not include the option of dose reduction, including the highest dose arm, which had an all-in discontinuation rate of 16%, a far cry from pemvidutide's 42%. A more relevant trial was the massive phase-2 for semaglutide in obesity, which had seven different dosage arms and ran over the course of 52 weeks. All-in discontinuation rates were 12-26% with AE-related discontinuation rates of 4-17%. Notably, the highest-dose arm with a rapid dose-escalation schedule had an all-in discontinuation rate of 12% and an AE-related discontinuation rate of 8%. Again, not even close to the 42%/20% comparable rates for pemvidutide. Not a single arm in either of these trials had a "30% adverse discontinuation rate" as claimed by Altimmune.

  In the case of tirzepatide, there's really only one significant phase-2 trial of which to speak, and it's focused on patients with type-2 diabetes. In the 5mg and 10mg arms, all-in discontinuation rates were about 14% with adverse discontinuation rates 6-9%. The 15mg arm of this trial *did* have very high discontinuation rates – 34% all-in and 25% AE-related. But the experience of the other arms (as well as the further experience of the phase-3 trial, which we discuss next) indicates that this result was a fluke (there were only about 50 patients in each arm, and 3-4 outlier events had a disproportionate impact), while pemvidutide's discontinuation rates were consistently high in all the dosage arms (which all had about 100 patients in them). Altimmune's claim here is – at best – a disingenuous cherry-picking exercise.

- Did Novo and Lilly "get [discontinuation] rates down to single digits in phase-3 by extending dose titration?" This claim is both stupid and wrong. First of all, as we mentioned earlier, there's really no good evidence that dose titration does much to affect patients' compliance in clinical trials. Second of all, the semaglutide phase-3 STEP-1 trial's 16-week dose-escalation period is *the same length* as the dose escalation period for the equivalent 0.4mg-daily dose in the semaglutide phase-2 obesity trial discussed in the previous bullet point. There was no lengthening of the dose titration period. Finally, the reason the phase-2 tirzepatide trial had short dose-escalation periods is because it was a 26-week trial. In fact, the longer dose-escalation period in the phase-3 SURMOUNT-1 trial did nothing to change the tolerability of the 5mg and 10mg doses.

- Is it true that "if you look at the phase-3 tirzepatide and semaglutide programs, 30% of patients had either dose-reduced or never got up to the upper dose?" Nope.

  The tolerability in the semaglutide STEP-1 trial is very easy to assess. Only one dose – 2.4mg-weekly – was studied, and dose reductions were allowed. Of over 1300 trial participants in the experimental arm, the all-in discontinuation rate was 17%, the adverse discontinuation rate was 7%, and 8.6% of trial participants reduced their dose to below 2.4mg. What Altimmune probably means is that if you add up the 17% and 8.6%, you get to about 26%. But 26% is still a lot lower than 42%, and the 9% that reduced their dose stayed on the drug and had their weight-loss count towards the final statistics. By contrast, the medium- and low-dose arms of the pemvidutide trial had all-in discontinuation rates of 36% and 29%, respectively. Dose reduction doesn't help if the tolerability of the lower doses is still very bad!

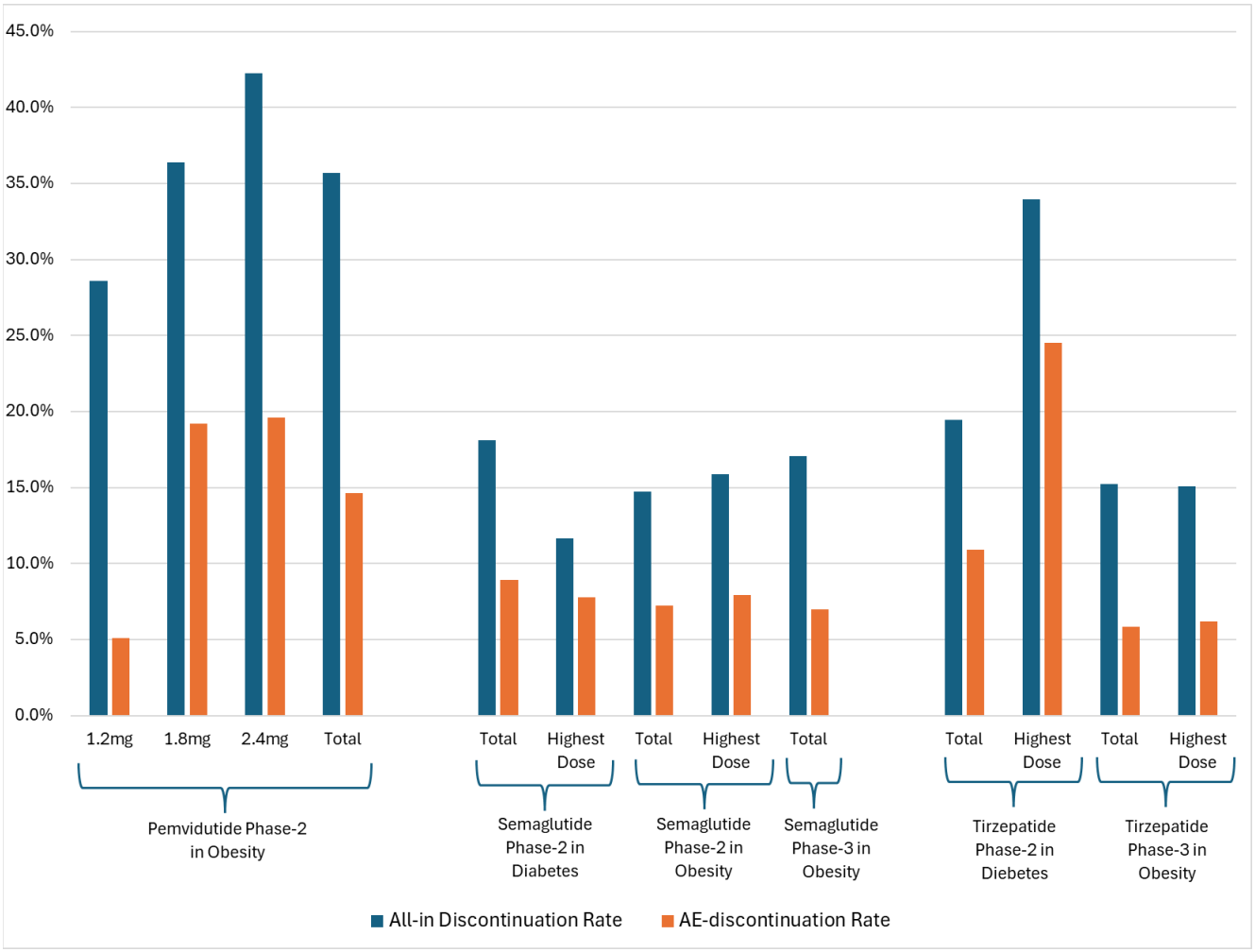
  The tirzepatide phase-3 SURMOUNT-1 trial had 3 weekly dosage arms – 5mg, 10mg, and 15mg. While the trial protocol does allow for dose reduction in cases of extreme intolerability, no one has any idea about the proportion of dose-reducers because that data has not been released anywhere (neither in the study's supplementary appendix, nor in the FDA's review files, which have not yet been completely posted). Here too, though, the tolerability data is crystal clear: Among *all three dosage arms*, the all-in discontinuation rate did not vary much and stayed in a very tight 14-16% range. The adverse discontinuation rate varied only slightly more coming in at 4%, 7%, and 6% for the 3 dosage arms, respectively. In other words, tirzepatide's tolerability was *spectacular* among the 1900 patients taking the drug, and dose reduction is completely irrelevant because tolerability was statistically identical among the different dosage arms.

The chart on the next page summarizes the discontinuation data from pemvidutide's phase-2 trial and compares it to the various discontinuation data from several semaglutide and tirzepatide trials. The most important takeaways in our view are:

- The discontinuation rate on the lowest pemvidutide dose is still higher than the phase-3 discontinuation rate for any dose of semaglutide or tirzepatide.

- The discontinuation rate for the highest dose of pemvidutide is simply astronomical and has no analog in the semaglutide or tirzepatide universe.

**Discontinuation Rates for Pemvidutide vs Semaglutide and Tirzepatide**




*Source: Altimmune presentations and press releases, published semaglutide and tirzepatide studies, Kerrisdale analysis*

So Altimmune's claims regarding semaglutide and tirzepatide are, at best, selectively cited statistics shorn of context. In many cases, they're just wrong, which – whether intentionally or unintentionally – reflects very poorly on this management team. It's also comical that management talks about improving tolerability in the eventual phase-3 trial through enabling dose-reduction. Dose reduction isn't going to improve tolerability if patients on the lower dose are also quitting the drug at an astronomical rate!

## *Phase-3 data for pemvidutide will look terrible compared to other GLP-1s*

Maybe an even bigger problem for Altimmune than the drug's tolerability profile is the impact that profile will have on the phase-3 efficacy results. The statistical complexities of weight-loss trials have been a topic of discussion at the FDA for at least the last 30 years, over which the agency has issued guidance multiple times on pharmaceuticals for weight management. One of the key topics of contention has been how to assess the efficacy of weight-loss medication given how common patient discontinuation tends to be whether due to side-effects or to discovering the drug is ineffective (i.e., if the patient's not losing any weight or not suffering side effects, they may assume that they're on placebo or that the drug is just not effective for them, and subsequently quit the trial). The way this has been dealt with in the landmark STEP-1 and SURMOUNT-1 trials has been to report two different efficacy numbers:

- The treatment effect – using all trial participants, *including those who discontinued the drug but remained in the trial*. The trial sponsors are supposed to do their best to keep these patients coming back for their appointments even after they discontinue use of the drug. So, for example, in the STEP-1 trial, 223 of 1306 trial participants discontinued the use of semaglutide, but only 66 of those withdrew from the trial. The treatment effect is the weight-loss efficacy *including the data points of patients who discontinued their use of the drug*.
- The hypothetical effect – is the weight-loss efficacy including only the data points of trial participants who remained on the drug the entire length of the trial, *hypothetically* assuming that all trial participants remained on the drug and estimating what their weight loss would have been given different parameters such as sex, initial BMI, pre-diabetic status, etc.

Obviously the hypothetical effect is going to be greater than the treatment effect. Including the results of patients who discontinued the drug and either stopped losing weight or even gained back some of their weight is going to work against the net weight-loss efficacy numbers. For a variety of reasons – including both statistical integrity as well as the desire for trials to reflect the reality of patient outcomes most accurately – the FDA's guidance is that *weight-loss headline efficacy results are reported using the treatment effect*, though the FDA endorses publishing both efficacy estimates.

In other words, when you look at the STEP-1 or SURMOUNT-1 *headline* trial results, the ones that are included in the package insert, those *include patients who discontinued the drug*. The headline efficacy reported in the tirzepatide phase-2 diabetes trial was also the treatment effect, as was the headline result reported in the semaglutide phase-2 obesity trial. In all the trials, the published study summarizing the results also included the hypothetical effect for the sake of completeness. So, just as an example, the "primary estimand" reported in the STEP-1 trial was a weight loss of 14.9% at week-68 (12.4% placebo-adjusted), which was the treatment effect, but the "trial product estimand," or what we've termed the hypothetical effect, was a weight-loss result of 16.9% (15.3% placebo-adjusted).

What about the pemvidutide results? Unsurprisingly, Altimmune reported only one result: the more aggressive hypothetical effect. One funny consequence of this has been sell side analysts

comparing the pemvidutide *hypothetical* effect to the semaglutide *treatment* effect and concluding that pemvidutide was superior when in fact, on a like-for-like *hypothetical* basis, the weight-loss result at week-48 was about the same for semaglutide and pemvidutide.[7]

But the real story underlying Altimmune's aggressive reporting is that the treatment effect results were probably a disaster. In STEP-1, the difference between the treatment effect and hypothetical effect was 2% weight-loss. In SURMOUNT-1, the difference was 1-2% depending on the dose-arm. But in both of those, the all-in discontinuation rate was relatively low, in the 15-17% range. Even if the weight-loss of the quitters was 0, the total impact on the results would be to lower the weight-loss effect by about 2.5%. At the 42% all-in discontinuation rate in the highest pemvidutide dose-arm, the same scenario would lower the weight-loss result by more than 6%. That's almost certainly an unrealistic downside scenario, but considering that the discontinuation rate for pemvidutide was 2-2.8x greater than for semaglutide or tirzepatide, we think the negative effect on the headline weight loss number was in the 2.5-5.5% range – at the lower end of the range for the lower-dose pemvidutide arms and at the higher end of the range for the higher-dose arms. *That 15.6% weight-loss would look a lot less impressive if it were just 10%, right?*

If and when Altimmune runs a proper phase-3, it's going to have to report its primary efficacy result the same way Novo and Lilly did – in the form of a treatment effect that includes the weight-loss of patients who discontinue the drug. And the headline number is going to look awful compared to the results of semaglutide and tirzepatide because the drug has a much worse tolerability profile. Of course, Altimmune will be free to *also* report the hypothetical effect, just like Novo and Lilly did, but it's going to be embarrassing if the hypothetical effect diverges so massively from the treatment effect because it will only call attention to how bad pemvidutide is on tolerability. Either way, we expect that phase-3 results will be a disaster, and that pemvidutide's commercial prospects will suffer accordingly.

## *Will pemvidutide effectively treat NASH? No one knows and it doesn't matter*

So if it won't be used in obesity or diabetes, what's pemvidutide really useful for anyway? Altimmune would like you to think that the answer to this is NASH – or non-alcoholic steatohepatitis, which was the original target of the drug when Altimmune acquired it. NASH is the advanced stage of non-alcoholic fatty liver disease (NAFLD), at which point in addition to excess liver fat, the liver tissue is inflamed and its cells start to balloon. If early-stage NASH goes untreated, it will progress towards liver-cell-death and fibrosis (scarring of the liver), then

[7] As discussed previously, even that comparison is overly favorable to pemvidutide as it doesn't account for the semaglutide titration period, or the fact that semaglutide comes with a decade of physician experience and a mountain of clinical data, or the fact that semaglutide controls blood-sugar. Pemvidutide would have to materially outperform semaglutide in weight-loss to even be *considered* by physicians.

cirrhosis, and then finally liver failure, which necessitates a liver transplant. The primary rationale Altimmune articulated for pemvidutide being used to treat NASH was straightforward:

- Weight-loss had been shown to reduce liver-fat and reverse liver inflammation and cell-ballooning that characterized early-stage NASH.
- Pemvidutide would lead to greater weight-loss than other GLP-1s.
- Therefore, pemvidutide would be the best GLP-1 to treat NASH (diabetes was out of the question because the glucagon agonism in pemvidutide offset the GLP-1 glycemic control).

Obviously, that rationale is dead because pemvidutide's weight-loss has turned out to be inferior to other GLP-1s. The other rationale that was sometimes mentioned alongside the weight-loss mechanism was that glucagon agonism would have a "direct effect on the liver," which is true but not particularly relevant. Glucagon stimulates the liver's breakdown and release of glucose into the blood stream (hence the negative blood-sugar impact from pemvidutide), as well as the breakdown of triglycerides into fatty acids to be used by the body as a source of energy. The latter mechanism could theoretically lead to more liver-fat reduction than weight-loss alone. And there is some evidence that pemvidutide is effective in reducing the liver-fat that is one of the hallmarks of the NASH. Using an MRI-based measure of liver fat, Altimmune's phase-1b for pemvidutide showed that at 24 weeks, the drug was able to reduce liver fat in patients with NAFLD by a relative 56% in the lowest-dose 1.2mg arm and by 75% in each of the two higher-dose arms. On its face, that seems better than the 40% liver-fat reduction demonstrated by semaglutide in patients with cirrhosis in a phase-2 trial, though it's about the same as the 74% liver fat reduction seen in the tirzepatide SYNERGY-NASH phase-2 trial.[8] But there's a huge caveat: unlike in the tirzepatide trial, the patients in Altimmune's subgroup analysis didn't have NASH! They just had fatty liver. Actual NASH is diagnosed via biopsy, the way it was for tirzepatide's phase-2. The standard end-points for NASH trials, in which it's notoriously difficult to succeed, are NASH resolution and fibrosis reduction.[9] Obviously Altimmune tested for neither and there's simply no articulated mechanism for how glucagon "directly affecting the liver" would help reduce fibrosis or resolve NASH at the cellular level.

The only complete study that's looked at this in the GLP-1 space was a larger phase-2 run by Novo with several different semaglutide dose-arms. The patients in this trial were required to have biopsy-diagnosed NASH and fibrosis between stages 1-3.[10] On the one hand, the highest dose (in this case 0.4mg-daily) did lead to a higher rate of NASH resolution than placebo at 72 weeks (60% of patients in this group had their NASH resolved compared to 17% in the placebo group). On the other hand, none of the experimental arms showed fibrosis improvement over

[8] See the recent Lilly earnings presentation, page 17.

[9] The NASH Clinical Research Network defines NASH resolution as "no more than mild residual inflammatory cells [score of 0 or 1] and no hepatocyte ballooning [score of 0]" (as quoted in Newsome et al, *A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis*). In other words, it's not just liver fat is reduced, but the other hallmarks of NASH – liver inflammation, and the ballooning of liver cells (hepatocytes) – are reversed.

[10] Fibrosis in NASH is graded on a scale of 0-4 with 0 and 1 being no or mild fibrosis, respectively, 2 and 3 being significant fibrosis, and 4 being cirrhosis.

placebo at a statistically significant rate (though it's worth noting that a whopping 33% of the patients in the placebo arm saw fibrosis improvement vs. 43% in the highest-dose arm, so it's possible that the study didn't evaluate the effect positively enough due to an abnormally positive placebo showing).

Part of the problem for GLP-1s in NASH may be that *rapid weight-loss actually exacerbates fibrosis* because the stress of the liver rapidly oxidating fat leads to more inflammation. That's why some patients who lose weight quickly after gastric bypass surgery suffer liver failure. The patients in the semaglutide cirrhosis trial actually experienced *both* a reduction in liver fat *and worsening fibrosis* (at a higher rate than placebo!) *simultaneously*. It's even possible that the glucagon effect that leads to more dramatic liver-fat loss may lead to more dramatic fibrosis deterioration. But the reality is that no one knows. As we said at the outset, there's still a lot the scientific community doesn't understand about the different cellular pathways being impacted by GLP-1, GIP, glucagon, etc.

Altimmune is currently running a phase-2 to test pemvidutide in NASH more rigorously, with study completion expected in late 2025.[11] We actually don't think the study will be completed by late 2025 because NASH recruitment is famous for having a very high screening failure rate and the prevalence of GLP-1s is actually going to make it even more difficult.[12] The primary endpoints of the trial are NASH resolution and fibrosis improvement at 24 weeks, with secondary endpoints measuring those bogeys at 48 week, and the trial will probably fail its fibrosis endpoint because it's recruiting patients with significant fibrosis. Given what we've learned from the two semaglutide trials in NASH, as well as the widely understood effect of rapid weight-loss on fibrosis, those patients are highly unlikely to see their fibrosis improve contemporaneous with the rapid weight loss that is typical of the first year on a GLP-1.

But the results of that trial won't be all that relevant. For NASH with significant fibrosis (stages 1 and 2), Madrigal's resmetirom is likely to be approved in the next few months. Just for some context on how difficult it is to run clinical trials in NASH, Madrigal was running a phase-2 on resmetirom back in *2016*. So the GLP-1s – whether semaglutide or pemvidutide or tirzepatide – have their work cut out for them.[13] Resmetirom is a *well-tolerated oral medication* that exclusively targets the liver in treating pre-cirrhotic NASH. For the foreseeable future, NASH with significant fibrosis is going to be treated with resmetirom, and in obese patients it will be treated with resmetirom and an appropriate GLP-1 (i.e., not pemvidutide). Will a GLP-1 ever be

[11] It's a risky study in that fibrosis improvement is a function of time and the trial seems designed to test the primary endpoints only at 24 weeks (though that might still be changed given that some of the secondary endpoints will be evaluated at both 24 and 48 weeks)

[12] One of the FDA-required exclusion criteria for these trials is anyone who has lost more than 5% of their bodyweight over the prior 3 months or 10% over the prior 6 months.

[13] Tirzepatide's SYNERGY-NASH phase-2 in fact missed on the fibrosis endpoint, which further confirms our skepticism about pemvidutide. Semaglutide is the only GLP-1 with a phase-3 trial currently running in NASH and to get a sense of how difficult recruitment is, Novo started this trial in April of 2021 and it's *still recruiting*! Even then, the endpoints reference liver fibrosis improvement at 72 weeks and, well, we're skeptical.

approved for the NASH indication? Maybe, but it will take a long time to recruit for the trials and will probably require longer range measurements of fibrosis improvement past the one-year mark, once the rate of weight-loss has decelerated. It's also likely that the overwhelming benefit of a GLP-1 in NASH will be a function of weight-loss rather than the speculative and mysterious glucagon effect, which means pemvidutide doesn't have any sort of edge.[14]

As for NASH with fibrosis in stages 0-1, NASH and the fatty liver disease that precedes it do not occur in a vacuum. They occur in people who are obese, or who have type-2 diabetes, often both (82% of NASH patients are obese and 44% have diabetes). These patients also possess the cardiovascular risk factors typical of obesity and diabetes such as high cholesterol, high blood pressure, high triglycerides, and so on. Obviously, given pemvidutide's complete lack of glycemic reduction, it's a non-starter for the diabetic population. But after speaking with dozens of doctors, it's clear that for obese patients – even the non-diabetic ones – treating CV risk, obesity, blood-sugar, and metabolic dysfunction takes precedence over treating fatty liver. Fatty liver and early-stage NASH are widely understood to take care of themselves if the other problems, especially the obesity, are being addressed effectively. As a result, the idea that anyone would prefer pemvidutide to semaglutide or tirzepatide (or the next generation GLP-1s we'll be discussing momentarily) because it might target NASH a bit more effectively (though even that's not actually true) is laughably naïve. Choosing the best drug to reduce obesity is the sensible way to address early-stage NASH.

NASH with significant fibrosis is far far away from being an approved indication for GLP-1s, and in its early stages is going to be the domain of the best weight-loss drugs in the GLP-1 category. Which is to say, pemvidutide for NASH isn't happening.

## *Pemvidutide is Altimmune's lone and flimsy weapon in a highly competitive GLP-1 arms race*

It's hard to overstate how crowded the field of GLP-1-based weight-loss drugs is about to become. While semaglutide and tirzepatide are currently the only approved drugs in the category (excluding the first generation of GLP-1s like liraglutide-Victoza), there's a tidal wave of molecules making their way through clinical trials that make pemvidutide seem like an after-thought. We'll divide these into a few categories.

### Oral Formulations

Both Novo and Lilly are testing oral formulations of GLP-1s. In a phase-2 obesity trial, Lilly's orforglipron resulted in 12-15% weight-loss at 36 weeks (using a hypothetical estimate) but

[14] The speculation around dual GLP-1/glucagon agonists in NASH basically comes down to "well, there are glucagon receptors in the liver." That's as far as we've been able to get from speaking to hepatologists. There's never an actual causal mechanism – like there is for resmetirom – that is articulated, and the fact that tirzepatide leads to just as much liver-fat reduction confirms our suspicion that there may not be one.

tolerability was iffy – all-in discontinuation rates ranged from 17-38%. In a phase-2 T2D trial, orforglipron reduced A1C by 2% and body-weight by about 10% at 26-week with no major differences among the 3 higher dose-arms, though as in the obesity trial, tolerability wasn't great with all-in discontinuations in the 20-30% range. The safety data in the T2D trial also left something to be desired with about 10% of patients suffering from treatment-related adverse cardiac events.

Meanwhile Novo has already conducted a phase-3 of oral-semaglutide, with weight-loss efficacy at 68-weeks similar to the injectable version, and tolerability only slightly worse. But manufacturing capacity is a bottleneck for Novo, and the FDA hasn't yet approved the drug at Novo's suggested dose for the obesity indication (a lower-dose version has been approved for diabetes since 2019).

Finally, still on the oral-GLP-1 front, Structure Therapeutics has a compound (still unnamed and going by GSBR-1290) that has shown impressive short-term weight-loss results in phase-1 and phase-2, though the tolerability seems underwhelming. The dosing strategy and titration schemes are still being tested in phase-2 with interim data expected in the first half of this year.

It's hard to imagine the oral versions of GLP-1s becoming the dominant form of administering the treatment considering the unimpressive tolerability profiles in the space. But we expect that the desirability of a daily pill over a weekly injectable for many patients, and the fact that the oral formulation will still be tolerable to a large proportion, even a majority, of the target market, will make these GLP-1s formidable contenders in the weight-loss space.

**Multi-agonism**

Just as tirzepatide adds GIP-agonism to GLP-1 and pemvidutide adds glucagon-agonism to GLP-1, there's an array of dual and triple agonists currently being studied, some at quite an advanced stage:

- Retatrutide: perhaps the most prominent of these is Lilly's retatrutide, which is a triple GLP-1/GIP/glucagon agonist with tantalizing efficacy in weight-loss (over 20% at 48 weeks), a tolerability profile similar to semaglutide and tirzepatide, and a liver-fat reduction in phase-2 of over 80% that goes further than pemvidutide's 75%. 4 phase-3 trials are currently recruiting for retatrutide, including placebo-controlled trials in obesity and diabetes, as well as a study focused on patients with established cardiovascular disease.
- CagriSema: almost as anticipated as retatrutide, CagriSema is Novo's combined semaglutide-cagrilintide combination. Cagrilintide is a pharmaceutical analogue for amylin, another hormone that plays a role in glycemic regulation and satiety. In a phase-2 study in diabetics in which CagriSema was pitted against semaglutide, the former led to more weight loss (16% at 32 weeks) and greater A1C reduction than the latter while exhibiting approximately the same level of tolerability. 5 phase-3 trials are currently recruiting for CagriSema, including a head-to-head comparison with tirzepatide in obesity, a head-to-head comparison with semaglutide in diabetes, and a placebo-controlled study of the impact on cardiovascular events.

- Survodutide: Like pemvidutide, survodutide is a dual GLP-1/glucagon agonist. Unlike pemvidutide, in its phase-2 trials (explained in Zealand Pharma's investor presentation) survodutide's two highest dose-arms achieved greater weight loss than semaglutide at 46 weeks, but like pemvidutide had much worse tolerability. Unlike pemvidutide, the drug was designed to emphasize GLP-1 more than glucagon agonism, which resulted in solid glycemic control in diabetic patients, a massive segment of the obese population in which pemvidutide's lack of glycemic control makes it useless. The inferior tolerability of survodutide somewhat affirms the idea that glucagon has a particularly nasty impact on the tolerability of weight-loss drugs, but survodutide's efficacy in both weight-loss and glycemic control at least give it some optionality if glucagon agonism turns out to be useful. Co-developed by Zealand and Boehringer-Ingelheim, there are currently 5 phase-3 trials for the drug that are recruiting, testing the drug's efficacy in obesity and diabetes, and its impact on cardiovascular disease.
- CT-388: much earlier in the drug-development process, CT-388 is – like tirzepatide – a dual GLP-1/GIP agonist. The drug is still in phase-1, and the only reason we mention it is that at 4 weeks, the drug resulted in 8% weight loss in a fairly large phase-1 cohort with no treatment discontinuations. The drug's developer – Carmot Therapeutics – was recently acquired by Roche, and has a next-generation dual-GLP-1/GIP agonist in its pipeline as well.
- AMG-133: Amgen's AMG-133 deserves special mention here because it took a counterintuitive tack – instead of adding a GIP-agonist to GLP-1, it added a GIP-*antagonist* to GLP-1. The very preliminary phase-1 results have shown some interesting features including a *once-monthly injection* leading to rapid weight loss (up to 15% over 12 weeks) and patients keeping their weight off for the 15 weeks they were observed after no longer receiving treatment. The pharmacokinetic profile that allows for AMG-133 to be dosed monthly also seems to be responsible for high levels of tolerability. On the other hand, it doesn't seem like there's a material glycemic control aspect to the drug, but there's been very little released by Amgen so it's hard to know. The drug is expected to begin recruiting for a phase-2 trial in obesity shortly.

The above is by no means an exclusive list, but those are some of the major contenders. There's also Lilly's mazdutide (GLP-1/glucagon agonist), which has so far only been studied in the Chinese population, but which resulted in more than 10% weight loss at 26 weeks with excellent tolerability, among others.

**More Potent GLP-1s**

There are also other solely-GLP-1 agonists being developed that may be more potent than semaglutide and some of the other multi-agonists, or just target different effects. Ecnoglutide from Sciwind demonstrated more than 11% weight-loss at 26 weeks in an obesity phase-2 and a 2% reduction in A1C in a diabetes phase-2. Also notable is Sun Pharma's utreglutide, which showed 11% weight loss at 8 weeks in a phase-1 trial that included only males, which is a significant accomplishment considering that male weight-loss has been inferior to female weight-loss in every single GLP-1 study we've reviewed. What's also interesting with utreglutide

is that Sun is a generic drug maker that will bring significant capacity to bear on this project and could single-handedly change the pricing dynamics in the field.

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The upshot of the pipeline dynamics in the GLP-1 space is that there are many very strong weight-loss candidates making their way through the pipeline. They have weight-loss data that's better than pemvidutide. Most of them also effectively control blood-sugar, even survodutide, which has a mechanism of action that's similar to pemvidutide. They also overwhelmingly exhibit better tolerability and many of them have potentially novel and differentiated aspects that would allow them to compete with the formidable incumbents, semaglutide and tirzepatide. They all belong to large pharmaceutical organizations that have the capabilities to invest in trials, marketing, and differentiated clinical positioning. In most cases, these organizations have a few different shots on goal in the weight-loss space. Altimmune has none of this. The company hangs by a single compound being developed by a management team with a long track record of embarrassing failure. It has no capital – financial or human – to invest in a major clinical program, and its data is not remotely good enough to attract a partner that will do it for them. Altimmune is a dwarf among giants.

## V. Conclusion

With only $85 million left in the bank as of the end of last year's third quarter (and likely less by the end of the year), Altimmune has less than a year of runway before running out of cash, and that's without running the phase-3 trial that management says it's going to begin this year. The refrain from management has been that they're going to find a partner for running the phase-3, but given the quality of their phase-2 data and the likely dead-end the drug will eventually face, it's hard to imagine a quality partner signing up to spend hundreds of millions of dollars on a phase-3 trial in such a crowded field. If they do find a partner, it will be a classic case of adverse selection: only a basket case of a partner would be willing to stake their reputation on a drug with data this bad, and a low-quality partner is likely to run the trial badly too.

The other possibility is that management, taking a page from its past, will conveniently raise capital and run a disaster of a phase-3 trial on their own. As we described above, it's very likely that the headline phase-3 results, adjusted for pemvidutide's awful tolerability, will look horrible compared to the rest of the GLP-1 field. At that point, it won't even be worth trying to get approval. It's not exactly how things went down for Garg at Tranzyme and Neos, but it's pretty close. Altimmune shareholders should be ready for some indigestion of their own.

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