kotak Institutional Equities

Pharmaceuticals

India

Sector View: **Neutral** NIFTY-50: **21,545** **January 09, 2024**

GLP-1: The weight of expectations

GLP-1 drugs continue to hog the limelight given the huge demand across the US and other markets for Type 2 diabetes and chronic weight management. As of CY2023, we estimate ~8.8 mn patients were consuming GLP-1 drugs for diabetes and weight loss globally. Despite factoring in the intermittent hit from genericization, we expect the global branded formulation sales of GLP-1 drugs to report a robust 10-year CAGR of 12% to reach ~US$106 bn by CY2033E with Tirzepatide and Semaglutide being the key contributors. While the market is still nascent, our analysis of the long-term opportunity suggests missing obvious Indian CDMO winners as well as heightened generic competition, thereby curbing any outsized gains for Indian companies.

While GLP-1 drugs are not new, recent advancements have opened horizons

Led by meaningful reduction in weight coupled with a better safety profile, the market for GLP-1 drugs and their combinations hold a lot of promise. Across various studies, GLP-1 drugs have demonstrated weight loss of 15-25% compared to 3-11% for non-GLP drugs. In our view, the development of GLP-1 drugs for weight loss has just picked up pace, and several additional advances can be expected in the coming years. Building on to Liraglutide and Semaglutide, the incremental success of combinations such as Tirzepatide and Retatrutide provides further impetus. Apart from these injectables, companies continue to invest heavily in developing oral alternatives such as Rybelsus. In addition to diabetes and weight loss, companies continue to explore multiple other potential benefits of GLP-1 drugs.

We expect the branded global GLP-1 market to reach ~US$106 bn by CY2033E

In our estimates for the global GLP-1 market, we either build in generic launches as soon as the patents expire or factor in settled launches prior to expiry. We have also accounted for future launches of combination drugs, such as Retatrutide and Cagrisema. We forecast the global GLP-1 API and intermediates market size (ex-generics) to stand at US$2.9 bn and US$1.5 bn, respectively, by CY2033E. While insurance coverage is not widespread yet, we expect access to gradually increase as insurers witness the long-term benefit of these drugs in reducing claims.

Missing obvious winners could curb outsized gains for Indian companies

With the supply-demand mismatch yet to be completely resolved amid burgeoning demand, there remains a possibility of the innovators (Novo Nordisk, Eli Lilly, Pfizer) increasingly utilizing the services of CDMOs. From an Indian context, we believe Divi's GLP-1 exposure as a CDMO is limited just to amino-protecting groups (a relatively smaller portion of value chain). Nevertheless, using our forecasts for the overall market size as well as factoring in Divi's eventual entry in GLP-1 APIs in CY2027E, we optimistically estimate an NPV of Rs258/share from the GLP-1 opportunity for Divi's. Given the steep valuations on elevated earnings, we believe the GLP-1 opportunity is already well-captured at Divi's CMP. In addition, several Indian pharma companies have developed or are developing the generic formulations of the GLP-1 drugs. However, beyond Liraglutide, we expect the GLP-1 generic opportunity to play out only over the long term in the US. While the market is vast, our analysis of the crowded competitive landscape for GLP-1 generics suggests limited scope for inordinate gains for individual companies.

Company data and valuation summary

	Rating	Fair Value (Rs)	P/E (X) 2024E	P/E (X) 2025E
Pharmaceuticals				
Aurobindo Pharma	SELL	840	21.5	18.5
Biocon	REDUCE	235	64.5	30.7
Cipla	ADD	1,320	26.4	23.2
Concord Biotech	REDUCE	1,300	53.2	41.5
Divis Laboratories	SELL	2,775	61.9	48.0
Dr Reddy's Laboratories	REDUCE	5,375	17.8	17.0
Gland Pharma	SELL	1,365	35.8	30.0
Glenmark Life Sciences	NR	–	NA	NA
Laurus Labs	SELL	270	60.4	34.9
Lupin	SELL	1,005	36.1	31.1
Mankind Pharma	ADD	2,000	45.6	36.6
Sun Pharmaceuticals	ADD	1,280	34.6	28.8
Torrent Pharmaceuticals	REDUCE	1,950	48.2	38.8
Pharmaceuticals	**Neutral**		**33.1**	**27.8**

Source: Bloomberg, Company data, Kotak Institutional Equities estimates

Prices in this report are based on the market close of January 09, 2024

Quick Numbers

As of CY2023, we estimate ~8.8 mn patients were consuming GLP-1 drugs for diabetes and weight loss globally

We expect the global branded formulation sales of GLP-1 drugs to report a robust 12% CAGR from ~US$35 bn in CY2023E to ~US$106 bn by CY2033E

We forecast the global GLP-1 API and intermediates market size (ex-generics) to stand at US$2.9 bn and US$1.5 bn, respectively, by CY2033E

We optimistically estimate an NPV of Rs258/share from the GLP-1 opportunity for Divi's, which is already well captured at CMP

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While GLP-1 drugs are not new, recent advancements have opened horizons

GLP-1 agonists are a class of drugs that help people with Type 2 diabetes manage their blood sugar levels. Some GLP-1 drugs can also aid in chronic weight management. These drugs are also referred to as 'Glucagon-like peptide-1 agonists', 'GLP-1 receptor agonists', 'Incretin mimetics', or 'GLP-1 analogs'. Currently, most of the approved GLP-1 drugs are subcutaneous injectables. In CY2005, the US FDA approved the first GLP-1 agonist, Exenatide. Later in CY2010, Liraglutide was approved for use as a Type 2 diabetes medication. Since then, approvals have picked up pace with the approvals of Dulaglutide in CY2014, Semaglutide in CY2017, and Tirzepatide in CY2022. While Tirzepatide, Semaglutide and Liraglutide have caught attention given the resultant weight loss post intake, researchers are still learning about their other possible applications and advantages.

GLP-1 agonists are a class of drugs that help people with Type 2 diabetes manage their blood sugar levels

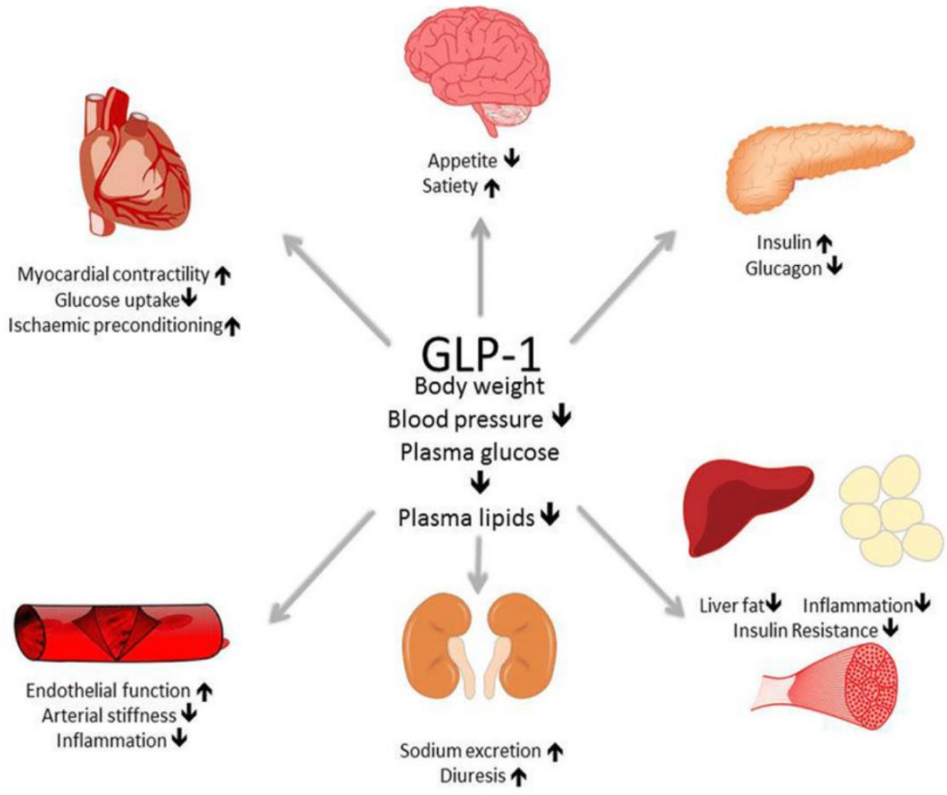
How do they function?

The GLP-1 agonist can be traced back to the naturally occurring GLP-1 hormone, which is produced by the small intestine. It serves numerous functions, including:

- **Triggering pancreatic insulin release**: Insulin is a necessary hormone that allows the body to convert food to energy. It reduces the level of glucose (sugar) in blood. Lack of insulin increases blood sugar levels, which then leads to diabetes. GLP-1 triggers the pancreas to release insulin.
- **Glucagon secretion inhibition**: Glucagon is a hormone that the human body employs to elevate blood sugar levels when necessary. GLP-1 stops more glucose from entering the bloodstream.
- **Slower digestion & feeling of fullness**: Slower stomach emptying implies that the body releases less glucose from the food into the bloodstream. GLP-1 influences parts of the brain that handle appetite and satiety, making one feel fuller after eating.

GLP-1 triggers insulin secretion while inhibiting glucagon secretion resulting in slower stomach emptying

Exhibit 1: Functions of GLP-1 hormone



Source: Canadian Science Publishing

We note these drugs are chronic in nature, which means, there is likely to be a reversal in weight loss when a patient stops taking the drug

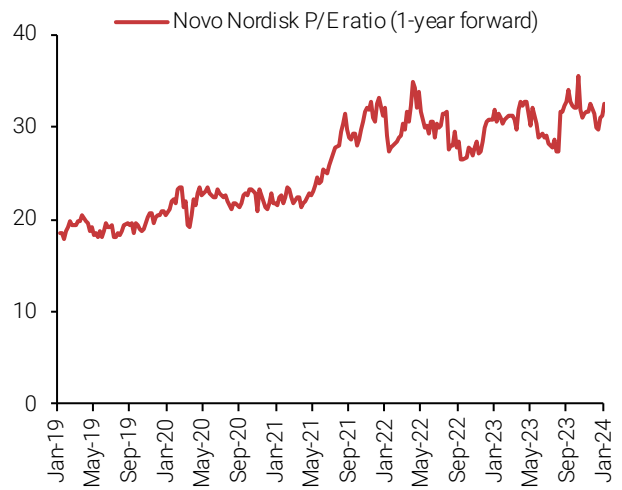
GLP-1 agonists act by simulating this natural hormone. An agonist is a synthetic drug that binds to a cell receptor and performs the same function as the naturally occurring chemical. GLP-1 drugs, in other words, bind to GLP receptors to activate the effects of the GLP-1 hormone. The greater the GLP-1 agonist dose, the stronger the effects. For Type 2 diabetes patients, these drugs help control blood sugar by causing the pancreas to produce more insulin. Slowing digestion also helps to reduce blood sugar spikes. GLP1-agonists' satiety effect reduces food intake, appetite, and hunger. As a result, weight reduction is frequently the outcome of these combined actions.

Everyone wants a piece of the pie

While GLP-1 drugs have been around since the past two decades, they have been in the news over the past few years due to their huge demand across the US and other markets for chronic weight management. Novo Nordisk and Eli Lilly, the two major players in this category, have been rapidly expanding their capacities in order to meet the surging demand. Apart from Type 2 diabetes, the extreme demand can also be explained by the increased off-label use of these drugs for weight-loss management. This indicates that although medications such as Ozempic are only approved to treat diabetes, individuals who require them for weight reduction but do not have diabetes can be prescribed GLP-1 drugs since they contain the same active ingredient. Driven by the huge demand for the GLP-1 drugs, the stocks of the innovators have seen a strong rerating in the past few years.

Novo Nordisk's stock price has rallied 3.4X in the past 3 years

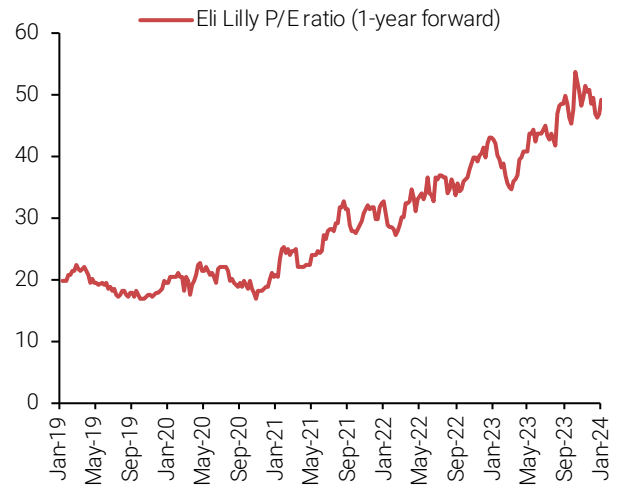
Exhibit 2: Novo Nordisk P/E ratio, December calendar year-ends, 2019-23 (x)



Source: Bloomberg, Kotak Institutional Equities

Eli Lilly's stock price has rallied 3.7X in the past 3 years

Exhibit 3: Eli Lilly P/E ratio, December calendar year-ends, 2019-23 (x)



Source: Bloomberg, Kotak Institutional Equities

Occasionally, pharmacies may produce their own versions of these drugs. It is a process called compounding, by which certain specialized pharmacists can re-formulate drugs and market them. The US FDA may allow compounding under a few situations, including when the drug is in shortage, as is the case with Tirzepatide and Semaglutide. We note compounded drugs are not subject to the US FDA quality, safety, or efficacy inspections. As a result, the agency is clear there is a higher risk associated with compounded drugs than with those manufactured directly by manufacturers.

It is also critical to note that these drugs are chronic in nature. There is likely to be a reversal in weight loss when a patient stops taking the drug. Consequently, these medications are prescribed as a continuing treatment for weight loss. As per scientists, GLP-1 agonists alone cannot give best results for the treatment of Type 2 diabetes or obesity. Both these conditions require other treatment strategies, such as lifestyle and nutritional adjustments.

GLP-1 drugs can be used on a standalone basis as well as in combinations

There are multiple versions of GLP-1 drugs in the market along with several versions under development. We can classify these drugs majorly into two categories:

- **GLP-1 only drugs**: These involve single GLP-1 molecules such as Semaglutide, Dulaglutide, Liraglutide and Exenatide.
- **GLP-1 combinations with other hormones**: These drugs involve GLP-1 molecules combined with one or more hormones in order to enhance the effect of GLP-1s. The most common drug in this class is Tirzepatide, which is a combination of GLP-1 and GIP. GLP-1 and GIP both act on the pancreas to increase production of the hormone insulin, which lowers blood glucose. They also decrease production of glucagon, which normally increases glucose levels when they are too low.

While three injectables have been approved, there are no oral GLP-1 drugs approved for weight loss by US FDA

Exhibit 4: Details of key GLP-1 drugs in the market

Drug name	Innovator	Dosage	Dosage form	US FDA approval date	Approved for	Other benefits
Byetta (Exenatide)	AstraZeneca	Twice daily	Injectable	Oct-09	Type 2 diabetes	Weight loss
Bydureon BCise (Exenatide)	AstraZeneca	Once weekly	Injectable	Jan-12	Type 2 diabetes	Weight loss
Victoza (Liraglutide)	Novo Nordisk	Once daily	Injectable	Jan-10	Type 2 diabetes	Heart, kidneys, weight loss
Saxenda (Liraglutide)	Novo Nordisk	Once daily	Injectable	Dec-14	Weight loss	N/A
Trulicity (Dulaglutide)	Eli Lilly	Once weekly	Injectable	Sep-14	Type 2 diabetes	Heart, kidneys, weight loss
Ozempic (Semaglutide)	Novo Nordisk	Once weekly	Injectable	Dec-17	Type 2 diabetes	Heart, kidneys, weight loss
Rybelsus (Semaglutide)	Novo Nordisk	Once daily	Oral solid	Sep-19	Type 2 diabetes	Weight loss
Wegovy (Semaglutide)	Novo Nordisk	Once weekly	Injectable	Jun-21	Weight loss	N/A
Mounjaro (Tirzepatide)	Eli Lilly	Once weekly	Injectable	May-22	Type 2 diabetes	Weight loss
Zepbound (Tirzepatide)	Eli Lilly	Once weekly	Injectable	Nov-23	Weight loss	N/A

Source: Companies, US FDA, Kotak Institutional Equities

While three injectables have been approved, there are no oral GLP-1 drugs approved for weight loss by US FDA

Byetta (Exenatide)

Exenatide is a GLP-1 analog medication used to treat Type 2 diabetes. Byetta is a twice daily injectable prescription medication. Its frequent dosage is a major cause for its unpopularity among patients and doctors.

- **US FDA approval:** Developed by AstraZeneca, Byetta (Exenatide) was the first US FDA-approved GLP-1 agonist for treatment of Type 2 diabetes in Oct 2009.
- **Indication:** Byetta is injected twice a day around meals. Byetta injection pens come in two strengths: 1.2-mL prefilled pen that contains 5 mcg per dose & 2.4-mL prefilled pen that contains 10 mcg per dose.
- **Efficacy in weight loss:** It can also cause weight loss as a side effect. However, Byetta does not offer the same heart-related benefits as the other GLP-1 options.
- **Side-effects:** In a clinical study with Exenatide, 1.9% of Exenatide-treated patients and 1.4% of placebo-treated patients reported an acute event of gallbladder disease, such as cholelithiasis or cholecystitis.
- **Generic entry:** Byetta's exclusivity in the US is expiring in Nov 2024. Teva has settled with AstraZeneca and can launch once exclusivity expires. Other ANDA developers include Amneal, Gland Pharma, Orbicular Pharma, Sun Pharma, USV and Zydus Cadila.

Bydureon BCise (long-acting Exenatide)

Exenatide is a GLP-1 analog medication used to treat Type 2 diabetes. Bydureon BCise (Exenatide) is a longer-acting version of Byetta. It is a weekly injectable prescription medicine.

- **US FDA approval:** It was approved to lower blood sugar levels in people ages 10 and older with Type 2 diabetes by the US FDA in Jan 2012.
- **Indication:** Bydureon BCise is injected once weekly. It comes in one strength: 2 milligrams (mg) per 0.85 milliliters (ml).
- **Efficacy in weight loss:** Similar to Byetta, Bydureon BCise does not have the same heart-related benefits seen with other GLP-1 agonists. It may not result in the same amount of weight loss either.
- **Sales:** In 9MCY23, Bydureon BCise generated global sales of US$123 mn (annualized sales of ~US$164 mn) for AstraZeneca.
- **Side-effects:** Bydureon BCise may cause serious side effects such as acute pancreatitis, hypoglycemia, acute kidney injury, immunogenicity and acute gallbladder disease.
- **Generic entry:** Manufactured by AstraZeneca, the new patient population exclusivity of Bydureon BCise is expiring on Jul 2024. Other ANDA developers are Dr Reddy's, Orbicular Pharma and MSN Labs.

Victoza (Liraglutide)

Liraglutide is another GLP-1 receptor agonist developed by Novo Nordisk. Victoza (Liraglutide) is an anti-diabetic medication used to treat Type 2 diabetes, and chronic obesity. It is a second-line therapy for diabetes following first-line therapy with Metformin.

- **US FDA approval**: Victoza was approved for use in people ages 10 and older with Type 2 diabetes by the US FDA in Jan 2010.
- **Indication:** Victoza (Liraglutide) is a once-daily injection for Type 2 diabetes. Victoza injection 1.2 mg or 1.8 mg is an injectable prescription medicine used along with diet and exercise to lower blood sugar (glucose) in adults and children who are 10 years of age and older with Type 2 diabetes as well as to reduce the risk of major cardiovascular events such as heart attack, stroke, or death in adults with Type 2 diabetes with known heart disease. Excluding Exenatide, it is also injected more frequently (daily) than other GLP-1 injectables.
- **Efficacy in weight loss:** During clinical trials, weight loss was around 5 lbs on an average. Victoza can lower the risk of heart attack and stroke if one also has heart disease. There is also evidence that it may help prevent kidney problems from getting worse.
- **Sales:** In 9MCY23, Novo Nordisk generated global sales of US$1.03 bn (annualized sales of ~US$1.4 bn) from Victoza.

In 9MCY23, Novo Nordisk generated global sales of US$1.03 bn (annualized sales of ~US$1.4 bn) from Victoza

- **Side-effects:** The more common side effects of Victoza include headache, nausea, vomiting, diarrhea, constipation, indigestion, loss of appetite and hypoglycemia (low blood sugar), which is more common in children than in adults.
- **Generic entry:** Novo Nordisk is the innovator, and there have been 10+ Para IV filers, namely Teva, Viatris, Sandoz, Hikma, Sun Pharma, Biocon, Orbicular Pharma, Lupin, ScinoPharm, Meitheal Pharma and Dr Reddy's. Teva has the FTF. Teva filed a Para IV and was litigated. Later, Novo Nordisk settled with Teva, and according to the settlement Teva can launch the generic version of Victoza in Dec 2023 in the US. Viatris and Sandoz also filed a Para IV and were subsequently litigated. Later in Mar 2021, the case was settled between Novo Nordisk and Viatris on undisclosed terms. Later on, in Jun 2021, Sandoz won a couple of patents. In Mar 2022, Novo Nordisk settled with Sandoz on patents '833 and '893. According to settlement agreement, Sandoz can launch their generic on Jun 22, 2024. There are 25+ other ANDA developers.

Saxenda (Liraglutide)

Saxenda (Liraglutide) is an injectable prescription medicine used for adults and children aged 12-17 years with obesity to help them lose weight and keep the weight off. Saxenda and Victoza use the same active ingredient and Saxenda is the version of Liraglutide approved by the US FDA for weight loss.

- **US FDA approval**: Saxenda is the version of Liraglutide approved for weight loss. It was approved by the US FDA in Dec 2014. Similar to Wegovy, it can be used in adults with a BMI of 30 mg/kg² or greater, or at least 27 mg/kg², with one or more weight-related medical conditions.
- **Indication:** Saxenda injection 3mg is an injectable prescription medicine used for adults with excess weight (BMI ≥27) who also have weight-related medical problems or obesity (BMI ≥30), and children aged 12-17 years with a body weight above 132 pounds (60 kg) and obesity to help them lose weight.
- **Efficacy in weight loss:** In a large clinical trial, adults using Saxenda lost an average of 8% of their starting body weight. In a separate trial, adolescents lost a little over 2.5% of their starting body weight on an average. One head-to-head study showed significantly more weight loss in adults with Wegovy (16%) than Saxenda (6%). One also needs to inject Saxenda more frequently (daily) than Wegovy (weekly).
- **Sales:** In 9MCY23, Novo Nordisk generated global sales of US$1.3 bn (annualized sales of ~US$1.7 bn) from Saxenda.

In 9MCY23, Novo Nordisk generated global sales of US$1.3 bn (annualized sales of ~US$1.7 bn) from Saxenda

- **Side-effects:** The most common side effects of Saxenda include nausea, low blood sugar (hypoglycemia), dizziness, diarrhea, headache, stomach pain, constipation, vomiting, upset stomach (dyspepsia), tiredness (fatigue) and change in enzyme (lipase) levels in blood.
- **Generic entry:** Novo Nordisk is the innovator, and there are 5 Para IV filers, namely Teva, Cipla, Sun, Biocon and Lupin. For Saxenda, exclusivity expired in Dec 2023. Teva is the FTF and has settled for the patent expiring in Feb 2026. The settlement document suggests the injection device is different from Novo Nordisk and hence Teva's likely launch is between May 2024 and Feb 2026. We note there are 15+ other ANDA developers of Saxenda.

Trulicity (Dulaglutide)

Manufactured by Eli Lilly, it is sold in the US under the brand Trulicity. Dulaglutide, is a medication used for the treatment of Type 2 diabetes in combination with diet and exercise.

- **US FDA approval**: Eli Lilly got the US FDA approval to market Trulicity in Sep 2014. Trulicity has been approved only for Type 2 diabetes and not for weight loss. But some patients are using it to lose weight as a side effect.
- **Indication:** Trulicity is a once-weekly injectable prescription medicine to improve blood sugar (glucose) in adults and children 10 years of age and older with Type 2 diabetes mellitus. It should be used along with diet and exercise. It comes as a single-use pre-filled pen.
- **Efficacy in weight loss:** One study found that adults taking the highest Trulicity dose (4.5 mg) were able to lose up to 10 lbs over 9 months. Similar to Ozempic, Trulicity can lower the risk of heart attack and stroke in adults who also have heart disease. But it can also provide this benefit if one has heart disease risk factors. Trulicity may also have some kidney-related benefits.
- **Sales:** In 9MCY23, Eli Lilly generated global sales of US$5.5 bn (annualized sales of ~US$7.3 bn) from Trulicity.
- **Side-effects:** The most common adverse reactions experienced with Trulicity are nausea, diarrhea, vomiting, abdominal pain, decreased appetite, indigestion and fatigue. The rates of nausea, vomiting and diarrhea, while numerically higher in each of the higher Dulaglutide groups compared with the 1.5 mg group were similar between the Dulaglutide 3.0 mg and 4.5 mg groups in a clinical trial.
- **Generic entry:** The patent for this drug is set to expire in Jan 2028, post which generics can launch in the US.

Ozempic (Semaglutide)

Ozempic (Semaglutide) injection is a once-weekly GLP-1 medicine that, along with diet and exercise, may help improve blood sugar in adults with Type 2 diabetes. By mimicking the action of the incretin GLP-1, it increases the production of insulin, the hormone that lowers the blood sugar level.

- **US FDA approval**: Developed by Novo Nordisk, Ozempic was approved by the US FDA in Dec 2017. We note Ozempic is not approved for weight loss, but approved for Type 2 diabetes. However, one may notice weight loss as a side effect.
- **Indication:** Ozempic (Semaglutide) injection 0.5 mg, 1 mg, or 2 mg is an injectable prescription. It is a once-weekly injection for adults with Type 2 diabetes. It comes in a multi-dose pre-filled pen.
- **Efficacy in weight loss:** During clinical trials**,** those who received Ozempic, had a mean change in body weight of -14.9% after 68 weeks compared with -2.4% seen in the placebo group. In addition, 86% of participants who received the treatment attained at least a 5% reduction in total body weight. On average, those taking it lost 8 to 10 lbs during the trials.
- **Sales:** In 9MCY23, Novo Nordisk generated global sales of US$9.8 bn (annualized sales of ~US$13.1 bn) from Ozempic.
- **Side-effects:** The most common adverse reactions, reported in ≥5% of patients treated with Ozempic are nausea, vomiting, diarrhea, abdominal pain, and constipation.
- **Generic entry:** Novo Nordisk is the innovator, and there have been 7 Para IV filers, namely Sun Pharma, Alvogen, Aurobindo Pharma, Dr Reddy's, Rio Biopharmaceuticals, Zydus Cadila and Viatris to date. Natco Pharma has the solo FTF for Semaglutide pen (8mg/3ml). The NCE exclusivity expired on Jan 2023. The last patent expires in Feb 2032. Generics cannot launch before it. Other ANDA developers are USV, Accord (Intas Pharma), Aurobindo Pharma, Biocon, Cipla, Gland Pharma, Lupin, Macleods, MSN Labs, Natco Pharma, Orbicular Pharma and Extrovis.

In 9MCY23, Novo Nordisk generated global sales of US$9.8 bn (annualized sales of ~US$13.1 bn) from Ozempic

Rybelsus (Semaglutide)

Rybelsus is once-daily prescription medicine used along with diet and exercise to improve blood sugar in adults with Type 2 diabetes. It is the oral solid version of Semaglutide. Rybelsus is the only GLP-1 approved by US FDA that does not need to be injected.

- **US FDA approval**: Rybelsus was approved by the US FDA in Sep 2019. Rybelsus is not approved for weight loss, but for Type 2 diabetes. Additionally, Rybelsus is not approved for the same heart-related benefits.
- **Indication:** Rybelsus tablets 7 mg or 14 mg is a prescription drug used along with diet and exercise to improve blood sugar (glucose) in adults with Type 2 diabetes. Rybelsus is taken by mouth once daily. It is possible for a patient to switch from Ozempic to Rybelsus (and vice versa). But if a patient's Ozempic dose is 1 mg or greater, this may not be possible.
- **Efficacy in weight loss:** One study showed that participants on the highest standard dose (14 mg) of oral Semaglutide lost an average of 4.4 kg (less than 5% of their body weight) after 52 weeks. People who took a placebo only lost an average of 0.5 kg (0.5% of their body weight) in this period.
- **Sales:** In 9MCY23, Novo Nordisk generated global sales of US$1.9 bn (annualized sales of ~US$2.6 bn) from Rybelsus.
- **Side-effects:** Common Rybelsus side effects may include upset stomach, heartburn, nausea, vomiting, stomach pain, loss of appetite, diarrhea, constipation, runny nose or sore throat, headache, dizziness, tiredness and stomach flu symptoms.
- **Generic entry:** Novo Nordisk is the innovator, and there are 10 ANDA developers, namely MSN Labs, Aurobindo Pharma, Viatris, Sotac Pharma, Lupin, Torrent Pharma, Micro Labs, Alkem Labs, Macleods and Aizant. Its NCE exclusivity expired on Dec 2022. The patent expires in Feb 2034.

Wegovy (Semaglutide)

Wegovy (Semaglutide) is a once-weekly GLP-1 injectable weight-loss medication for adults with obesity or excess weight with weight-related conditions. Wegovy works by mimicking the GLP-1 hormone that targets areas of the brain that regulate appetite and food intake.

- **US FDA approval**: Wegovy was approved by the US FDA for weight loss management for adults and adolescents ages 12 and older in Jun 2021. It is not used to treat diabetes, and one does not need to have a diabetes diagnosis to use it.
- **Indication:** Wegovy (Semaglutide) injection 2.4 mg is an injectable prescription drug that may help adults and children aged ≥12 years with obesity, or some adults with excess weight (BMI ≥27) (overweight) who also have weight-related medical problems to help them lose weight and keep it off.
- **Efficacy in weight loss:** In clinical trials, adults taking Wegovy saw an average weight loss of nearly 15% of their initial body weight. And adolescents saw an average weight loss of about 16% of their initial body weight.
- **Sales:** In 9MCY23, Novo Nordisk generated global sales of US$3.3 bn (annualized sales of ~US$4.3 bn) from Wegovy.
- **Side-effects:** The most common side effects of Wegovy may include nausea, diarrhea, vomiting, constipation, stomach pain, headache, fatigue, upset stomach, dizziness, feeling bloated, belching, gas, stomach flu, heartburn, runny nose and sore throat.
- **Generic entry:** Novo Nordisk is the innovator for Wegovy with the last patent expiring in CY2032, while Viatris has the FTF. In Dec 2022, Viatris filed litigations against four of Novo Nordisk's patents, and the litigation is ongoing. Generic launch can happen only after Jun 2025, if this gets settled. Other ANDA developers are Sun Pharma, Zydus Cadila, Aurobindo Pharma, Cipla, Lupin, Natco Pharma, Orbicular Pharma, Extrovis and Aizant.

Mounjaro (Tirzepatide)

Tirzepatide is part of a new class of drugs called GLP-1/GIP agonists. Tirzepatide works by mimicking two gut hormones, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). Marketed by Eli Lilly, it is sold in the US under the brand, Mounjaro.

In 9MCY23, Eli Lilly generated global sales of US$3 bn from (annualized sales of ~US$3.9 bn) Mounjaro

- **US FDA approval**: Mounjaro has been only approved by US FDA to treat Type 2 diabetes for now. This drug was approved by US FDA in May 2022. However, doctors have been prescribing it off-label for weight loss as well.
- **Indication:** Mounjaro is a once-weekly injectable prescription medicine to lower blood sugar. It comes in pre-filled single-dose pens or single-dose vials in multiple dosages: 2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL and 15 mg/0.5 mL.
- **Efficacy in weight loss:** Mounjaro has been studied head-to-head against Ozempic. After 40 weeks, subjects taking it saw a better reduction in hemoglobin A1C levels (average blood sugar over 3 months) compared to Ozempic. In addition, these subjects lost more weight too. Researchers found that patients taking Mounjaro were three times more likely to lose 15% weight than those on Ozempic.
- **Sales:** In 9MCY23, Eli Lilly generated global sales of US$3 bn from (annualized sales of ~US$3.9 bn) Mounjaro.
- **Side-effects:** Mild side effects of Mounjaro that have been reported include nausea and vomiting, diarrhea, decreased appetite, constipation, abdominal pain, injection site reactions, heartburn and mild allergic reaction.
- **Generic entry:** The patent for this drug is set to expire in Jun 2039, while exclusivity expires in May 2027. While currently there are not many known ANDA developers, similar to Ozempic, we believe Mounjaro is bound to witness significant interest from generic pharma companies.

Zepbound (Tirzepatide)

Zepbound is the version of Tirzepatide approved by US FDA for weight loss. Similar to Mounjaro, it mimics the two gut hormones, GLP-1 & GIP.

The most frequent adverse events of GLP-1 drugs are gastrointestinal, especially nausea, which are generally reported as mild to moderate and settle in 8–10 weeks

- **US FDA approval:** Marketed by Eli Lilly, Zepbound got US FDA approval for weight loss in Nov 2023.
- **Indication:** Launched in Dec 2023 in the US, Zepbound is available in six doses (2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg) as a once-weekly injectable prescription.
- **Efficacy in weight loss:** At the highest dose (15 mg), people taking Zepbound lost an average of 48 lbs., while at the lowest dose (5 mg), people lost 34 lbs on an average (compared to 7 lbs. on placebo). Additionally, 1 in 3 patients taking Zepbound at the highest dose lost over 58 lbs. (25% of body weight), compared to 1.5% on placebo, according to data not controlled for type-1 error. The average starting weight was 231 lbs.
- **Sales:** Given the commercial launch in the US happened only in Dec 2023, sales data is not available.
- **Side-effects:** Zepbound may cause side effects such as severe stomach problems, kidney problems (kidney failure), gallbladder problems, inflammation of the pancreas (pancreatitis), allergic reactions, low blood sugar (hypoglycemia), changes in vision in patients with Type 2 diabetes and depression or thoughts of suicide.
- **Generic entry:** Currently, there is no known ANDA developer.

Adlyxin (Lixisenatide)

Manufactured by Sanofi, it used to be sold in the US under the brand Adlyxin. The patent expires in Jul 2025. In Jan 2023, Sanofi announced that Adlyxin will no longer be available in the US market. As per the company, the discontinuation was a business decision due to rising competition in the GLP-1 segment and was not due to safety or efficacy issues.

2

GLP-1s fare much better than other weight loss drugs on efficacy and safety

Apart from Saxenda, Wegovy and Zepbound, five weight loss drugs have been approved by the US FDA. Most of these drugs work by making the patient feel less hungry or fuller, while some do both. The exception among these drugs is Orlistat, which affects the way body absorbs fat. These drugs are much less effective in weight loss as compared to GLP-1 drugs. We highlight GLP-1 drugs can result in a weight loss of about 15-25% whereas non-GLP weight loss drugs can result in weight loss of 3-11%. Apart from higher efficacy, the non-GLP drugs for weight loss tend to have more serious side effects such as suicidal thoughts or actions, seizures, increase in heart rate and blood pressure, insomnia, depression and benzyl alcohol toxicity. In comparison, GLP-1 agonists are generally well tolerated. Given lower efficacy as well as an inferior safety profile, acceptability of these non GLP-1 weight loss drugs has been low. As a result, in our view, GLP-1 drugs arguably offer the first credible option for weight-loss, thereby driving the global captivation.

Despite being relatively better, adverse effects are not completely uncommon in GLP-1 drugs

The most frequent adverse events of GLP-1 drugs are gastrointestinal, especially nausea, which are generally reported as mild to moderate and settle in 8–10 weeks. Since GLP-1s are gut hormones, scientists anticipate that most of their side effects will be concentrated in the gastrointestinal tract. Severe hypoglycemia is rare and occurs only when sulphonyl ureas are co-prescribed. Mild to moderate hypoglycemia occurs in approximately 10% of patients. However, it is still not confirmed whether GLP-1 drugs can cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of GLP-1 drug induced rodent thyroid C-cell tumors has not been determined.

In a research letter published in the Journal of the American Medical Association (JAMA), scientists at the University of British Columbia provide additional data on the magnitude of risks for people taking GLP-1 drugs purely for weight loss. As per the analysis, among 4,700 people without diabetes taking some form of GLP-1 drugs and 650 people taking an older, different combination of weight loss drugs, those taking GLP-1s had a nine times greater risk of pancreatitis and four times higher risk of both obstructed bowels and gastroparesis, which is a slower emptying of the stomach into the intestines. Another study found that patients who were prescribed GLP-1s had: (1) 4.22X higher risk of intestinal obstruction (ileus). Intestinal obstruction occurs when the intestines are unable to pass their contents. A blockage can occur due to nerve or muscle problems in the intestine. This condition is serious and potentially fatal when it occurs; (2) 3.67X higher risk of gastroparesis, sometimes called stomach paralysis. Gastroparesis is when the stomach takes too long to empty its contents. It is frequently accompanied by nausea and vomiting.

We highlight GLP-1 drugs can result in a weight loss of about 15-25% whereas non-GLP weight loss drugs can result in weight loss of 3-11%

We list drugs, other than GLP-1s, approved by the US FDA for weight loss below:

Contrave (Bupropion-naltrexone): Contrave is a prescription weight-loss drug that may help some adults with a BMI of 30 kg/m2 or greater (obese), or adults with a BMI of 27 kg/m2 or greater (overweight) with at least one weight-related medical problem such as high blood pressure, high cholesterol, or Type 2 diabetes, lose weight and keep the weight off. This drug could be especially beneficial for people who struggle with stress eating.

- **Efficacy**: Studies have found that the effects of Contrave can be seen after four weeks of using the medication. After 16 weeks, ~45% of study participants experienced a 5% or greater reduction in body weight. Four 56-week, multi-center, randomized, double-blind, placebo-controlled clinical trials enrolling 4,536 patients to evaluate the efficacy and safety of naltrexone/bupropion found 2-4 times more weight loss in patients taking Contrave compared to placebo. Additionally, weight loss was maintained throughout the 56 weeks in all these trials.
- **Side effects**: Major side-effects of Contrave include suicidal thoughts or actions, seizures, severe allergic reactions, increases in blood pressure or heart rate and liver damage or hepatitis.

Xenical & Alli (Orlistat): Orlistat belongs to a class of drugs called lipase inhibitors. Orlistat reduces the amount of fat absorbed in the gut after eating. When taking it, no more than 30% of calories should come from fat. Because of how it works, Orlistat is often a better choice for people who tend to eat fatty foods. Dosing for Xenical is usually 120 mg three times daily. Similar to Xenical, Alli contains the active ingredient, Orlistat. This version is available over the counter (OTC) and comes in a 60 mg capsule.

- **Efficacy**: One can expect to lose at least 5% of the body weight in one year. However, it may not be as effective as other weight-loss medications. In another study, people who took the drug Liraglutide (Saxenda and Victoza) lost more weight (about 17 pounds) than those on Orlistat (about 7 pounds) over a period of seven months.
- **Side-effects:** Orlistat can cause side effects such as having loose stool. In rare cases, people have had serious liver injury with Orlistat. Nevertheless, we note that researchers have not found direct evidence that the drug causes liver injuries.

Qsymia (Phentermine-topiramate): Phentermine-topiramate is a combination of a weight-loss drug called phentermine and an anticonvulsant called topiramate. Phentermine by itself (brands such as Adipex-P, Lomaira) is used for weight loss. It is one of the four similar weight-loss drugs approved for use for less than 12 weeks, or short-term use. The other drugs in this group are not often prescribed.

- **Efficacy**: In clinical trials, people treated with the highest dose of phentermine/topiramate ER in combination with a program of diet and exercise lost 10% to 11% of their body weight compared to 1% to 2% for those who received placebo. In addition, 62-70% of subjects receiving the recommended dose or top dose of phentermine/topiramate ER achieved ≥5% weight reduction by week 56 compared to 17-21% of those receiving a placebo.
- **Side-effects:** Phentermine has the potential to be misused because it acts like a stimulant drug called amphetamine. Other possible side effects include an increase in heart rate and blood pressure, insomnia, constipation, and nervousness. Topiramate also increases the risk of birth defects.

Imcivree (Setmelanotide): The US FDA has approved Setmelanotide only for people aged more than six years, who have obesity due to rare inherited conditions, such as, pro-opiomelanocortin deficiency, proprotein subtilisin-kexin type 1 deficiency, leptin receptor deficiency.

To take the drug, a patient needs to have test results showing one of these conditions. Setmelanotide does not treat any of the gene problems that cause these conditions. It can lessen the appetite and make one feel fuller and may help burn calories while the body is at rest.

- **Efficacy**: The effectiveness of Imcivree was assessed in 21 patients, 10 in the first study and 11 in the second. In the first study, 80% of patients with POMC or PCSK1 deficiency lost 10% or more of their body weight. In the second study, 46% of patients with LEPR deficiency lost 10% or more of their body weight. The study also assessed the maximal (greatest) hunger in 16 patients over the previous 24 hours using an 11-point scale in patients 12 years and older. In both studies, some, but not all, of patients' weekly average maximal hunger scores decreased substantially from their scores at the beginning of the study. The degree of change was highly variable among patients.
- **Side-effects:** The most common side effects of Imcivree include darkening of the skin, injection site reactions, nausea, headache, diarrhea, stomach pain, vomiting, depression and suicidal thoughts or actions, male and female sexual function problems and benzyl alcohol toxicity.

Apart from efficacy and safety, the dosage form is another differentiator between GLP-1 drugs and other weight loss drugs. While non-GLP drugs are primarily oral solids, majority of approved GLP-1 drugs are injectables. As OSDs have convenient dosage as well as are easier to manufacture than the single-use pen injectables, companies are actively working on developing oral GLP-1 drugs.

GLP-1 vs Insulin: Some impact on the insulin market remains a possibility

While there is surely some overlap, we note insulin therapy is more used for patients with Type 1 diabetes, while GLP-1 drugs are more used for patients with Type 2 diabetes and beyond that, the weight loss opportunity

GLP-1 agonists and insulin are both effective at lowering blood glucose levels. While there is surely some overlap, we note insulin therapy is more used for patients with Type 1 diabetes, while GLP-1 drugs are more used for patients with Type 2 diabetes and beyond that, the weight loss opportunity. According to Novo Nordisk, being a chronic therapy, insulin tends to be a sticky market. With growing population, even with introduction of better treatments such as GLP-1s taking some market share from insulin, the company expects global insulin volumes to remain flat. On the supply side, while insulin would not be driving capex, companies will continue to build platforms that can be simultaneously utilized for insulin with other therapies. Nevertheless, in our view, there is certainly a possibility of diabetes progression getting delayed due to GLP-1 drugs, which could impact the insulin market.

We note insulin is more effective than GLP-1 agonists in lowering the fasting plasma glucose concentration, while GLP-1 agonists were more effective in lowering the postprandial (occurring or done after a meal) glucose concentration. In addition, an insulin therapy is usually associated with weight gain while GLP-1 analogues consistently result in weight loss. GLP-1 drugs also reduce the risk of hypoglycemia (low blood sugar) as compared to insulin. According to a study, despite a similar decrease in HbA1c, the risk of hypoglycemia was 35% lower with GLP-1 therapies versus insulin. On the other hand, compared to insulin, GLP-1 analogues caused a significant decrease in systolic blood pressure and were associated with greater rate of gastrointestinal adverse events. Based on US epidemiologic observations derived from electronic health records of individuals initially diagnosed with Type 2 diabetes during or after CY2003 and followed for five years, agents belonging to GLP-1 receptor agonist class appear to pose no increased risk to people with Type 2 diabetes for triggering thyroid cancer compared with insulin, and may even pose a lower risk. Apart from these factors, GLP-1 agonists may also have other benefits, including lowering blood pressure, improving lipid disorders, improving fatty liver conditions and reducing the risk of heart and kidney diseases.

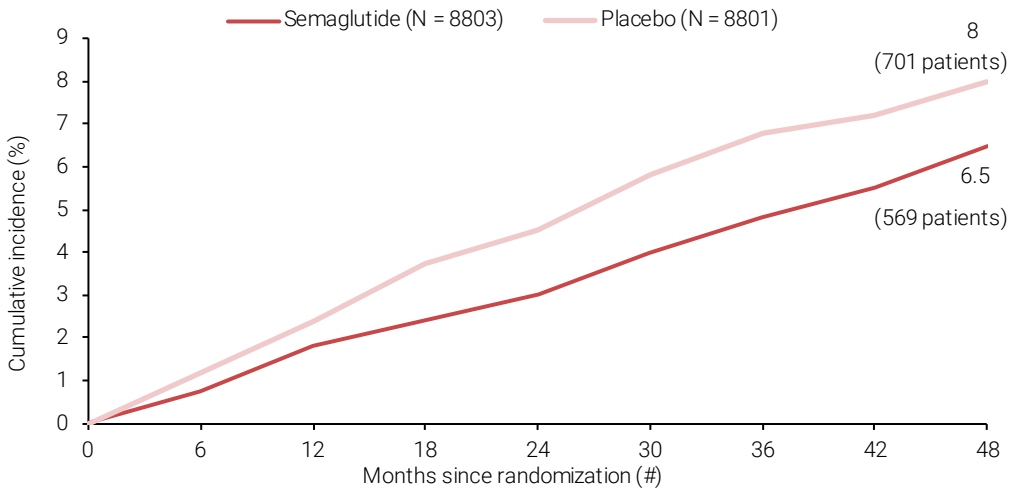
Other GLP-1 benefits: It goes beyond just weight loss

Wegovy has been found to reduce risk of adverse cardiovascular events in patients with diabetes

Companies are still exploring the other potential benefits of GLP-1 drugs. For instance, Eli Lilly is working on exploring the potential of GLP-1 combinations as a treatment for fatty liver, osteoarthritis in the knee, and obstructive sleep apnea apart from diabetes, weight-loss management and cardiovascular diseases. Research has found that some GLP-1 drugs may lower the risk of heart disease, such as heart failure, stroke and kidney disease. Patients taking these drugs have seen their blood pressure and cholesterol levels improve. Nevertheless, it is still not fully clear whether these benefits are primarily from the drug or the weight loss. A full dataset from a recent trial on Novo Nordisk's Wegovy was presented at the American Heart Association meeting in Philadelphia. The trial found that the treatment reduced the risk of another cardiovascular incident by 20%. 569 out of the 8,803 drug users experienced a heart attack or a stroke, or 6.5% of deaths were connected to heart problems, according to the trial results. In contrast, 701 out of 8,801 participants received a placebo, or 8%. The difference in those rates is what amounts to the reported 20% benefit.

Wegovy has been found to reduce risk of adverse cardiovascular events in patients with diabetes

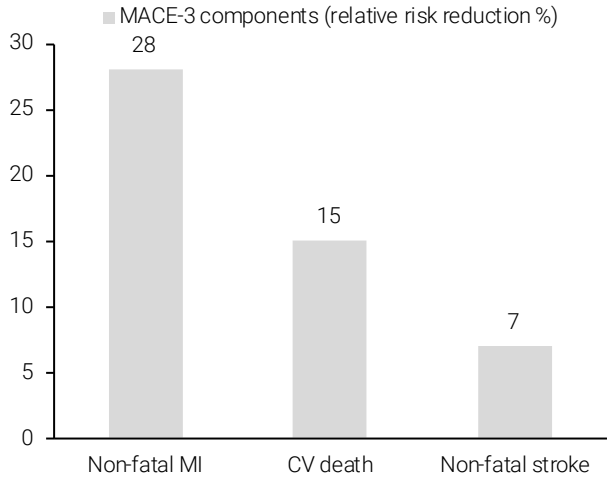
Exhibit 5: Death from cardiovascular causes, nonfatal MI, or strokes (%, #)



Source: The New England Journal of Medicine, Kotak Institutional Equities

Wegovy achieved 20% relative risk reduction in MACE-3 events

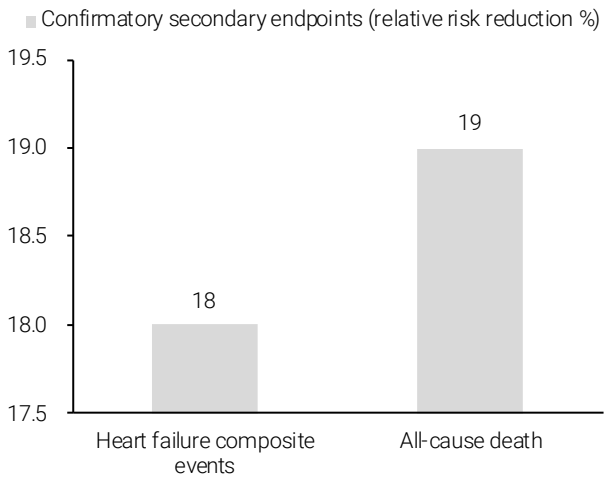
Exhibit 6: SELECT trial-benefits of Semaglutide 2.4 mg (%)



Source: IQVIA, Kotak Institutional Equities

Wegovy achieved 18% relative risk reduction in heart failures

Exhibit 7: SELECT trial-benefits of Semaglutide 2.4 mg (%)



Source: IQVIA, Kotak Institutional Equities

3

Road ahead: Several weight-loss trials underway with promising initial results

We believe the development of GLP-1 drugs for weight loss has just picked up pace, and several additional developments can be expected in the coming years. While the innovation started with single hormone GLP-1 drugs, with the recent incremental success of combinations such as Mounjaro (GLP-1 + GIP), it is clear that weight-loss results can be improved by altering and combining GLP-1 molecule with other hormones. In a head-to-head trial of Eli Lilly's Mounjaro (Tirzepatide) and Novo Nordisk's Ozempic (Semaglutide), patients taking Mounjaro were 76% more likely to lose at least 5% of their body weight, more than twice as likely to lose at least 10%, and more than three times as likely to lose at least 15%, compared to patients taking Ozempic. This is likely indicative of Tirzepatide's superiority as a weight-loss drug as compared to Semaglutide.

GLP-1 combinations deliver better results for weight loss compared to GLP-1 only drugs

Exhibit 8: Trial results for GLP-1 drugs, including combinations (Kg, %)

	Target hormone	Study phase	Route & frequency	Treatment duration (weeks)	Number of participants	Baseline weight (kg)	Placebo-subtracted weight loss (% body weight)	Body-weight loss (%)
Drug name								
Orforglipron 45 mg	GLP-1	2	Oral daily	36	57	105.2-110.9	12.3	14.7
Semaglutide 2.4 mg (Wegovy)	GLP-1	3	Injectable weekly	68	1306	105.4	14.4	16.9
Semaglutide 50 mg (Rybelsus)	GLP-1	3	Oral daily	68	334	104.5	15.6	17.4
Survodutide 4.8 mg	**GLP-1-GCG**	**2**	**Injectable weekly**	**46**	**54**	**105.9**	**16.7**	**18.7**
Tirzepatide 15 mg (Mounjaro)	**GLP-1-GIP**	**3**	**Injectable weekly**	**72**	**630**	**105.6**	**20.1**	**22.5**
Retatrutide 12 mg	**GLP-1-GIP-GCG**	**2**	**Injectable weekly**	**48**	**62**	**108**	**22.1**	**24.2**

Source: Companies, Kotak Institutional Equities

Retatrutide showcased ~24% weight reduction in Phase 2 clinical trials

Exhibit 9: Body weight loss % in clinical trials for different GLP-1 drugs (%)

Source: Companies, Kotak Institutional Equities

Apart from the already approved Tirzepatide, we analyze the GLP-1 combinations under development for weight loss and diabetes.

GLP-1 combinations deliver better results for weight loss compared to GLP-1 only drugs

Survodutide

In Oct 2023, Boehringer Ingelheim and Zealand Pharma A/S announced the initiation of Phase 3 trials investigating Survodutide (also known as BI 456906), a GLP-1 GCG combination for people living with overweight or obesity. In the Phase 2 trial, people living with overweight or obesity had achieved up to 19% weight loss. Additional Phase 2 data, presented at the European Association for the Study of Diabetes (EASD), demonstrated reductions in absolute waist circumference (up to 16.0 cm), absolute body weight (up to 19.5 kg) and absolute systolic and diastolic blood pressure (up to 8.6 mmHg and 4.8 mmHg, respectively) over 46 weeks.

Retatrutide

Post the success of the GLP-1-GIP combination, Mounjaro (Tirzepatide), Eli Lilly is working (Phase 3 trials started in Aug 2023) on a triple combination drug, Retatrutide. It is a triple hormone receptor agonist of GLP-1, GIP, and GCG receptors. It has been shown to achieve more than 24% mean weight reduction in adults without diabetes but with obesity during a Phase 2 trial. Retatrutide also had profound effects on fat in the liver. Eli Lilly is exploring its potential as a treatment for fatty liver and the possibility of this drug playing out better for complications of obesity-related liver ailments. Currently, the Retatrutide Triumph Phase III core registration trials are actively enrolling to pursue simultaneous indications for chronic weight management, obstructive sleep apnea and knee osteoarthritis.

Post the success of the GLP-1-GIP combination, Mounjaro (Tirzepatide), Eli Lilly is working (Phase 3 trials started in Aug 2023) on a triple combination drug, Retatrutide

83% of participants who received 12 mg dose of Retatrutide registered weight reduction of 15% or more

Exhibit 10: Retatrutide Phase 2 trial results (%)

	Duration	Participants with at least 5% weight reduction (%)	Participants with at least 10% weight reduction (%)	Participants with at least 15% weight reduction (%)
Dosage				
4 mg	48 weeks	92	75	60
8 mg	48 weeks	100	91	75
12 mg	48 weeks	100	93	83
Placebo	48 weeks	27	9	2

Source: National Library of Medicine, Kotak Institutional Equities

CagriSema

CagriSema is a recombinant and synthetic peptide under development by Novo Nordisk as a therapy for Type 2 diabetes. It is a combination drug that includes Semaglutide and Cagrilintide. Phase 2 clinical trial results published by Novo Nordisk found CagriSema to be a promising contender as a long-lasting treatment for Type 2 diabetes administered via a weekly injection. Those randomly assigned to the CagriSema group saw an A1C reduction of 2.2% and weight loss of 16%. Recently, Novo Nordisk launched its Phase 3 trial to compare its efficacy and safety against Zepbound, Eli Lilly's latest approved drug for weight loss. We note Novo Nordisk is expecting at least a 25% whopping weight reduction in a non-diabetes population from CagriSema. In addition, as per Novo Nordisk's current assessment, it is eyeing at least 20% weight loss with CagriSema in patients with Type 2 diabetes. Moreover, as per Novo Nordisk, CagriSema has a better safety profile against other GLP-1 products.

CagriSema group saw an A1C reduction of 2.2% and weight loss of 16% in its Phase 2 clinical trials

Exhibit 11: CagriSema Phase 2 clinical trial results (#, %)

		CagriSema	Semaglutide	Cagrilinitide
Measure	**Unit**			
Number of participants	#	31	31	30
Average decrease in A1C	%	2.2	1.8	0.9
Participants with an A1C ≤ 6.5%	%	75.0	48.0	17.0
Average decrease in body weight	%	15.6	5.1	8.1
Average increase in time in range	%	43.0	43.6	14.8

Source: The Lancet, Kotak Institutional Equities

GLP-1 pills

Given the ease of administration and prevailing mismatch in supply demand of injectables, there is a lot of interest in oral GLP-1 drugs. Companies such as Eli Lilly, Pfizer and Novo Nordisk continue to invest heavily in developing oral alternatives for weight loss. Currently, Novo Nordisk's, Rybelsus, is the only GLP-1 pill in the market that is approved for weight loss. However, its weight-loss potential is not at par with Mounjaro.

We list below some of the key oral solid GLP-1 drugs under development for diabetes and weight loss:

Orforglipron

Companies such as Eli Lilly, Pfizer and Novo Nordisk continue to invest heavily in developing oral alternatives for weight loss

Orforglipron is a non-peptide GLP-1 receptor agonist under development as a weight loss pill by Eli Lilly. The company published its Phase 2 trial results in 2QCY23 and initiated Phase 3 trials, which are expected to be completed in CY2025. With an overall mean body weight at baseline of 109 kgs, Orforglipron demonstrated an average of up to 14.7% body weight reduction at 36 weeks. At the second highest dose tested in the study, 75% of participants reached a weight reduction goal of 10% or more. A major consideration to evaluate in Phase 3 trials would be liver safety post intake of Orforglipron.

Danuglipron

Danuglipron is a small-molecule GLP-1 agonist pill being developed by Pfizer as a therapy for Type 2 diabetes. Recently, Pfizer published topline data from the Phase 2b clinical trial investigating Danuglipron, in adults with obesity and without Type 2 diabetes. Twice a day dosing of Danuglipron resulted in statistically significant reduction in body weight from baseline for all doses, with mean reductions ranging from 7-12% at 32 weeks, and 5-9% at 26 weeks. While the most common adverse effects were moderate and gastrointestinal in nature which are consistent with the mechanism, higher rates of adverse instances (up to 73% nausea; up to 47% vomiting; up to 25% diarrhea) were recorded. Going forward, Pfizer will focus on a once-daily formulation, with pharmacokinetic data expected in the 1HCY24.

Apart from the weight-loss drugs already discussed in this report, we would be keeping an eye on data readouts from the following clinical trials over the next few months.

Novo Nordisk's oral Semaglutide's phase 3 trials are expected to be completed by March 2024

Exhibit 12: Obesity clinical trial readouts to watch over the next 12 months, December calendar year-end, 2024E

	Dosage form	Event	Trial size	Trial length	Target
Therapy					
Novo Nordisk's Semaglutide	Oral	Phase III completion March 2024	281	75 weeks	GLP-1
Altimmune's Pemvidutide	Injectable	Phase II completion December 2023	320	87 weeks	GLP-1
Innovent Biologics' Mazdutide	Injectable	Phase III completion January 2024	610	61 weeks	GLP-1
Shionogi's S-309309	Oral	Phase II completion December 2023	300	39 weeks	MGAT2 Inhibitor
Tonix's Oxytocin	Intranasal	Phase II completion April 2024	60	56 weeks	CGRP Inhibitor

Source: Global Data, Clinical Trials Arena, Kotak Institutional Equities

Hydrogel based GLP-1s can reduce treatment burden and more effectively manage Type 2 diabetes

Recently, researchers at Stanford University School of Engineering, with assistance from Novo Nordisk, have developed a new medication delivery mechanism that they claim might reduce the dose schedule for GLP-1 treatments to a few times per year. According to the researchers' computational models, the hydrogel delivery system secreted therapeutic concentrations of Liraglutide for 42 days in rats, the equivalent of four months in humans, in a study published in Nov 2023. According to clinical data, adherence to injected Semaglutide ranges between 39-67% in Type-2 diabetes patients after one year, and is lower in those who take the medicine for weight loss.

4

We expect the branded global GLP-1 market to reach ~US$106 bn by CY2033E

The global GLP-1 market is evolving rapidly with swift adoption of the approved drugs and widespread anticipation regarding the drugs in the pipeline. Nevertheless, one thing is certain. These drugs hold a lot of promise in the treatment of diabetes and more importantly, weight loss. Particularly, developing a drug successfully driving weight loss has been a key challenge for pharma companies for the past several decades. Led by meaningful reduction in weight coupled with a decent safety profile, the market for GLP-1 drugs and their combinations holds a lot of promise. Given the market is still evolving, there is a glaring divergence in estimates on the potential market size, growth rate and winners among the GLP-1 drugs and their combinations.

WHO estimates there are ~750 mn obese people worldwide, including ~42% of adults in the US

WHO estimates there are ~750 mn obese people worldwide, including ~42% of adults in the US, where obesity-related illnesses incur a significant proportion of annual health care costs, and account for 5% of all fatalities. As per WHO, there could be 1 bn people with obesity and related conditions by CY2050E. Hence, the market has the potential to grow significantly in the coming years if the pace of innovation mirrors with the exuberance and demand. According to a study published in the New England Journal of Medicine, the annual cost to Medicare would likely range from US$13.6 bn (based on a 19% obesity rate from traditional Medicare diagnoses in CY2021) to US$26.8 bn (based on a 41.5% obesity rate from survey data for adults ages 60 and older), assuming that ~10% of obese Medicare beneficiaries in the US use a GLP-1 drug. Going forward, GLP-1 drugs could eventually have other uses, like helping prevent cardiovascular diseases among obese adults. There are also signs they could treat addiction and even Alzheimer's too.

Proportion of population with obesity has been on the rise and is expected to rise further

Exhibit 13: Percentage of the population with overweight or obesity, December calendar year-ends, 2020-35E (mn, %)

	Units	2020	2025	2030	2035
Number with overweight or obesity (BMI≥25kg/m²)	mn	2,603	3,041	3,507	4,005
Number with obesity (BMI ≥30kg/m²)	mn	988	1,249	1,556	1,914
Proportion of the population with overweight or obesity (BMI ≥25kg/m²)	%	38	42	46	51
Proportion of the population with obesity (BMI ≥30kg/m²)	%	14	17	20	24

Notes:

(a) For children and adolescents, overweight and obesity are defined using the WHO classification of +1SD and +2SD above median growth reference.

Source: World Obesity Atlas 2023, Kotak Institutional Equities

Currently, Novo Nordisk and Eli Lilly are dominating the GLP-1 space with their blockbuster drugs including Ozempic, Wegovy, Mounjaro, Rybelsus and Trulicity. In 9MCY23, global market sales of GLP-1 drugs stood at ~US$25 bn, with Novo Nordisk and Eli Lilly accounting for ~99% of the sales.

Annualized global sales of GLP-1 drugs in 9MCY23 stood at ~US$34 bn

Exhibit 14: Key GLP-1 drugs sales for 9-month period, December calendar year-end, 2023E (US$)

		9MCY2023 sales (US$ mn)			Annualized global sales (US$ mn)
	Innovator	US sales	Sales in ex-US markets	Global sales	
Drug name					
Bydureon BCise (Exenatide)	AstraZeneca	101	22	123	164
Victoza (Liraglutide)	Novo Nordisk	404	595	999	1,332
Saxenda (Liraglutide)	Novo Nordisk	459	800	1,259	1,679
Trulicity (Dulaglutide)	Eli Lilly	4,178	1,286	5,463	7,284
Ozempic (Semaglutide)	Novo Nordisk	5,983	3,550	9,533	12,710
Rybelsus (Semaglutide)	Novo Nordisk	1,074	791	1,864	2,486
Wegovy (Semaglutide)	Novo Nordisk	3,023	132	3,155	4,207
Mounjaro (Tirzepatide)	Eli Lilly	2,729	228	2,958	3,943
Total		**17,950**	**7,404**	**25,354**	**33,805**

Source: Companies, Kotak Institutional Equities

Evaluate Pharma expects the global incretin (incretins are gut hormones like GLP-1 & GIP that help with digestion and blood glucose control) market to be worth ~US$79 bn by CY2028E.

Evaluate Pharma expects the GLP-1 market to reach ~US$79 bn by CY2028E

Exhibit 15: GLP-1 branded drug sales and market size, December calendar year-ends, 2013-28E (US$ mn)

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023E	2024E	2025E	2026E	2027E	2028E
Global innovator formulations sales (US$ mn)																
Bydureon Bcise									385	280	197	172	154	143	134	125
Victoza	2,072	2,393	2,682	2,979	3,521	3,857	3,289	2,871	2,397	1,768	1,325	1,055	818	703	624	532
Saxenda			68	234	389	613	852	859	1,138	1,531	1,614	1,292	945	666	535	429
Trulicity		10	249	926	2,030	3,199	4,128	5,068	6,472	7,440	7,265	7,092	6,822	6,483	5,577	3,858
Ozempic						285	1,685	3,249	5,366	8,571	13,113	16,254	19,227	21,684	21,794	21,915
Rybelsus							7	287	770	1,621	2,642	3,445	4,378	5,169	5,364	5,820
Wegovy									200	888	4,451	8,372	11,101	13,203	14,596	14,941
Mounjaro										483	4,653	6,291	7,970	9,631	11,065	12,100
Zepbound												2,068	4,227	6,349	8,865	10,556
Orforglipron														193	1,164	2,817
Danuglipron															181	470
Adlyxin	12	36	42	37	29	66	83	89	78	115	165	173	156	123	102	88
CagriSema													38	628	2,376	4,697
Retatrutide														23	243	689
Others	736	855	959	998	882	762	665	524	92	60	47	49	51	53	83	95
Total	**2,820**	**3,293**	**3,999**	**5,173**	**6,851**	**8,782**	**10,708**	**12,948**	**16,898**	**22,756**	**35,473**	**46,263**	**55,888**	**65,050**	**72,702**	**79,133**
yoy growth (%)		16.8	21.4	29.3	32.4	28.2	21.9	20.9	30.5	34.7	55.9	30.4	20.8	16.4	11.8	8.8

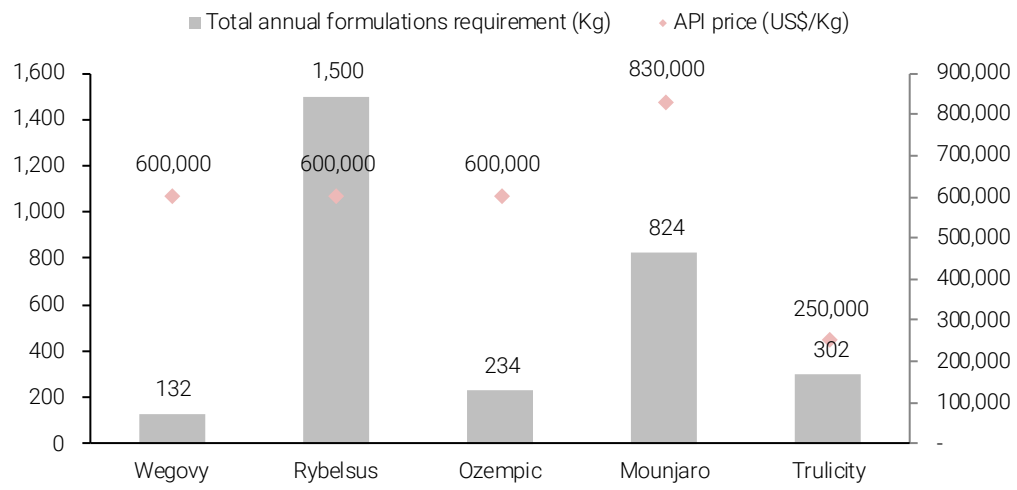
Source: Evaluate Pharma, Kotak Institutional Equities estimates

As of CY2023, globally, we estimate ~8.8 mn patients were consuming GLP-1 drugs for diabetes and weight loss treatments, of which ~60% of the total patients were from US

As of CY2023, globally, we estimate ~8.8 mn patients were consuming GLP-1 drugs for diabetes and weight loss treatments, of which ~60% of the total patients were from the US. Looking at the current pricing of APIs of various GLP-1 drugs, their dosage requirements and an estimate of the number of patients on each therapy, we estimate the global API market size of GLP-1 drugs to be ~US$1 bn. With increased penetration amid launches across multiple markets, we highlight the average global price of Semaglutide API has already decreased by ~80% over the past five years, from US$3,000K/kg to ~US$600K/kg. With further increase in penetration and then genericization in EMs and then DMs, we expect a further downward pressure on API prices of GLP-1 drugs over the long term. In addition, currently, there are ~25 API developers of Semaglutide API globally. As more players enter the market, the prices are likely to reduce further.

As of CY2023, we estimate the global GLP-1 formulations annual requirement at ~3,000 Kg

Exhibit 16: GLP-1 branded drug formulations annual requirement and API prices, December calendar year-end, 2023 (US$/Kg, Kg)



Source: Companies, Kotak Institutional Equities estimates

In Exhibit 17, we build on Evaluate Pharma forecasts and project revenues for the key GLP-1 drugs over a period of 20 years, i.e., CY2023-42E. According to our estimates, despite factoring in the negative impact of genericization intermittently across multiple drugs, global branded formulation sales of GLP-1 drugs are expected to report a 12% CAGR from ~US$35 bn in CY2023E to ~US$106 bn by CY2033E with Tirzepatide and Semaglutide being the key contributors.

Some of the key assumptions involved in estimating the branded GLP-1 market size include:

According to our estimates, despite factoring in the negative impact of genericization intermittently across multiple drugs, global branded sales of GLP-1 drugs are expected to report a 12% CAGR from ~US$35 bn in CY2023E to ~US$106 bn by CY2033E

- Given the large number of generic companies actively pursuing this opportunity, we expect generic versions to enter the market as soon as patents expire. For some drugs, such as Ozempic and Wegovy, we build in settlements or at-risk launches prior to patent expiry. Post generic entry, we build in a significant price erosion for the innovator product, ranging from 40-80%.
- We have accounted for launches of combination drugs, such as Retatrutide (Tirzepatide) and Cagrisema (Semaglutide and Cagrilintide.). Owing to the higher efficacies of these drugs, as evident from the Phase 2 and in some cases, Phase 3 trials, we estimate a meaningful sales uptick for these drugs post launch. Accordingly, due to competition from these drugs, we have built in a drop in the growth profile of the original innovator products, i.e., Mounjaro post Retatrutide launch and Ozempic, Wegovy and Rybelsus post Cagrisema launch.
- We have also considered sales from other products under development, given there are a lot of new drugs under development. Lots of companies have been attempting to develop combination drugs, and we estimate some of them will materialize in the future. We have captured the optionality of these products under the aforementioned category.

We expect the branded GLP-1 market to reach ~US$91 bn by end of this decade

Exhibit 17: GLP-1 branded drug sales and market size, December calendar year-ends, 2023-42E (US$ mn)

	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E	2033E	2034E	2035E	2036E	2037E	2038E	2039E	2040E	2041E	2042E
Global innovator formulations sales (US$ mn)																				
Bydureon	168	84	59	47	38	32	27	23	20	18	16	15	13	12	11	10	9	9	8	8
Victoza	1,365	1,024	665	449	314	228	171	132	106	87	73	61	51	43	37	31	27	23	20	18
Saxenda	1,721	2,048	2,397	2,684	1,342	872	698	576	489	428	385	349	317	290	267	247	230	215	202	191
Trulicity	7,466	8,960	10,707	12,741	14,652	16,410	6,564	3,282	1,969	1,378	1,103	910	773	677	609	563	524	490	460	435
Ozempic	13,028	16,937	21,510	26,242	30,965	34,371	36,090	21,654	14,075	9,853	7,389	5,912	4,877	4,145	3,627	3,265	2,971	2,733	2,542	2,389
Rybelsus	2,548	4,077	5,707	7,420	8,904	10,239	11,468	12,557	13,436	14,175	14,742	7,371	4,791	3,833	3,162	2,688	2,352	2,117	1,958	1,860
Wegovy	4,312	6,683	9,357	11,696	7,018	4,561	3,193	2,395	1,916	1,628	1,384	1,177	1,000	850	723	614	522	444	377	321
Mounjaro	4,042	6,063	8,791	12,308	16,000	19,520	22,838	25,579	27,369	29,148	30,897	32,597	34,227	35,767	37,197	38,499	13,475	6,737	4,379	3,503
Zepbound	135	1,000	1,600	2,480	3,720	5,394	7,012	8,941	11,176	13,690	16,428	18,893	20,782	22,756	24,804	26,912	9,419	4,710	3,061	2,449
Orforglipron				190	1,045	2,299	4,138	6,207	8,690	10,863	13,307	15,968	18,763	21,577	24,544	27,612	30,718	33,790	36,747	39,503
Danuglipron					180	450	900	1,530	2,142	2,785	3,342	3,676	3,859	3,859	3,666	3,391	3,052	2,671	2,270	1,873
CagriSema			30	630	1,890	3,024	4,082	5,103	6,124	7,195	8,275	9,309	10,240	11,008	11,778	12,544	13,296	14,028	14,729	15,392
Retatrutide				25	225	675	1,181	1,949	3,021	4,381	6,133	8,279	10,763	13,454	16,144	18,566	20,887	22,975	24,699	25,934
Other products under development					50	175	350	630	1,071	1,714	2,656	3,984	5,777	8,088	10,918	14,194	17,743	21,291	24,485	26,933
Total	**34,786**	**46,875**	**60,822**	**76,911**	**86,343**	**98,251**	**98,713**	**90,558**	**91,605**	**97,344**	**106,130**	**108,498**	**116,233**	**126,359**	**137,489**	**149,137**	**115,225**	**112,232**	**115,938**	**120,808**
yoy growth (%)		34.8	29.8	26.5	12.3	13.8	0.5	(8.3)	1.2	6.3	9.0	2.2	7.1	8.7	8.8	8.5	(22.7)	(2.6)	3.3	4.2

Source: Companies, Kotak Institutional Equities estimates

Novo Nordisk and Eli Lilly continue to invest in capacities to address the supply constraints

Owing to tremendous demand, availability of GLP-1 drugs has been a challenge over the past couple of years. For instance, while Wegovy was launched in the US in Jun 2021, it took until Dec 2022 for all doses to be available due to a production outage. Owing to the capacity constraints, both companies, Eli Lilly and Novo Nordisk, have been on an expansion spree. After announcing plans to invest US$500 mn into an API plant in Ireland, a US$450 mn expansion at its Research Triangle Park, North Carolina facility to help meet demand for Mounjaro and a US$1.6 bn commitment to its two new manufacturing sites in Indiana's LEAP Innovation Park in Boone County, Eli Lilly has recently announced plans to construct a new US$2.5 bn high-tech manufacturing site in Alzey, Rhineland-Palatinate, Germany (includes investment for GLP-1s and Alzheimer). Separately, Novo Nordisk announced in Nov 2023, that it would be investing US$6 bn to expand its current manufacturing facilities in Kalundborg, Denmark. A great majority of the expanded facilities will be used to increase capacity for APIs, including Semaglutide. Recently, Novo Nordisk announced the acquisition of an Alkermes pill factory in Athlone, Ireland for EUR85 mn. This would be in addition to construct a big facility spread over 1.6 mn square feet in the vicinity of Dublin to address the rapidly increasing demand for Ozempic and Wegovy. Going ahead, Novo

Nordisk plans to invest ~US$2.3 bn, toward expansion of its longstanding production facility located in Chartres, France, starting from CY2024. The enhancement will enable the site to produce more drugs for severe chronic diseases in the future. Apart from Novo Nordisk and Eli Lilly, Pfizer is another pharma major, which is betting big on this market.

The innovators have also been utilizing the services of CDMOs to meet the strong demand

While the innovators have been working on increasing their own capacities, they are also utilizing the services of CDMOs to address the supply-demand mismatch. Thermo Fisher is one of the CDMOs likely being utilized by Novo Nordisk in filling the injection pens for Wegovy at its facility in Greenville, North Carolina, through Patheon. We note Novo Nordisk appointed Thermo Fisher likely after its initial CDMO partner, Catalent, failed to deliver on its contracts. For instance, Catalent's Wegovy deliveries were temporarily stopped in late CY2021, just months after the drug's debut, after the US FDA discovered a number of issues at its syringe-filling plant in Brussels. After another US FDA inspection in Aug 2022 revealed more lapses, the factory was forced to shut down. The US FDA later downgraded the citation and allowed the plant to remain operational. Similarly, in Oct 2023, Eli Lilly engaged Switzerland-based CDMO, Corden Pharma, to develop the API for Mounjaro. We note, in Jan 2023, Corden Pharma had also announced that it had signed a multi-year agreement for contract manufacturing of a "large volume peptide" at its site in Boulder, Colorado, which could potentially be worth ~US$1 bn. Going forward, with new GLP-1 drugs getting launched amidst rising demand and increasing penetration, there remains a possibility of the innovators as well as the generic entrants increasingly utilizing the services of CDMOs for intermediates, APIs as well as formulations.

We expect insurance coverage for GLP-1 drugs to pick up gradually

In US, on a gross basis, GLP-1 drugs can cost up to 20 times as much as non-GLP-1 anti-obesity drugs, with monthly doses available at a high price tag of anywhere between US$900 and US$1,300. This is prior to any rebates or discounts given to payers, PBMs, or the government. For instance, Eli Lilly has kept the gross price for Zepbound at ~US$1,060 per month, 20% lower than its competitor, Wegovy. Actual pricing would eventually depend on the patient's insurance coverage, which means that some patients could end up paying as little as US$25 per month for their Zepbound prescription. Even if the patient's insurance plan does not include weight loss drugs, patients could still be eligible for an assistance program from the company that brings the cost down to US$550 per month.

According to a KFF (the Kaiser Family Foundation) analysis, inclusion of GLP-1 weight loss drugs within Medicare could cost the US federal program between US$13.6 bn and US$26.8 bn annually

Currently, around two-fifths of large employers in US cover GLP-1 drugs for the treatment of obesity

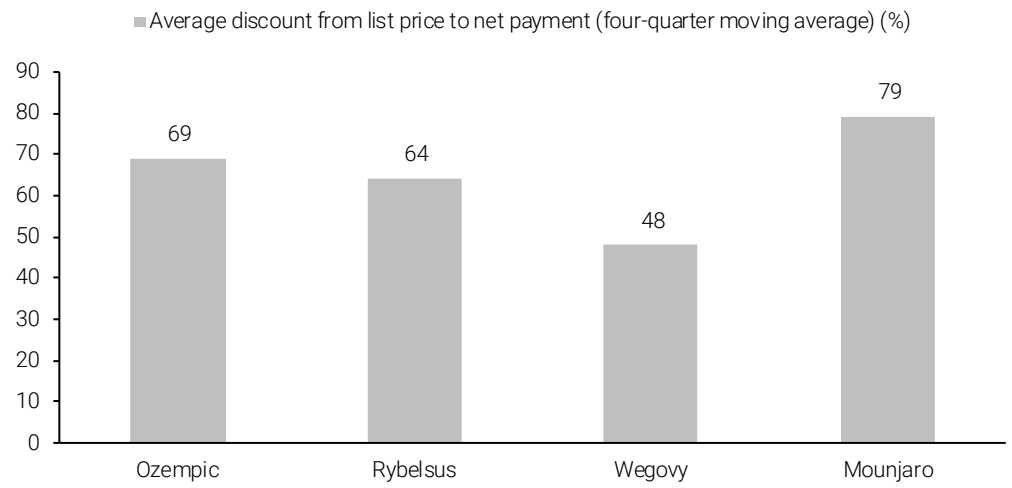
Exhibit 18: Estimated monthly prices of select GLP-1 drugs in US, December calendar year-end, 2023 (US$)

	Ozempic	Rybelsus	Wegovy	Mounjaro
Estimated monthly prices in US ($)				
List price	936	936	1,349	1,023
Implied net price (received by manufacturer)	290	337	701	215
Value of manufacturer coupons for patient out-of-pocket cost				
Insured with coverage for product	150	300	225	150
Insured without coverage for product	—	—	500	575
Cash pay (no coverage)	—	—	500	—
Implied out-of-pocket cost with coupons				
Insured without coverage	936	936	849	448
Uninsured	936	936	849	1,023

Source: American Enterprise Institute, Kotak Institutional Equities

The net price for select GLP-1 drugs is ~50-80% less than the list price

Exhibit 19: Estimated discount from list to net price, December calendar year-end, 2023 (%)



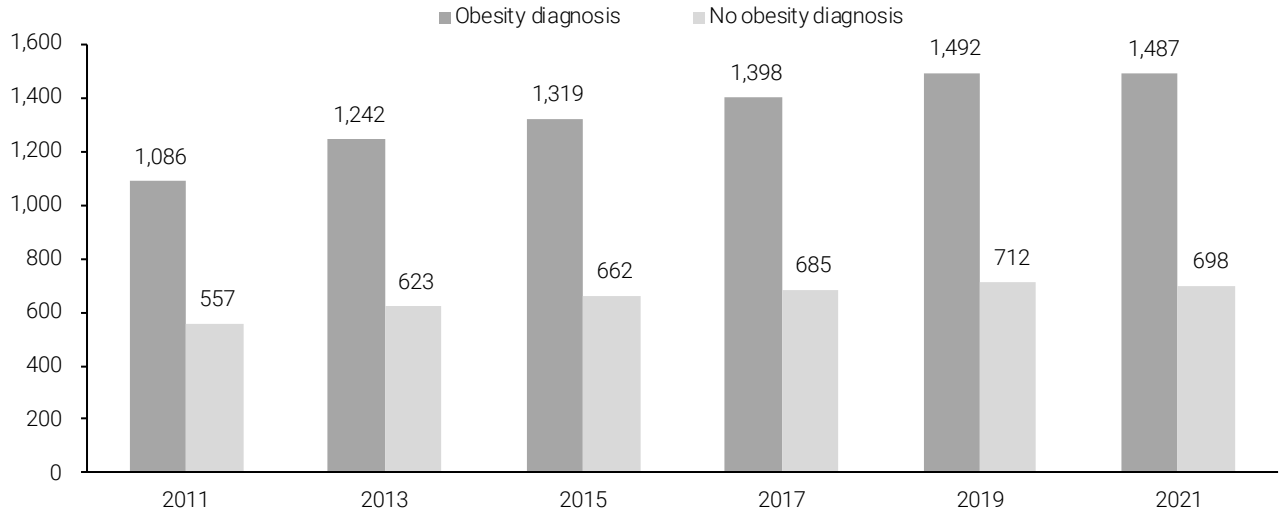
Notes:
(a) Mounjaro did not have 4 quarters of data, so the available data was used.

Source: American Enterprise Institute, Kotak Institutional Equities

Currently, Medicare coverage of obesity includes obesity screening, behavioral counseling and bariatric surgery in the US. However, it does not include drugs that are prescribed for weight loss. Eli Lilly and Novo Nordisk have been pushing for a change in law to allow coverage under Medicare. According to a KFF (the Kaiser Family Foundation) analysis, inclusion of GLP-1 weight loss drugs within Medicare could cost the US federal program between US$13.6 bn and US$26.8 bn annually. For context, annual Part D spending is ~US$100 bn. As per a study by obesity care provider, Found, 69% of the US patient population does not have insurance coverage for GLP-1 drugs. As per the analysis, the insurance coverage for GLP-1 drugs has declined by 50% since Dec 2022. While employers are increasingly open to seeking coverage of GLP-1 drugs, some insurers are still reluctant because of increasing costs in lieu of the strong demand.

On an average, OOP costs for 'obesity diagnosis' were ~2X 'no obesity diagnosis' costs for enrollees in US employer insurance plans

Exhibit 20: Average OOP cost for enrollees in US employer insurance plans, December calendar year-ends, 2011-21 (US$)



Notes:
(a) Includes enrollees with insurance plans from large employers who have a diagnosis of overweight or obesity.

Source: KFF analysis of Merative Market Scan Commercial Database, Kotak Institutional Equities

Rising demand for weight-loss drugs and general inflation have been driving up the average cost of employer-provided healthcare in the US. As per HR consultant, Mercer, upswing in the usage of GLP-1 drugs has had a notable impact on the higher growth of pharmacy benefit costs under health insurance plans. As per a survey conducted by Mercer, pharmacy benefit costs increased 8.4% yoy in CY2023, compared to 6.4% yoy in CY2022. These increases have been higher than the average annual increase seen over the past decade. While payers are concerned about the short-term budget impact, they understand that losing weight will have benefits. In the US alone, there are US$370 bn in direct medical costs associated with obesity comorbidities and US$1,000+ bn in indirect annual costs. Payors are likely to draw comfort from the fact that people living with obesity and overweight drive 2.7X greater health care costs than individuals with normal weight. As a result, we expect access to GLP-1 drugs to gradually increase as insurers witness the long-term benefit of weight-loss drugs in reducing claims.

5

Assessing the GLP-1 opportunity for Indian pharma companies

Several Indian companies such as Sun, Dr Reddy's, Cipla, Lupin, Aurobindo Pharma, Natco, Biocon and others have developed or are developing the generic formulations of the GLP-1 anti-diabetes and weight loss drugs. However, given the patent expiries are still several years away, generic launches are unlikely over the near to medium term. Currently, we are not factoring in generic sales of Liraglutide, Semaglutide and Tirzepatide in our estimates until FY2026E for any company under our coverage. The Street is hoping that a few Indian API/CDMO companies could benefit earlier if Novo Nordisk or Eli Lilly decide to outsource a portion of the value chain. For API/CDMO companies such as Divi's, we are factoring in a meaningful upside from unknown CSM contract wins, which implicitly assume some upside from GLP-1. Thus, implicitly we are factoring in upside from GLP-1 in our CDMO forecasts for Divi's.

Currently, we are not factoring in generic sales of Liraglutide, Semaglutide and Tirzepatide in our estimates until FY2026E for any company under our coverage

Before we analyze the opportunity for generic formulation sales for Indian pharma companies, we assess the potential opportunity from GLP-1 drugs for Indian CDMO companies.

A chunk of the CDMO opportunity for Indian companies is likely to be restricted to intermediates

Fmoc and Boc chemistry is an essential part of polypeptides manufacturing

Peptides, especially polypeptides, i.e., peptides consisting of a number of amino acid chains, can be chemically synthesized through solid phase synthesis or solution phase synthesis. The latter process is the classical method, based on the coupling of single amino acids in solution. The main benefit for using solution phase synthesis is that the intermediate products can be purified to obtain a high purity product. However, the reaction time is quite high, especially as manufacturing volumes scale up. Hence, solid phase synthesis is preferred nowadays by pharma companies. Solid phase synthesis involves Fmoc chemistry, and results in lower manufacturing costs due to economies of scale and technical improvements in chromatographic equipment and media. This method also has a faster turnaround time, is more flexible at each stage of the reaction, and less expensive. Sometimes, peptides such as human glucagon, salmon calcitonin, etc., are manufactured using recombinant technology. However, recombinant methods are more labor intensive, in spite of having lower production costs. Moreover, this method is restricted to peptides, where all the amino acid sequences are naturally occurring amino acids.

However, for GLP-1 peptides, if we take the example of Semaglutide, the second position has a non-natural amino acid, i.e., Alpha-aminoisobutyric acid (Aib). Thus, for manufacturing GLP-1 peptides, recombinant methods cannot be used and hence solid phase synthesis is mostly used for developing the building blocks. This method involves proper protection and subsequent deprotection of various functional groups of the amino acids, since it is the side group, that gives each amino acid its distinctive properties, thus controlling the action of the final protein. The process consists of multiple cycles with steps like coupling, washing, deprotection and again washing. A single such cycle includes cleavage of the alpha-amino protecting group, which is then washed to remove the cleavage reagent, then coupled with the protected amino acid and finally again washed to remove excess material.

Two such protecting groups are commonly used for this process, namely, t-Boc and Fmoc. The Fmoc method is milder and easier to deprotect. Usually, a base like piperidine (20–50%) in DMF is used to remove the Fmoc group and allow the α-amino group to react with an incoming activated amino acid. Cleavage under relatively milder conditions, as well as stability under acidic conditions also renders Fmoc chemistry better than the t-Boc method. The Boc-strategy involves anchoring groups, which are subject to repetitive TFA treatment. In the t-Boc method, a strong inorganic acid like HF is used for the final cleavage, which constraints the batch size and even the reactor size. Hence, the Fmoc method has gained popularity, among pharma companies, over the years, and it can be automated much easily and also scaled up faster.

Divi's has a history of Fmoc and Boc manufacturing

Among Indian companies, Divi's has been one of the earliest in manufacturing building blocks using the t-Boc method. We note Divi's has been manufacturing Bocs for more than two decades. It has also proven expertise in stereo-selective synthesis, using chiral ligands and high yield resolutions. Divi's has developed its own building block, the DiBoc (a protecting group). Even in these building blocks, there can be value addition by forward integration into dipeptides, tripeptides and up to at least four or five residues. It has also developed all the Boc-protected amino acids, Fmoc-protected amino acids, and manufactured di-peptides and tri-peptides and has supplied these building blocks to customers in the past. Overall, Divi's remains excited about the opportunity from peptides, particularly for GLP-1 drugs.

Among Indian companies, Divi's has been one of the earliest in manufacturing building blocks using the t-Boc method. We note Divi's has been manufacturing Bocs for more than two decades

Assessing the GLP-1 opportunity for Divi's

Given its experience in this field, Divi's could be one of the suppliers of these building blocks to GLP-1 innovators such as Novo Nordisk, Eli Lilly and Pfizer. Currently, most of the suppliers of these building blocks are located in China. Outside China, there are not many companies who can supply these building blocks, as these products are fertilized protected amino acids, with a lot of chemistry involved. Buying these various blocks separately and combining them will not be cost-effective as ability to control impurities is lowered, thereby potentially creating an edge for integrated suppliers such as Divi's. Since these building blocks are KSMs, US FDA approvals are not required. However, one potential roadblock is the difficult qualification processes, as it depends on where one is adding the KSM. If the KSMs are being added at the 31st (last) chain, the manufacturer of these building blocks might need an US FDA inspection. On the other hand, if KSMs are being added at the beginning of the chain, there is no need for US FDA approval for the KSM manufacturers.

After having commenced development of building blocks specifically for GLP-1 drugs since the beginning of FY2024, Divi's expects to start supplying some volumes of GLP-1 building blocks over CY2024-25E, once approvals and qualifications are completed. The company expects to supply significantly higher volumes beyond CY2025E. It already has the required capacities and there is no need for additional capex. All the reagents will be produced in Kakinada or at Unit 1 and 2, whereas all the building blocks, including the dipeptides and tripeptides, can be produced in existing facilities. With the commencement of the Kakinada facility, we believe Divi's has enough capacity to cater to high volume orders, ranging up to several tons. Divi's can also forward integrate with these building blocks, which could yield higher realizations.

Using our forecasts for the overall GLP-1 market as well as optimistically factoring in Divi's eventual entry in GLP-1 APIs in CY2027E, we estimate an NPV of Rs258/share from the GLP-1 opportunity for Divi's

Using our forecasts for the overall GLP-1 market as well as optimistically factoring in Divi's eventual entry in GLP-1 APIs in CY2027E, we estimate an NPV of Rs258/share from the GLP-1 opportunity for Divi's. Assuming Divi's does not enter the GLP-1 API market, the NPV/share drops by ~56% to Rs113/share. We expect the global intermediates market size (ex-generics) for GLP-1 drugs to stand at US$1.5 bn by CY2033E. In our estimates, we expect Divi's to garner a ~10% global market share in the GLP-1 intermediates market by CY2033E. Similarly, we expect the global API market size (ex-generics) for GLP-1 drugs to stand at ~US$2.9 bn by CY2033E. Within this market, we expect Divi's to garner a ~7% market share by CY2033E. We note currently bulk of the API manufacturing is being directly done by the innovators and going forward, we expect the innovators to continue to have a lion's share of the API market, albeit with higher outsourcing. In our model, we are implicitly baking in the GLP-1 upside for Divi's. For instance, we are factoring in Rs12.5 bn cumulative increase in CSM sales over FY2024-26E. Barring the two fast-track CSM projects (including Sacubitril Valsartan), the Gadolinium CSM project and the GLP-1 opportunity, Divi's has not indicated about any new CSM projects. While the two fast-track projects are partially reflecting in CSM sales in FY2024E, Gadolinium and GLP-1 will contribute only beyond FY2024E. Thus, a healthy majority of the Rs12.5 bn incremental CSM uptick built in our estimates for Divi's over the next two years, can be attributed to GLP-1 and the Gadolinium project.

We expect the global intermediates market size (ex-generics) for branded GLP-1 drugs to stand at US$1.5 bn by CY2033E

Exhibit 21: Global branded GLP-1 API and intermediates market, December calendar year-ends, 2023-42E (US$ mn)

	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E	2033E	2034E	2035E	2036E	2037E	2038E	2039E	2040E	2041E	2042E
Global branded GLP-1 API and intermediates market																				
Global GLP-1 formulations market size (US$ mn)	34,786	46,875	60,822	76,911	86,343	98,251	98,713	90,558	91,605	97,344	106,130	108,498	116,233	126,359	137,489	149,137	115,225	112,232	115,938	120,808
yoy growth (%)		34.8	29.8	26.5	12.3	13.8	0.5	(8.3)	1.2	6.3	9.0	2.2	7.1	8.7	8.8	8.5	(22.7)	(2.6)	3.3	4.2
Global API market size (US$ mn)	966	1,302	1,690	2,137	2,399	2,729	2,742	2,516	2,545	2,704	2,948	3,014	3,229	3,510	3,819	4,143	3,201	3,118	3,221	3,356
yoy growth (%)		34.8	29.8	26.5	12.3	13.8	0.5	(8.3)	1.2	6.3	9.0	2.2	7.1	8.7	8.8	8.5	(22.7)	(2.6)	3.3	4.2
Global intermediates market size (US$ mn)	483	651	845	1,068	1,199	1,365	1,371	1,258	1,272	1,352	1,474	1,507	1,615	1,755	1,910	2,072	1,601	1,559	1,610	1,678
yoy growth (%)		34.8	29.8	26.5	12.3	13.8	0.5	(8.3)	1.2	6.3	9.0	2.2	7.1	8.7	8.8	8.5	(22.7)	(2.6)	3.3	4.2

Source: Kotak Institutional Equities estimates

Building in optimistic expectations, we expect the GLP-1 opportunity for Divi's to contribute to an NPV of Rs258/share

Exhibit 22: NPV calculations for Divi's, December calendar year-ends, 2024-42E (US$ mn, Rs)

	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E	2033E	2034E	2035E	2036E	2037E	2038E	2039E	2040E	2041E	2042E
Divi's revenues																			
Intermediates revenues (US$ mn)	33	49	69	87	109	120	119	124	135	151	158	174	193	215	238	188	187	197	210
Divi's share in the GLP-1 intermediates market (%)	5.0	5.8	6.5	7.3	8.0	8.8	9.5	9.8	10.0	10.3	10.5	10.8	11.0	11.3	11.5	11.8	12.0	12.3	12.5
API revenues (US$ mn)				120	150	165	157	165	183	206	219	242	269	298	329	259	257	271	287
Divi's share in the GLP-1 API market (%)				5.0	5.5	6.0	6.3	6.5	6.8	7.0	7.3	7.5	7.7	7.8	8.0	8.1	8.3	8.4	8.6
Total revenues for Divi's (US$ mn)	33	49	69	207	259	285	277	289	318	357	377	416	462	513	568	447	444	468	497
Total revenues for Divi's (Rs mn)	2,751	4,105	5,868	17,482	21,911	24,041	23,384	24,461	26,850	30,208	31,837	35,130	39,006	43,329	47,963	37,800	37,543	39,531	41,971
yoy growth (%)		49.2	42.9	197.9	25.3	9.7	(2.7)	4.6	9.8	12.5	5.4	10.3	11.0	11.1	10.7	(21.2)	(0.7)	5.3	6.2
Divi's financials																			
EBITDA (Rs mn)	1,375	2,052	2,934	8,741	10,955	12,021	11,692	12,230	13,425	15,104	15,918	17,565	19,503	21,664	23,981	18,900	18,771	19,765	20,986
EBITDA margin (%)	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
Post-tax FCF (Rs mn)	619	924	1,320	3,933	4,930	5,409	5,261	5,504	6,041	6,797	7,163	7,904	8,776	9,749	10,792	8,505	8,447	8,894	9,444
EBITDA-FCF conversion (%)	60.0	60.0	60.0	60.0	60.0	60.0	60.0	60.0	60.0	60.0	60.0	60.0	60.0	60.0	60.0	60.0	60.0	60.0	60.0
Discount factor (X)		1.00	2.00	3.00	4.00	5.00	6.00	7.00	8.00	9.00	10.00	11.00	12.00	13.00	14.00	15.00	16.00	17.00	18.00
Discounted FCF (Rs mn)		832	1,072	2,876	3,247	3,210	2,813	2,651	2,621	2,657	2,523	2,508	2,509	2,511	2,504	1,778	1,591	1,509	1,443
NPV calculation																			
Sum of discounted cash flows (Rs mn)	40,853																		
Terminal value (Rs mn)	27,683																		
Total value (Rs mn)	68,536																		
No of shares (mn)	265																		
NPV (Rs/share)	258																		

Source: Kotak Institutional Equities estimates

Within the Indian API companies, apart from Divi's, Neuland Labs has been focusing on development of APIs of Liraglutide, Semaglutide and Tirzepatide and is in lot of active discussions with generic companies for supplying these APIs, particularly Semaglutide and Tirzepatide. As per the company, GLP-1 would be a much longer-term opportunity, with ANDA filers launching the generic versions post-CY2030E, or even in the latter half of the next decade. It is not looking to enter into building blocks. Currently, Neuland is not supplying APIs to any of the innovators for GLP-1 products. Apart from Divi's and Neuland having an exposure to the GLP-1 API/CDMO space, Gland also has an exposure to this segment as a CDMO partner for generics clients. Gland is working on the development of generic versions of Saxenda, Victoza and Ozempic.

Several Indian companies have filed US DMFs for Liraglutide and Semaglutide

Exhibit 23: DMF filings for GLP-1 products by Indian players, December calendar year-end, 2024E

	Company	Filing date
List of DMFs		
Semaglutide	Dr Reddy's	Aug-21
Semaglutide	Sun Pharma	Oct-21
Semaglutide	Zydus	Oct-21
Semaglutide	MSN Life Sciences	Sep-23
Liraglutide	Dr Reddy's	Jun-20
Liraglutide	Biocon	Sep-21
Liraglutide	Sun Pharma	Dec-21
Liraglutide	Aurobindo Pharma	Jan-23
Exenatide	Sun Pharma	Dec-15
Exenatide USP	MSN Life Sciences	Feb-20

Source: US FDA, Kotak Institutional Equities

Apart from CDMO and generic API opportunities, several Indian generic companies have been actively working on developing GLP-1 formulations.

While the market size is vast, competition is likely to inhibit opportunities for generic companies

While most of the generic GLP-1 opportunities are back-ended and only likely to play out over the medium-to-long term, we note these drugs are already well under development by Indian generic companies. Companies are gearing up for patent expiries as well as litigations in the US and other markets, including India. Nevertheless, the competitive intensity remains quite elevated across most of the GLP-1 drugs, especially Liraglutide and Semaglutide. In most of these drugs, at present, there are more than 10 generic ANDA developers. In India, while generic launches in Liraglutide have started, the generic launches of Semaglutide are expected only in the next 2-3 years, at the earliest. In fact, Novo Nordisk is yet to launch Ozempic and Wegovy in India. The company is targeting a CY2026 launch for Wegovy in India, significantly later than the US launch. On the other hand, Rybelsus, was launched in India by Novo Nordisk in India in January 2022, almost two years post its launch in the US.

Beyond Liraglutide, the GLP-1 generic opportunity is likely to play out only over the long term in the US

We assess the GLP-1 opportunity in the US as well as India for key Indian generic formulations companies.

Beyond Liraglutide, the GLP-1 generic opportunity is likely to play out only over the long term in the US

Aurobindo Pharma: ARBP is present in Liraglutide (Saxenda and Victoza) and Semaglutide (Para IV filer for Ozempic and developing Wegovy) and expects to be in the GLP-1 market over the long term. We note ARBP has not specifically highlighted any progress of its GLP-1 pipeline so far. Given its strong presence and capabilities in injectables, we expect ARBP to be one of the key generic players in this crowded market.

Biocon: Biocon is a known Para IV filer for Liraglutide (both Victoza and Saxenda) and is also developing Ozempic. Biocon intends to leverage on its existing capabilities in fermentation-based processes. The company is also adding capacity to augment its peptides presence. While Biocon believes its insulin portfolio would be complementary to its GLP-1 portfolio, as discussed above, there is certainly a possibility of diabetes progression getting delayed due to GLP-1 drugs, which could impact insulin sales for Biocon.

Cipla: Cipla intends to tap the GLP-1 space both in US and India. Given its prevailing capabilities in peptides, we believe Cipla is well-poised to capitalize on the GLP-1 opportunities. Cipla has developed ANDAs for Liraglutide (Saxenda and Victoza) and Semaglutide (Ozempic and Wegovy) for the US market. In India, Cipla is targeting Semaglutide and plans to develop both the oral and injectable versions of the drug.

Dr Reddy's: DRRD has global aspirations for its GLP-1 portfolio. It plans to be an early generic entrant as soon as patent expiries kick in. The company intends to launch these drugs across multiple geographies. Among relevant products, DRRD has filed ANDAs for both brands of Liraglutide (Saxenda and Victoza). For Semaglutide, DRRD has currently developed the formulation for Ozempic and is developing the ANDA for Wegovy. DRRD has developed and established a complete quality management system to ensure the conformity of peptide products and to maintain the underline standard operation processes, including raw material controls, synthesis, purification, quality control, packaging, shipping, and customer complaints. As per DRRD, it has complete peptide API therapeutics development capabilities with state-of-the-art process facilities, supported by a formulation optimization platform and cGMP quality system. DRRD's expertise includes downstream purification, isolation, impurity profiling, and physicochemical characterization. Also, it has scientific knowledge of solid, solution, and hybrid technology. In addition, it has access to unnatural amino acid building blocks via asymmetric hydrogenation/biocatalysis.

Lupin: Lupin is a known Para IV filer for Liraglutide (both Saxenda and Victoza). In its 2QFY24 concall, Lupin had expressed hope of launching Liraglutide in FY2026E subject to the litigation outcome. On the other hand, Semaglutide (Ozempic and Wegovy) remains under development.

Natco Pharma: Natco Pharma has been an early mover in the GLP-1 space and has a sole FTF for Ozempic 8mg/3ml pen in the US. Natco has filed for it from a CMO, and has partnered with Viatris for marketing. While we believe Natco is also developing the generic version of Wegovy, Natco has not yet developed Liraglutide.

Sun Pharma: Sun is a Para IV filer in Liraglutide (Saxenda and Victoza) as well as Semaglutide (Ozempic and Wegovy). As per Sun, the development process is quite complex, and securing approvals would be difficult. In addition to Semaglutide and Liraglutide, Sun has also developed Exenatide. Apart from its generics portfolio, Sun is also working on its novel GLP-1 candidate, Utreglutide. In one of the two Phase 1 studies, GL0034 reduced body weight in individuals without diabetes. In the other study, reduction of body weight of 10% was observed after a different dose of GL0034. The company is very excited with these initial results and will be starting Phase 2 trials in early CY2024. SUNP is contemplating whether to commercialize this product on its own, going forward. In the future, the company is not ruling out M&A to aid commercialization of this drug and other such drugs in non-core therapeutic areas of derma and ophthalmology.

Zydus Cadila: Zydus is a Para IV filer in Semaglutide (Ozempic). It has also developed ANDAs for some of the other GLP-1 drugs like Liraglutide. While for Liraglutide, Zydus is aiming for both Victoza and Saxenda, it is only targeting Semaglutide injectables and not the oral form (Rybelsus). The company does not expect the US launches over the near term. Zydus remains optimistic about the peptide launches, especially in India, and thereafter plans to launch in EMs, followed by DMs.

Apart from the above-mentioned companies, Piramal Pharma, Macleods, Laurus Labs and others also intend to be present in the GLP-1 segment. Currently, Piramal has 14 peptide APIs in its portfolio and another 12 peptide APIs under development, including Liraglutide and Semaglutide. Macleods is also developing ANDAs for few GLP-1 drugs. We believe Laurus is also working on developing APIs of certain oral GLP-1 drugs.

Among Indian ANDA filers, competition appears to be fierce

Exhibit 24: Indian ANDA developers, March fiscal year-end, 2024E

	Known Indian Para IV filers	Other Indian ANDA developers
Drugs		
Byetta	----	Gland Pharma, Sun Pharma, Orbicular Pharma, Zydus Cadila, USV
Victoza	Dr Reddy's, Lupin, Sun Pharma, Orbicular Pharma, Biocon	Wockhardt, Zydus Cadila, Alembic, Aurobindo, Macleods, Cipla, Unichem, Gland Pharma, Enzene Biosciences, Biological E., Kashiv Biosciences, Reliance Life Sciences, Piramal Healthcare, FTF Pharma, Hetero Pharma, USV
Saxenda	Biocon, Lupin, Sun Pharma, Orbicular Pharma	Aurobindo, Alembic, Dr Reddy's, Zydus Cadila, Cipla, Gland Pharma, Reliance Life Sciences, Unichem Labs, Biological E.
Ozempic	Sun Pharma, Aurobindo, Dr Reddy's, Zydus Cadila	Natco, Cipla, Biocon, Macleods, Lupin, Gland Pharma, Intas Pharma, Orbicular Pharma, MSN Labs
Rybelsus	----	MSN Labs, Aurobindo, Lupin, Torrent Pharma, Alkem, Macleods, Aizant, Sotac Pharma, Micro Labs
Wegovy	Sun Pharma	Zydus Cadila, Natco, Aurobindo, Cipla, Lupin, Aizant, Orbicular Pharma, MSN Labs, Dr Reddy's

Source: US FDA, Kotak Institutional Equities

As per the National Family Health Survey in India, nearly one in every four Indians is overweight. As per media articles, despite Ozempic and Wegovy not being authorized for sale in India, these drugs are available in certain pharmacy stores through illegal imports, thereby indicating the strong potential demand for these drugs in India despite the high price tag (a single Rybelsus tablet is available for Rs350 in India). While the demand is likely to be high for GLP-1 drugs in India, we are circumspect of any meaningful upside for any individual generics company from it given the space is expected to be very crowded.

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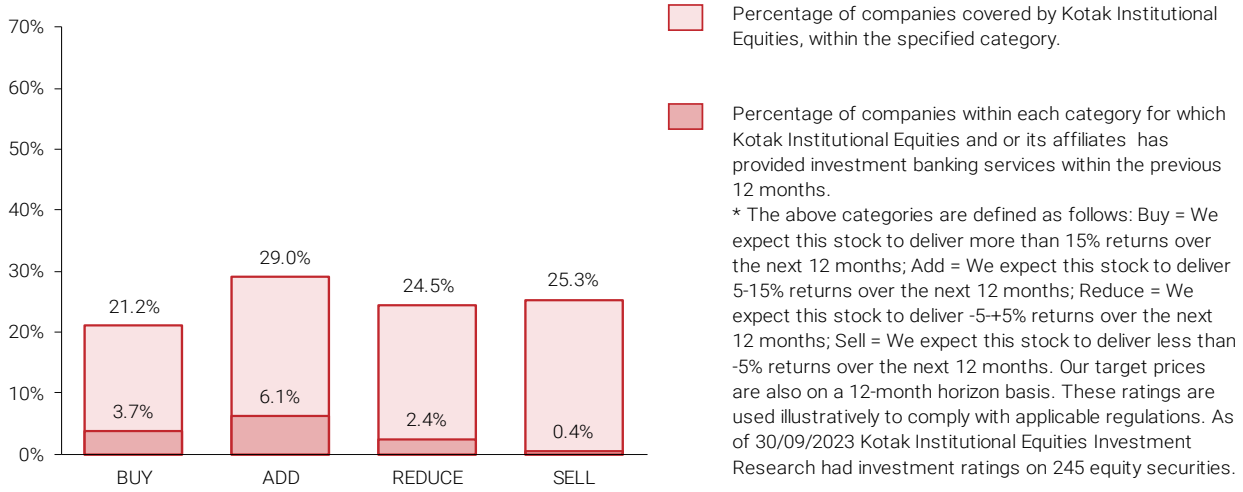

Source: Kotak Institutional Equities

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CEO	Mr. Jaideep Hansraj		022-42858301	ceo.ks@kotak.com

In absence of response/complaint not addressed to your satisfaction, you may lodge a complaint with SEBI at SEBI, NSE, BSE, Investor Service Center | NCDEX, MCX. Please quote your Service Ticket/Complaint Ref No. while raising your complaint at SEBI SCORES/Exchange portal. Kindly refer https://www.kotaksecurities.com/contact-us/