February 2024

Australian Equities: GLP-1s A Weighty Debate

Glucagon-like peptide 1 (GLP-1) agonists, although extensively covered in the media, are not novel drugs. While they hold promise in addressing the substantial need for safe weight loss treatments, their limitations and long-term impacts remain uncertain. Here our expert investment partner, Northcape Capital, discusses the implications of this drug and the opportunities for contrarian investors with a long-term perspective.

This information has been prepared by Northcape Capital, the underlying investment manager for the Warakirri Ethical Australian Equities Fund and the Warakirri Concentrated Australian Equities Fund.

What are GLP-1s?

Glucagon-like peptide 1 (GLP-1) agonists are drugs which mimic the action of hormones that are released in the gastrointestinal tract after eating. Blood sugar levels rise after eating. These drugs stimulate the body to produce more insulin which helps lower blood sugar levels and control Type 2 diabetes. Another effect of these drugs is that they slow the movement of food from the stomach into the small intestine. They also interact with the brain to send signals of satiety, which reduces appetite. As a result, people feel full faster and for longer, which causes them to eat less and lose weight.

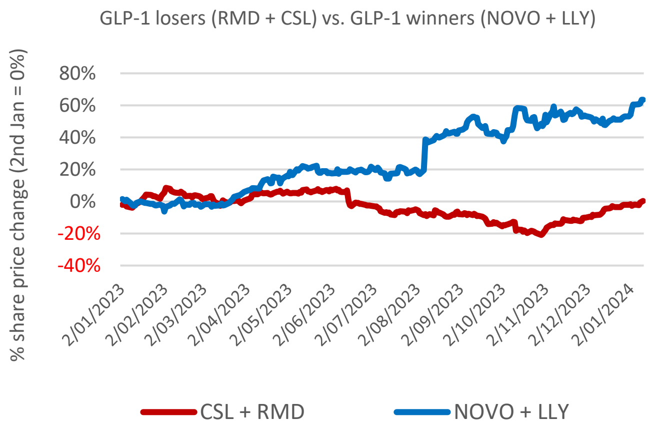
While the media has hyped up these drugs over the past year, it's important to note that they are not new. 'First gen' GLP-1 drugs (e.g. Saxenda) have been on the market for a decade but did not previously demonstrate material weight loss. Even the hyped 'second gen' drugs (e.g. Ozempic/Wegovy) have been around for 7 years but were predominantly only used for treating diabetes.

Why have they gained attention now?

In August 2023, Novo Nordisk released new top-line data from its SELECT study that demonstrated a 20% reduction in the risk of heart attack or stroke for people treated with Wegovy. This got the market excited at the prospect that GLP-1s could be effective in treating multiple indications outside of diabetes which could lead to broader reimbursement across the US in time. 2023 also saw approvals of newer generation GLP-1s (Eli Lilly’s Munjaro/ Zepbound) which demonstrated even greater weight-loss, while trial results of oral versions of GLP-1s showed promising outcomes.

The stock market reacted in a typical ‘shoot first, ask questions later’ fashion. Across our domestic healthcare coverage, the stocks most impacted were ResMed and to a lesser extent, CSL. CSL’s share price fell 25% between June and October and was trading on its lowest relative P/E level in 8 years, while ResMed’s share price fell by a whopping 33% during this time!

At its lows, ResMed was trading on a discount to the market, where historically it has traded on a substantial premium. With nearly 40% of the global population currently obese or overweight , we think these drugs will be critical in addressing a large unmet need. However, we think the market has gotten ahead of itself from a valuation standpoint. Since the start of 2023, the share prices of GLP-1 ‘losers’ such as CSL and ResMed have underperformed GLP-1 ‘winners’ by a whopping 65%! Below we outline some reasons why we are cautious.



Results may vary

‘Second gen’ drugs have demonstrated more than double the weight loss of ‘first gen’ drugs in clinical trials (e.g. around 16% vs 6% mean weight loss after 1 year) . Newer drugs, such as Mounjaro/Zepbound, have demonstrated average weight reduction of 22% after 1 year . However real-world outcomes rarely match those of a closely controlled clinical trial. For example, real world weight loss of ‘second gen’ drugs have only been around 5%, a far cry from the 16-22% weight loss seen in clinical studies.

These results make sense when you consider that the clinical study environment is tightly controlled, and diet and exercise is strictly monitored (i.e. not an accurate reflection of the real world). Of course, real-world outcomes would likely be better than 5% if adherence and lifestyle changes are implemented. We should expect the magnitude of weight loss to increase over time as more efficacious drugs are introduced, but translating clinical results into sustainable, real-world outcomes will remain a key challenge.

No free lunch

Wegovy costs patients around US$1,300 per month out-of-pocket. Although several corporate health insurance plans cover it, it is not reimbursed by US Medicare for weight loss. Consider that the US already has the most expensive healthcare system in the world - Federal spending on healthcare totalled $1.9 trillion in FY23. If the US healthcare system covered GLP-1s for weight loss, it would soon be bankrupt! We expect prices will likely come down over time thanks to new entrants and generics down the track, while reimbursement could expand if trials for new indications are successful. We are reminded of blockbuster drugs like Viagra which cost $88 per pill a decade ago and now cost only $2 per pill for the generic version. Ultimately the cost of reimbursing GLP-1s will have to be weighed against the cost to healthcare systems from untreated obesity and other co-morbidities. We note that the benefit from reducing co-morbidities alone could be enough to justify their cost to the healthcare system (90% of people who are obese also have co-morbidities).

Stick it out – or not

Adherence to GLP-1s has improved from prior generations but remains low. Real world studies show only 1/3 of people adhered to new generation drugs after 1 year. The most alarming thing is that patients who discontinue the therapy regain almost all the weight they lost (within 2-5 years) or put on even more, according to Novo Nordisk. The reason is partly due to intolerable side-effects, lack of commitment to lifestyle changes, unaffordability or just plain forgetfulness. Whatever the reason, weight loss is not maintained if the drug is discontinued.

Slim chance of no side effects

Gastrointestinal adverse effects (e.g. nausea, diarrhoea, vomiting and constipation) are common with GLP-1s, particularly at the early stages of taking the drug. Acute pancreatitis, pancreatic and thyroid cancer have also been noted as risks. Suicidal thoughts and self-harm have also been observed as unwelcomed side-effects – unsurprising in the context of a drug that removes your cravings and appetite for an extended period.

In addition, clinical studies looking at GLP-1 related weight loss found that lean body mass contributed up to 50% of the total weight loss. Lean body mass is crucial for bone health and decreases as we age, which means GLP-1s are not suitable for the elderly or infirm. Loss of lean body mass can also exacerbate obstructive sleep apnoea by contributing to the weakening of airway integrity. Any additional longer-term side effects of the drugs will only be uncovered through continuous monitoring and study – we don't have the full picture yet.

Portfolio Implications

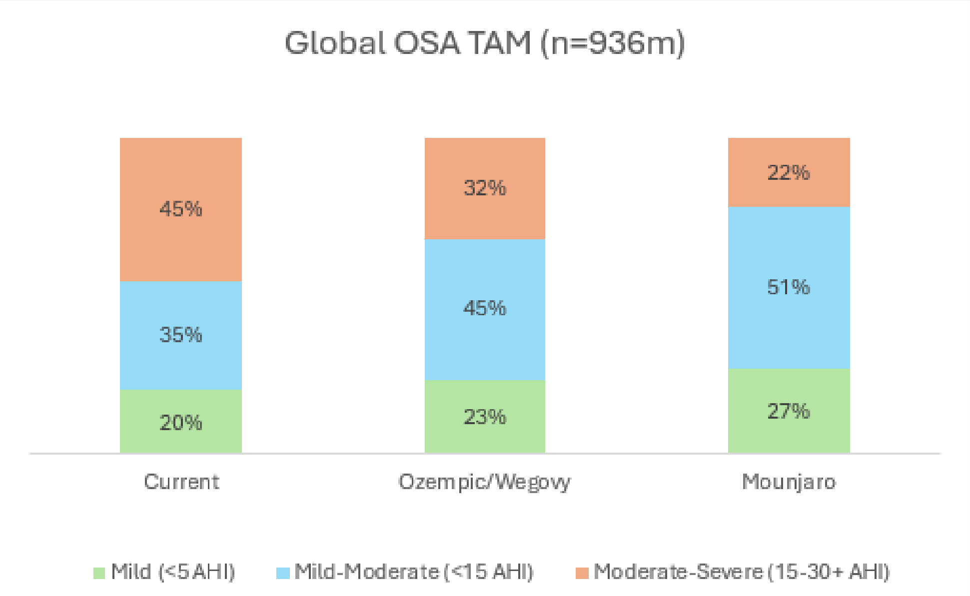
ResMed

ASX: RMD

ResMed is the leading manufacturer of continuous positive airway pressure (CPAP) machines and masks used for obstructive sleep apnoea (OSA). As 70% of OSA is related to excess weight, material weight loss from GLP-1s is likely to result in a reduction of OSA and hence CPAP use.

What is less clear is whether the reduction in sleep apnoea is large enough such that patients can throw away their CPAP machines. The extent of this will be determined in a Phase 3 study from Eli Lilly called the SURMOUNT-OSA trial which is due this quarter.

Prior studies have shown that a 10% weight loss predicted a ~25% reduction in sleep apnoea scores (AHI). Considering Mounjaro's ~20% weight loss (under clinical trial conditions), this implies that we should expect to see a roughly 50% decrease in AHI from the SURMOUNT-OSA trial. Studies estimate around 45% of the addressable global population fall in the Moderate-Severe category of OSA (AHI score of 15-30+). With a 50% reduction in AHI, severe patients should move into the moderate category (AHI of 15+) but would likely still have OSA and still require CPAP. In essence, all it does is push more people into the Mild-Moderate category, although some mild patients may end up not requiring CPAP at all.



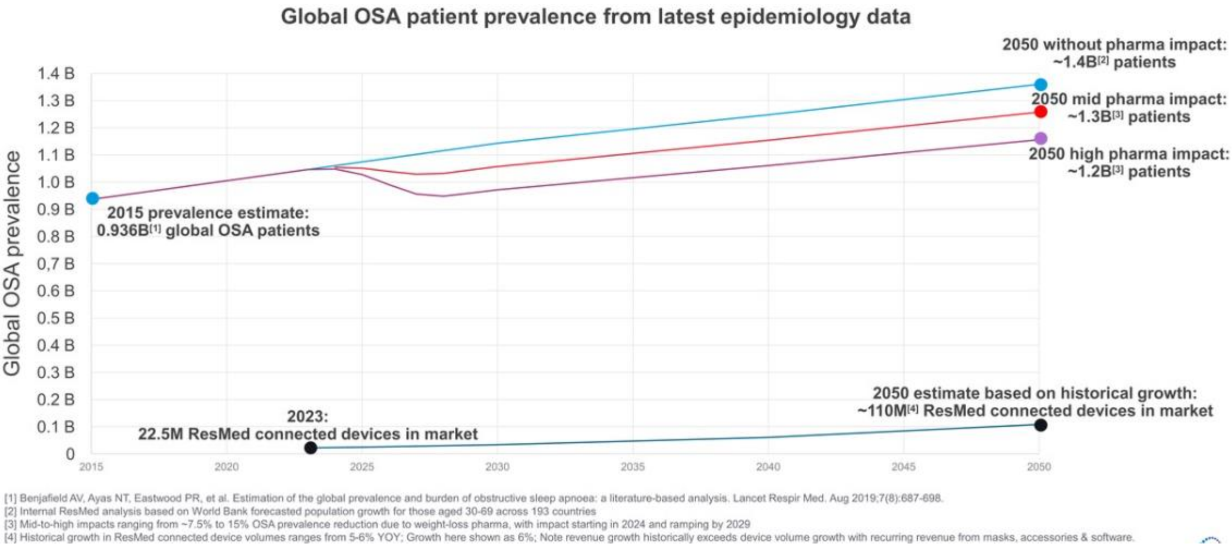
Source: Northcape estimates, company reports

It is important to note that GLP-1s could lead to an increase in patients being treated for OSA if a weight loss-induced reduction in sleep apnoea allows a patient to be treated for CPAP where they previously couldn't or wouldn't. Currently there is high avoidance of the healthcare system of patients with BMIs over 30. Thus, lowering BMI may bring more patients into the funnel to be treated for sleep apnoea. ResMed's analysis suggests patients on GLP-1s increase CPAP starts by 10% and resupply by 3-5%.

The total addressable market of OSA sufferers is immense and growing by the day. Diagnosis rates remain low.

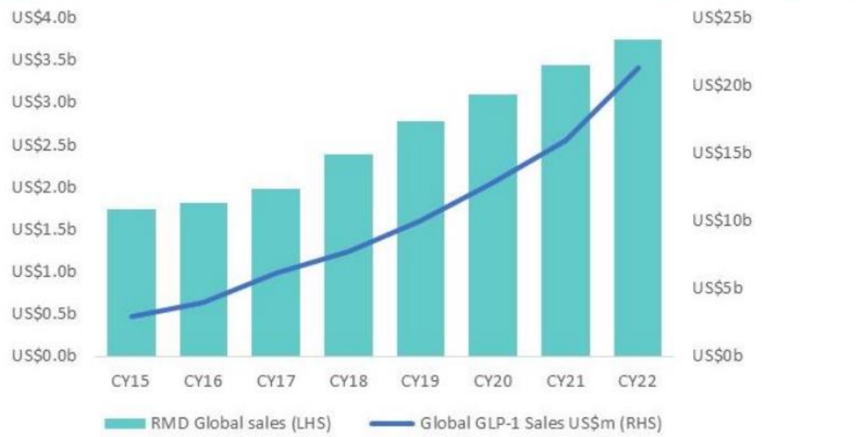
Assuming strong adoption and adherence to GLP-1s, ResMed believes there could be up to 15% reduction in the total addressable OSA market by 2050. Even under this extremely disruptive scenario, the global OSA TAM is still estimated to reach 1.2bn by 2050, with ResMed expected to have only around 9% penetration of this market. If we assume ResMed will sustain a 70% market share, this suggests across all OSA manufacturers CPAP will only be around 13% penetrated. This highlights that OSA will still be a large and underserved market, despite the proliferation of GLP-1s.

As mentioned previously, GLP-1 drugs have been in the market for almost a decade and have delivered huge revenue growth to the companies that manufacture them but have not had any discernible impact on ResMed's CPAP sales. As a result, we think it is likely that CPAP will remain the low-cost, high-efficacy first-line treatment for OSA and will likely be used in conjunction with GLP-1s where required for the best results.



Source: ResMed JPM Conference 2023 presentation

Figure 15: Global sales GLP-1 vs RMD. GLP-1 success not come at the expense of RMD growth.



Source: MST Marquee research. While GLP-1s have only been approved for weight loss in the last few years (previously only for diabetes), there is a very large number of people who suffer from both Type 2 diabetes and sleep apnoea (80%).

Warakirri ASSET MANAGEMENT

CSL

CSL, along with other dialysis stocks, was hit hard in October after news that Novo Nordisk planned to stop their Phase 3 trial early after demonstrating slower onset of Stage 4 Chronic Kidney Disease. Nephrology accounts for around 7% of CSL Vifor's Group revenues and earnings, and dialysis an even smaller part of this, yet the stock fell 10% during the month as the market threw CSL in as part of the 'GLP-1 losers' basket.

While we acknowledge there could be some impact to CSL Vifor's dialysis patient population, we think this is more likely to be at the margin. Novo's trial demonstrated that GLP-1s delay, rather than cure, chronic kidney disease progression, meaning patients will likely still need dialysis at some point in the future. GLP-1s may also act to prolong a kidney failure patient's lifespan, which means they will spend more time on dialysis. Further, CSL Vifor's IV iron is used across many other indications outside of chronic kidney disease, including in heart failure and oncology, with new indications being discovered over time. Lastly, having diabetes or being obese are only two of the diseases that can lead to end-stage renal failure, the other causes commonly being hypertension, autoimmune or genetic diseases, which GLP-1s do not treat.

In terms of the impact on CSL's trial in recurring heart attacks (CSL112), we believe GLP-1s may reduce the incidence of heart attacks, but they do not mitigate ageing (as you age, the risk of a heart attack goes up).

Portfolio Activity

We have been actively adding to our positions in both CSL and ResMed during the quarter given their attractive valuations. Both stocks have rerated but there could be further upside in our view.

For ResMed, some investors continue to sit on the sidelines ahead of the read-out of Lilly's SURMOUNT-OSA trial. Outside of GLP-1s, ResMed should continue to enjoy further margin improvement throughout the year as component and freight costs normalise and a mix of benefits come through. Philips (a major CPAP competitor) has been burdened by recall issues which has afforded ResMed a generational opportunity to capture market share.

For CSL we expect double digit earnings growth over the medium term and improved ROIC over the next few years as capex is set to decline 30% this year. We maintain a substantial active position in the name.

Conclusion

There is clearly a large and unmet need for safe and effective weight loss treatments. We believe GLP-1s will help people lose weight and improve their overall health, while generating attractive profits for the drug companies producing them. But as we've outlined, these drugs have some major limitations, and their longer-term impacts are still unknown.

The market reaction to news on GLP-1 drugs last year looked excessive to us and created opportunities to buy some great healthcare businesses at attractive prices. In recent years, we think the market has become increasingly focused on near-term news flow and less interested in long-term earnings. This creates volatility but also generates opportunities for investors who are prepared to go against the crowd.

For more information, please contact us on 1300 927 254 or visit warakirri.com.au