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Podder since 2020

Insulet Corporation

Market Opportunity & Impact of GLP-1s

September 2023

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Introduction

- Ongoing adoption of the GLP-1 class of drugs in diabetes and recent news surrounding the expansion of use of GLP-1 in obesity have led to several questions regarding the impact on the insulin therapy market
- This report is intended to provide investors and other interested parties with an overview of Insulet's end markets in type 1 and type 2 diabetes, and the potential impact of GLP-1s on those markets
- Insulet will periodically provide updates to this report as more information becomes available

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Overview

- There are two distinct types of diabetes, type 1 and type 2. Both are comprised of large patient populations, and represent significantly underpenetrated markets for insulin pump therapy (p. 5).
- Type 1 diabetes is an autoimmune disease that presents acutely and always requires insulin for patient therapy (p. 7). This is despite recent news suggesting GLP-1s may reduce insulin needs for a temporary period after diagnosis.
- Type 1 diabetes is a large underpenetrated market that is not expected to be impacted by GLP-1 therapy (pp. 8-9)
- Type 2 diabetes is a progressive disease that presents gradually, but leads inevitably to insulin therapy in advanced stages (p. 11)
- The GLP-1 class of drugs has been indicated for use in type 2 diabetes since 2005. Nearly two decades of adoption have shown that while they can delay the time to progression to insulin therapy, they do not stop beta cell decline, and they have not changed the population prevalence of advanced disease. (pp. 12-13)
- Insulin and GLP-1s are often used in combination. GLP-1s make insulin therapy more efficacious. (p. 14-15)
- The insulin market in type 2 is large and under-penetrated. It is fed by very large populations that progress inevitably from many factors (e.g., obesity), through pre-diabetes, into type 2 diabetes, and eventually onto insulin therapy. The market for insulin therapy will remain large and underpenetrated for the foreseeable future. (p. 16-17 with FAQs pp. 18-20)

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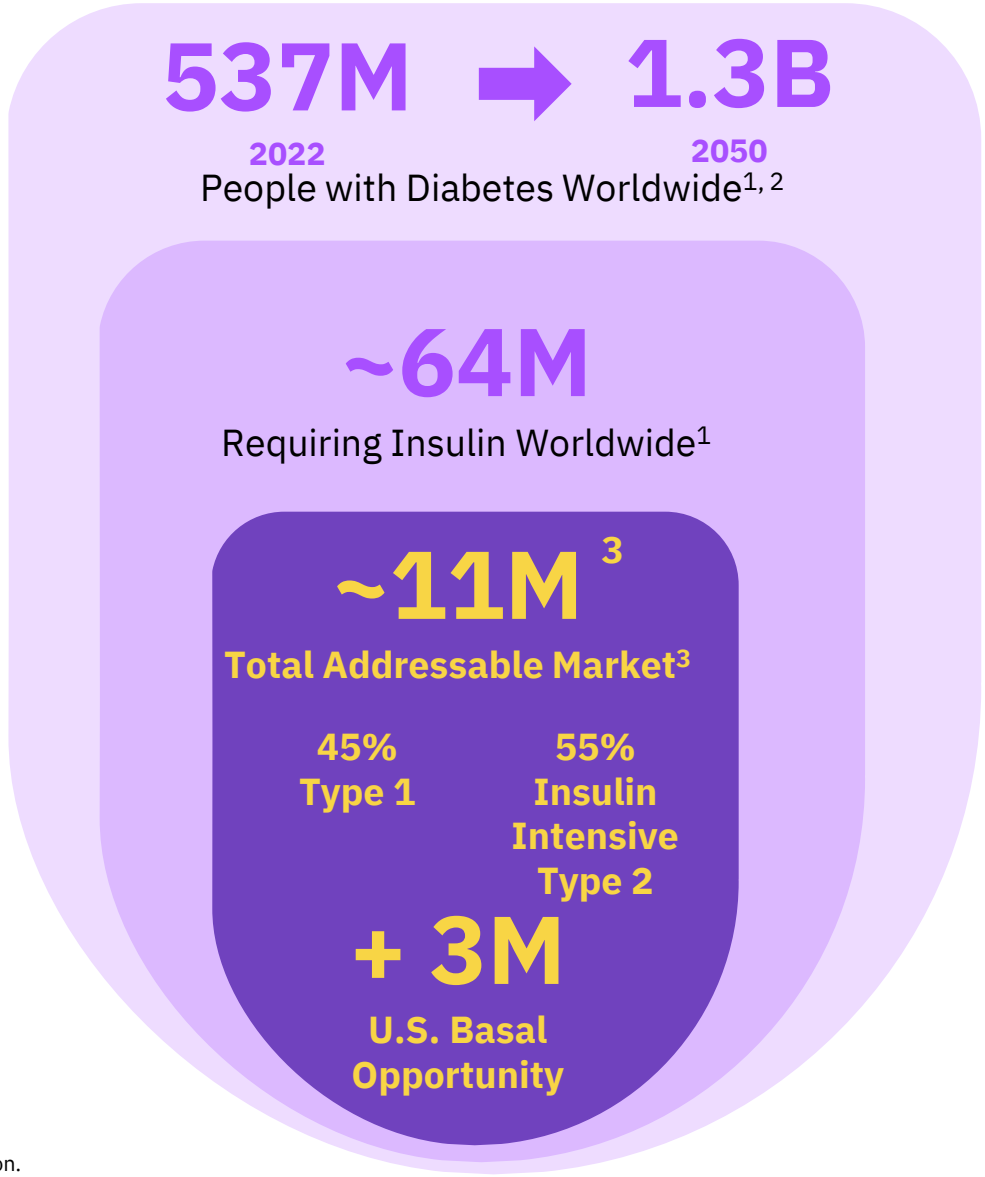
Massive Market Opportunity



The Obvious Choice

Omnipod Platform

- No needles or tubes
- Discreet, wearable, disposable
- Pay-as-you-go economics for customers and payors in the U.S. and certain int'l markets
- Easy access through pharmacy

+

Omnipod 5 with AID

- Novel algorithm using micro-dosing technology
- Industry leading time in range
- Very few hypoglycemic events
- Cleared down to age 2 years

1. Source: IDF Atlas 10th Edition.
2. Lancet, Diabetes: a defining disease of the 21st century, June 2023.
3. Comprised of ~1.5M type 1 and ~2.5M type 2 insulin-intensive (basal-bolus) in the U.S. and ~3.5M type 1 and ~3.5M type 2 insulin-intensive in the international markets we serve today.

Type 1 Diabetes

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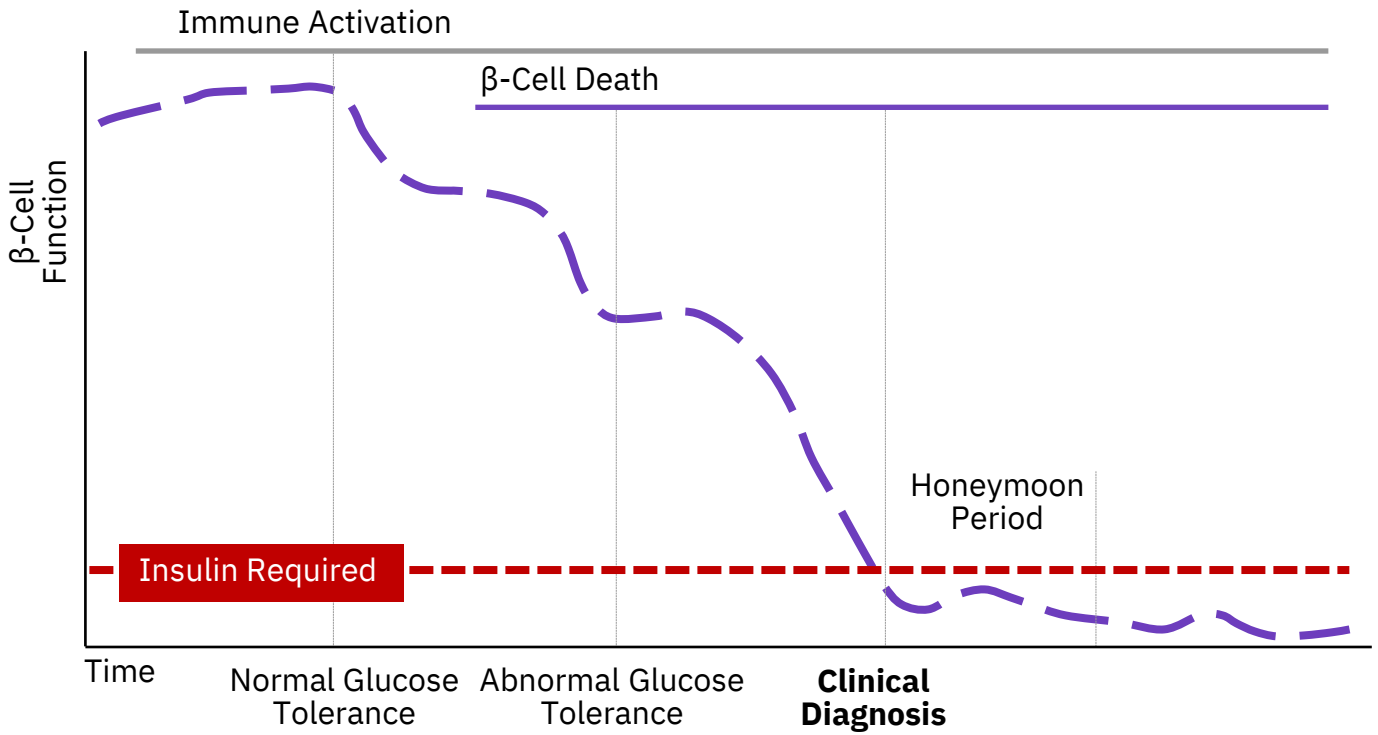
Type 1 diabetes is an autoimmune condition with rapid onset, permanent loss of beta cells, and no cure

The body attacks beta cells resulting in cell death and the need for exogenous insulin

Type 1 Pathophysiology



Adapted from Insel R, Dutta S, and Hedrick J. Type 1 diabetes: disease stratification. Biomed Hub 2017

What causes type 1 diabetes?

- Type 1 diabetes is an immune-mediated disease associated with destruction of the insulin-producing beta cells of the pancreas[1]

What are the symptoms of type 1 diabetes?

- Symptoms include increased thirst, frequent urination, and weight loss occurring over days or weeks. Patients are often completely well prior to these symptoms.
- If undiagnosed, patients can present with lethargy, nausea, vomiting, and abdominal pain due to ketoacidosis. In severe cases, they may present with altered mental state and, in some cases, death.
- An immediate treatment with exogenous insulin is required and lifetime insulin therapy is needed[1]

What is the honeymoon period?

- The honeymoon period occurs after diagnosis when some beta cells remain viable, and insulin is still being produced[2]. Exogenous insulin needs often come down but rise again once beta cells are progressively destroyed by the autoimmune process.
- The honeymoon period can last for months or years

How is type 1 diabetes treated?

- Type 1 diabetes is treated with insulin therapy delivered through injections or infusion with an insulin pump[2]
- There is no cure for type 1 diabetes

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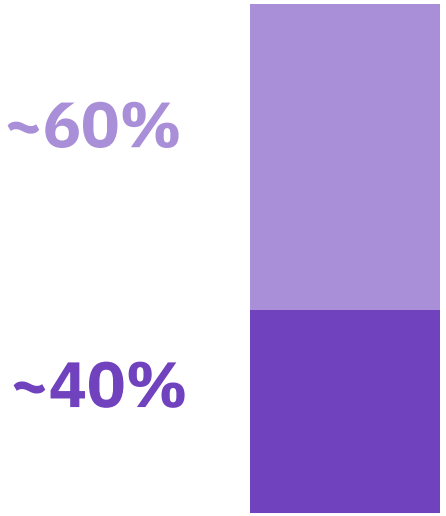
1. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet 2014.
2. Levitsky LL, Misra M. Insulin therapy for children and adolescents with type 1 diabetes mellitus. UpToDate. https://www.uptodate.com/contents/insulin-therapy-for-children-and-adolescents-with-type-1-diabetes-mellitus.

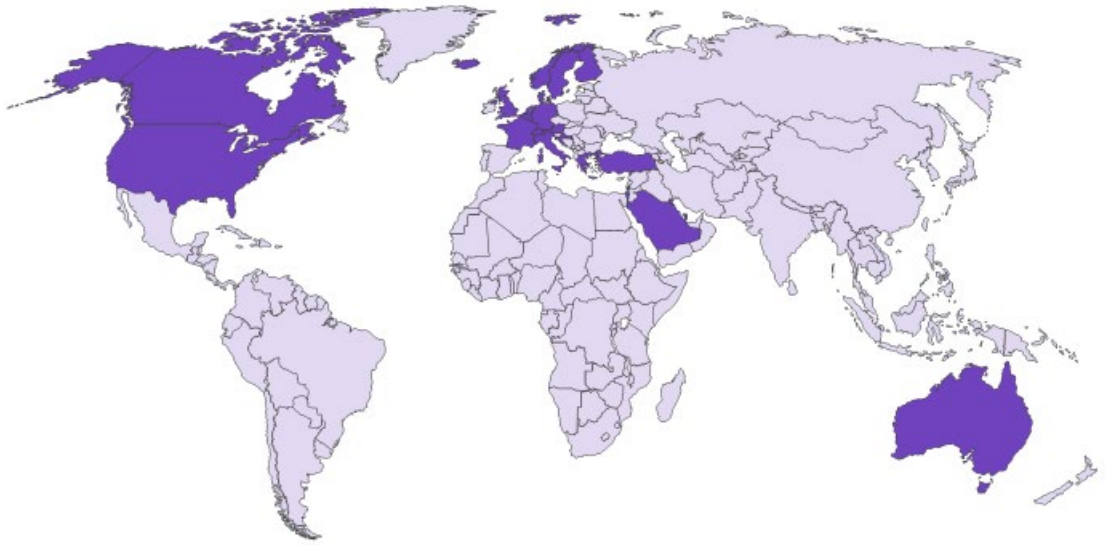
Underpenetrated Type 1 Diabetes Market

U.S. Type 1 Diabetes Population

2022

~1.5M

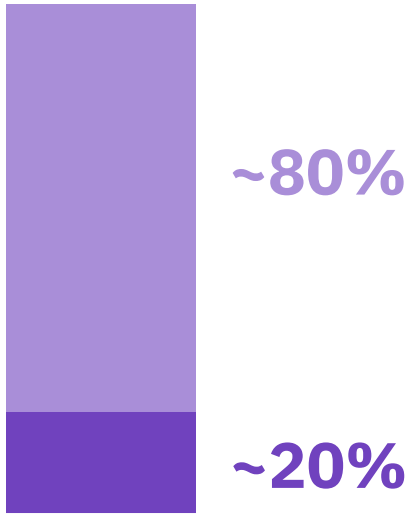




International Type 1 Diabetes Population[1]

2022

~3.5M



Insulin Pumps
Multiple Daily Injections

Insulin Pumps
Multiple Daily Injections

Note: Insulet internal estimates
1. In the markets we serve today.

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Type 1 Diabetes and GLP-1s

SUMMARY

There is no known cure for type 1 diabetes

GLP-1s do not eliminate the need for insulin and insulin delivery technology in type 1 diabetes

- GLP-1s do not eliminate the need for insulin treatment. GLP-1s have not been shown to change the natural course of beta cell loss in type 1 diabetes.

GLP-1s have been studied in type 1 diabetes and are not indicated for use

- Several studies have evaluated the impact of liraglutide in patients with long-standing type 1 diabetes as well as in newly-diagnosed patients[1-3] with modest results. There was a small reduction in insulin requirements while on liraglutide, however there was no evidence of reversal of beta cell loss. Side effects include increased rates of hypoglycemia and hyperglycemia with ketosis, thus cautioning clinical use in type 1 diabetes.
- GLP-1s are not indicated for use in type 1 diabetes, but have been prescribed off-label with careful safety monitoring, as an adjunct to insulin in selected patients, in particular in the obese population with evidence of insulin resistance[4]

We do not expect GLP-1s will have a material impact on the type 1 total addressable market for insulin therapy

1. Mathieu C. et. al. Efficacy and safety of liraglutide added to insulin treatment in type 1 diabetes: The ADJUNCT ONE treat-to-target randomized trial. Diabetes Care 2016.
2. Ahren B. et. al. Efficacy and safety of liraglutide added to capped insulin treatment in subjects with type 1 diabetes: the ADJUNCT TWO randomized trial. Diabetes Care 2016.
3. Dejgaard T. Liraglutide preserved insulin secretion in adults with newly diagnosed type 1 diabetes: The NewLira Trial. Diabetes 2019;68(Supplement_1): 59-OR Abstract only.
4. Dimitrios P. et. al. Liraglutide as adjunct to insulin therapy in patients with type 1 diabetes: a systematic review and meta-analysis. Current Diabetes Reviews 2020.

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Type 2 Diabetes

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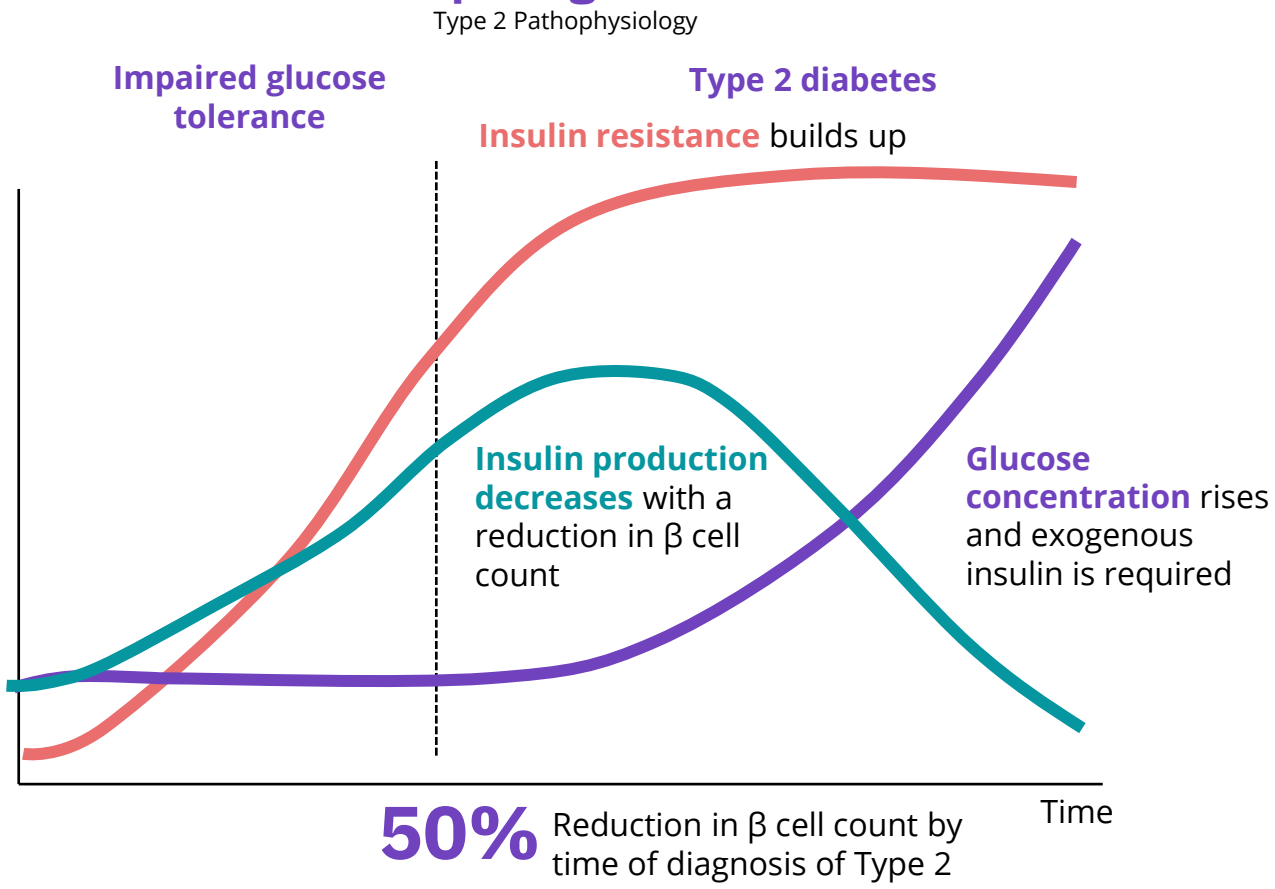
Type 2 diabetes is a progressive disease driven by stress on the endocrine system and irreversible beta cell decline

Over time the body produces less insulin while requiring more[1]



What causes type 2 diabetes?

- Type 2 diabetes is a progressive disease that is diagnosed when insulin production from the pancreas is not sufficient to keep up with the body's demand[2]
- This can result from an increase in insulin resistance, a decrease in insulin production, or a combination of the two[2]
- Risk factors include obesity, genetic susceptibility, ethnicity, and age[2]

What are the symptoms of type 2 diabetes?

- Type 2 diabetes itself is often present without symptoms[2] but may also present with symptoms related to high glucose including increased thirst, urination, weight loss, and tiredness

How is type 2 diabetes treated?

- Type 2 diabetes treatment often starts with lifestyle modification (diet and exercise) followed by oral medications and then injectable medications including insulin[3]
- There is a non-reversible component of loss of beta cell mass that occurs in type 2 diabetes and a reversible component related to beta cell function. Several medications (e.g., GLP-1s) and therapy (e.g., bariatric surgery) can improve beta cell function, but no therapy has been shown to reverse loss of beta cell mass.

1. Adapted from: Holman RR. Diabetes Res Clin Pract. 1998;40(suppl):S21-S25.
2. ElSayed NA et. al. Classification and diagnosis of diabetes: Standards of Care in Diabetes 2023. Diabetes Care 2023;46(Suppl.1):S19–S40.
3. ElSayed NA et. al. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes 2023. Diabetes Care 2023;46(Suppl.1):S140–S157.

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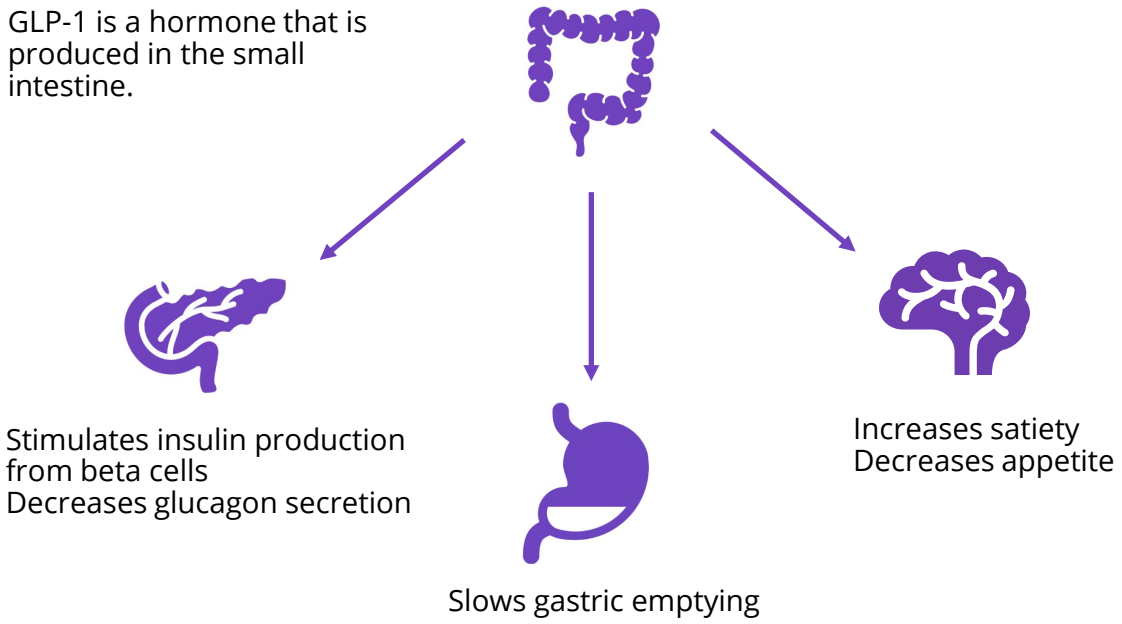
GLP-1s are one component of the treatment pathway for type 2 diabetes

Mechanism of Action of GLP-1 Receptor Agonists[1]



What are the benefits of GLP-1s?

- Improves glucose control and promotes weight loss[2]
- Reduces the risk of cardiovascular events[2]
- Can be used in combination with other diabetes medications including insulin in type 2 diabetes[3]

What are the side effects?

- Gastrointestinal side effects include nausea, vomiting, diarrhea, and constipation[2]
- Pancreatitis and cholecystitis have been reported in clinical trials[3]

Are GLP-1 a cure for type 2 diabetes?

- GLP-1s are a treatment for type 2 diabetes, not a cure

What happens if a patient stops using GLP-1s?

- Therapeutic benefits occur only while taking the medication

1. Figure adapted from Ussher J. et. al. Endocrine Reviews, April 2012, 33(2), 187-215.
2. Nauck MA. et. al. GLP-1 receptor agonists in the treatment of type 2 diabetes – state-of-the-art. Mol Metab 2021.
3. ElSayed NA. et. al. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes 2023. Diabetes Care 2023;46(Suppl.1):S140–S157.

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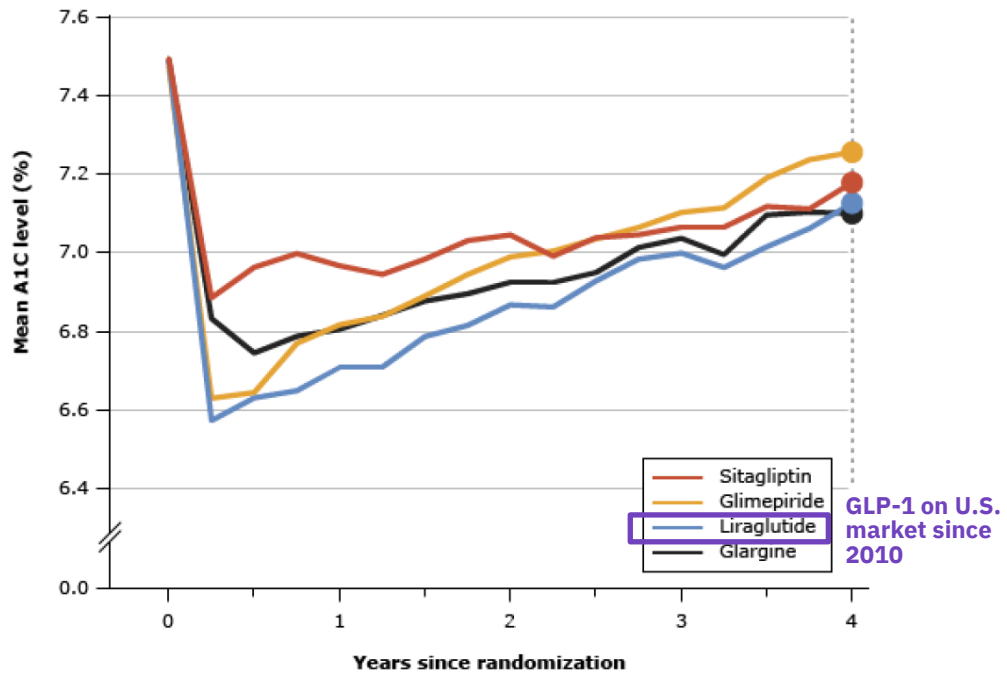
Available therapies do not stop the underlying progression of type 2 diabetes

Therapies drive initial benefit, however progression persists

A1C (marker of average blood glucose) progression after second agent introduction[1]



Most patients with type 2 diabetes will require insulin therapy as disease advances

- Multiple classes of drugs are available to treat type 2 diabetes. The most common agents are: Metformin, Sulfonylureas, DPP-4 inhibitors, SGLT2s, GLP-1s and insulin.[2]
- The progressive nature of type 2 diabetes causes the initial benefits of combination treatment to decline over time (figure)[1]
- No drug class, including GLP-1s, has demonstrated an ability to reverse disease progression
- Insulin is recommended therapy for advanced type 2 diabetes where there is evidence of persistent hyperglycemia[2]
- Unlike other medications where efficacy can plateau once a maximum dose is reached, there is no ceiling effect with insulin.

1.The GRADE Study Research Group. Glycemia Reduction in Type 2 Diabetes — Glycemic Outcomes. N Engl J Med 2022; 387:1063.
2. ElSayed NA. et. al. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes 2023. Diabetes Care 2023;46(Suppl.1):S140–S157.

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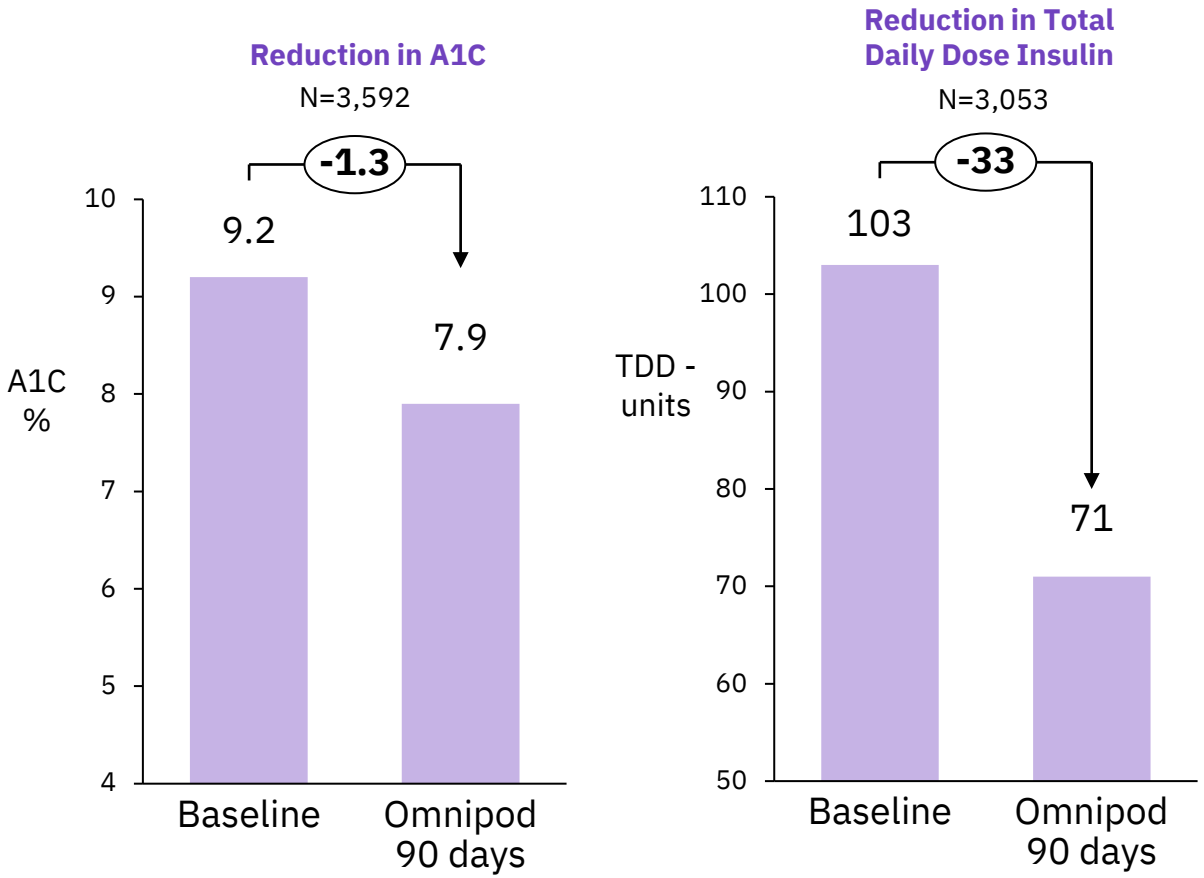
Omnipod is proven and effective in type 2 diabetes

Omnipod Classic and DASH improve glycemic control in type 2 diabetes with 32% less insulin usage



Omnipod Classic and Omnipod DASH have been used to treat type 2 diabetes since coming to market

- In this study[1], 73% of users came from MDI (multiple daily injections) and 15% came from other pumps, indicating that almost all users came from intensive insulin therapy
- In people with a baseline A1C >9%, there was a 2.3% improvement in A1C at 90 days[1]. The mean A1C reduction was 1.3%.
- Overall, there was a 32% (33 units absolute) reduction in insulin usage

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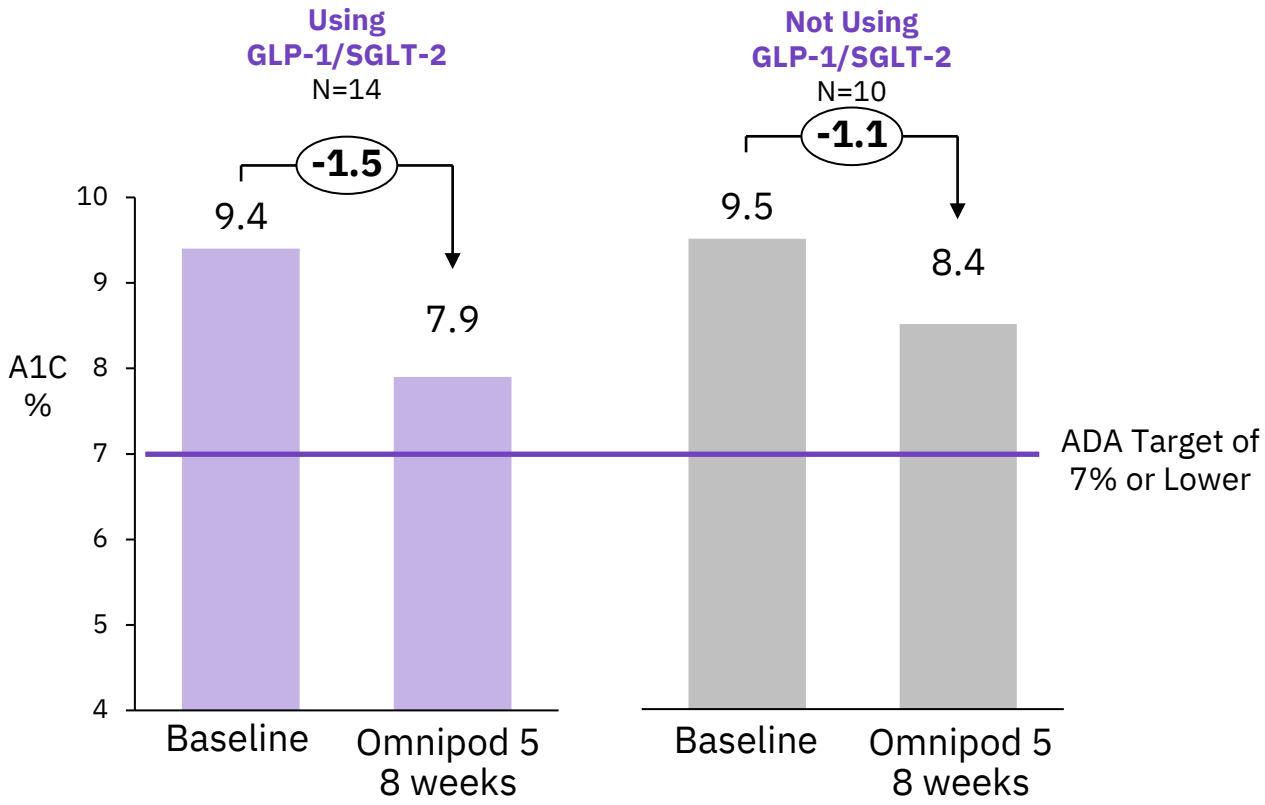
1. Carlson A. et. al. Improved glycemic control in 3,592 adults with type 2 diabetes mellitus initiating a tubeless insulin management system. Diab Research and Clinical Practice. 2021.

Insulin and GLP-1s are often used in combination, producing better results than either therapy alone

Results highlight insulin delivery through Omnipod 5[1,2] is complementary to existing GLP-1 therapy

Reduction in A1C with Omnipod 5 n=24



Newer diabetes agents work effectively in combination with insulin

- The combination of insulin and a GLP-1 agonist has been shown to be more effective than either agent alone[3]
- GLP-1s enhance insulin action
- In a recent feasibility study[1] among people with type 2 diabetes using **Omnipod 5**, subjects using GLP-1 or SGLT2 inhibitors had a greater improvement in A1c than subjects not using these agents (figure)

Omnipod 5 type 2 pivotal study (SECURE-T2D[4]) is enrolling a broad range of patients, and we expect approximately half will already be on GLP-1

1. Davis G. et. al. Safety and efficacy of the Omnipod 5 automated insulin delivery system in adults with type 2 diabetes: From injections to hybrid closed-loop therapy. Diabetes Care 2023.
2. CAUTION: Investigational device, limited to investigational use. Not FDA cleared / Not available for sale
3. Rosenstock J et. al., Benefits of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide, Versus Insulin Glargine and Lixisenatide Monocomponents in Type 2 Diabetes Inadequately Controlled on Oral Agents: The LixiLan-O Randomized Trial. Diabetes Care 2016;39:2026–2035.
4. Clinical trials number: NCT05815342

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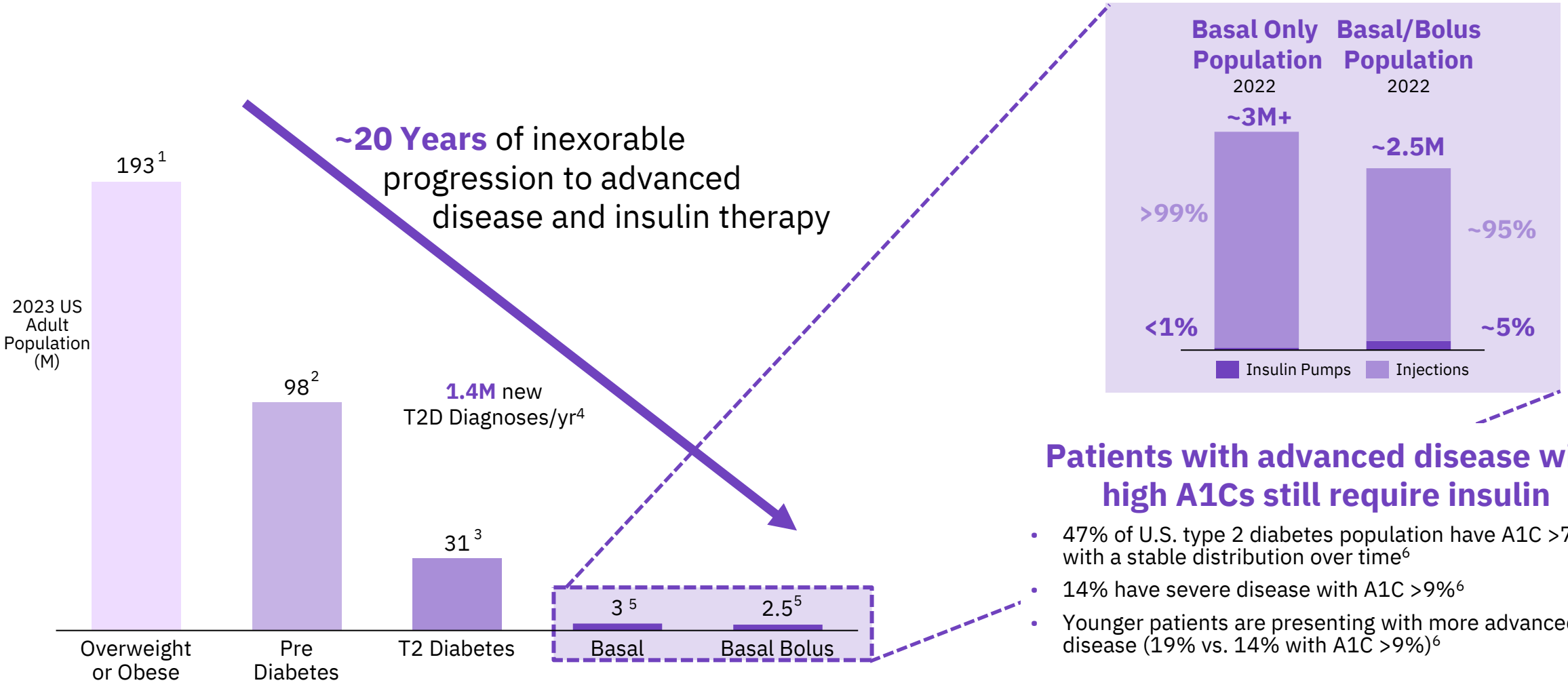
Large populations progress to insulin therapy, which remain significantly under-penetrated by pumps



Patients with advanced disease with high A1Cs still require insulin

- 47% of U.S. type 2 diabetes population have A1C >7% with a stable distribution over time[6]
- 14% have severe disease with A1C >9%[6]
- Younger patients are presenting with more advanced disease (19% vs. 14% with A1C >9%)[6]

1. US Census data, CDC obesity data.
2. CDC 2019 prediabetes prevalence, Insulet estimate.
3. CDC 2020, Insulet estimate.
4. CDC 2019 estimate of 1.4M total diabetes incidence, Insulet estimate.
5. CDC 2020 data, Internal estimate, MDI = Multiple Daily Injections.
6. National Diabetes Statistics Report 2020. Table 9. https://www.cdc.gov/diabetes/data/statistics-report/appendix.html

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Type 2 Diabetes and GLP-1s

FAQS (PART 1 OF 3)

How does type 2 diabetes contribute to Insulet's growth?

- The percentage of U.S. new type 2 diabetes customers has ranged from approximately 15% to 40% each quarter since 2019. We also recently disclosed that in Q2 2023, we had a record number of new customer starts from people with type 2 diabetes. This is in addition to very strong type 1 diabetes new customer starts.

How will GLP-1s impact the type 2 diabetes total addressable market?

- We do not expect a material impact to the type 2 diabetes market. The type 2 diabetes insulin therapy market is large and underserved, with minimal pump penetration. We expect this to continue to be a large market in coming years because of the non-reversible underlying beta cell death that occurs in both pre-diabetes and type 2 diabetes. The popularity of GLP-1s in obesity may also lead to people seeking care earlier, which may result in earlier diagnosis of type 2 diabetes and earlier insulin intervention, potentially expanding the market.

Are GLP-1s impacting Insulet's business today?

- No. GLP-1s have been on the market since 2005 for type 2 diabetes and since 2015 for obesity. Despite this, glycemic outcomes have not changed on a population level with the percentage of people with an A1C >9% remaining at 14%[1]. This is a marker of advanced disease where intensive insulin therapy is recommended. In this segment, Insulet's proven growth in insulin delivery reflects the large, underpenetrated market in need of more simple and effective insulin therapies.

1. National Diabetes Statistics Report 2020. Table 9. https://www.cdc.gov/diabetes/data/statistics-report/appendix.html

Type 2 Diabetes and GLP-1s

FAQS (PART 2 OF 3)

Do GLP-1s eliminate the need for insulin in type 2 diabetes? Do they drive remission?

- GLP-1s do not eliminate the need for insulin in type 2 diabetes. Insulin is recommended in patients whose A1C remains uncontrolled after >3 months of combination therapy, if there is evidence of catabolism, if symptoms of hyperglycemia are present, or when A1C >10% or blood glucose is >300mg/dL[1].
- GLP-1s do not cure or induce durable remission of type 2 diabetes. They have been shown to reduce insulin requirements in those with early-stage type 2 diabetes but are less effective in those with advanced disease[2].

What is the adherence of GLP-1s?

- A real-world study using a claims-based database showed 50% of patients stop taking GLP-1s after 12 months and the majority (70%) discontinued therapy by 24 months[3]. This evidence suggests that clinical benefits found in clinical trials are not well replicated in the real world. Current real-world adherence to GLP-1 therapy may further limit its impact on population progression to advanced disease.

What about newer agents such as Mounjaro (tirzepatide), which is a dual agonist, and the triple agonists (retatrutide)? Will these prevent type 2 diabetes?

- There are currently no long-term data demonstrating newer agents' potential incremental efficacy in type 2 disease progression, and importantly there is no mechanistic reason to suggest that these medications will reverse the beta cell loss that occurs in type 2 diabetes

1. ElSayed NA. et. al. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes 2023. Diabetes Care 2023;46 (Supplement_1):S140-S157.
2. Rosenstock J. et. al. Impact of a weekly GLP-1 receptor agonist, albiglutide, on glycemic control and on reducing prandial insulin use in type 2 diabetes inadequately controlled on multiple insulin therapy: a randomized trial. Diabetes Care 2020.
3. Weiss T. et. al. Real-world adherence and discontinuation of GLP-1RA therapy in type 2 diabetes mellitus patient in the United States. Patient Prefer Adherence 2020.

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Type 2 Diabetes and GLP-1s

FAQS (PART 3 OF 3)

Are GLP-1s ever used with insulin?

- Yes. Because type 2 diabetes is a progressive disease, maintenance of glycemic targets often requires combination therapy[1]. There are coformulations available that deliver both GLP-1 and long-acting insulin such as Xultophy and Soliqua. In clinical practice, GLP-1s and insulin are commonly prescribed together to treat advanced type 2 diabetes. GLP-1s have an additive effect to insulin therapy[2].

1. El Sayed NA. et. al. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes 2023. Diabetes Care 2023;46 (Supplement_1):S140-S157.
2. Blonde L. et. al. Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomized, open-label, phase 3, non-inferiority study. Lancet 2015.

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