The Modern Therapeutic Landscape of Type 2 Diabetes: A Comparative Analysis on the Efficacy of Semaglutide and its Alternatives

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Abstract

Context: Celebrity use has driven up the demand for Ozempic (semaglutide) as a weight loss drug, leading to a shortage that has lasted for over a year.

Object: This study aims to explore alternatives to semaglutide that can be utilized during the shortage, as well as present more effective long-term replacements.

Methods: This paper gathered secondary quantitative and qualitative data from past studies on the National Library of Medicine and other private research. Additionally, pathways and chemical structures were found and analyzed using the KEGG and PubChem from the National Institute of Health.

Results: Monjarou (tirzepatide) and Metformin (biguanide) are viable long-term alternatives to Ozempic for different reasons, some being: cost-effectiveness, weight loss effectiveness, and accessibility.

Conclusion: Until Ozempic becomes a consistently accessible treatment after its speedy ascent and descent from the public eye, there are excellent alternatives available, and to prevent such a shortage in the future, several steps need to be taken by both Novo Nordisk and individuals in the healthcare industry who have the ability to make an impact when it comes to affordable, accessible healthcare.

Keywords: *ozempic shortage; type 2 diabetes mellitus (T2DM); receptor agonists; semaglutide; tirzepatide; biguanide.*

1. Introduction

What is Ozempic, and why is it popular? On social media, due to celebrities such as Amy Schumer, Elon Musk, or Chelsea Handler, it is highly lauded and practically synonymous with weight loss because of its astonishing effectiveness, and it is considered by some to be a shortcut in order to achieve an optimal figure. However, because of this sudden surge in popularity (in part to celebrity usage as well as doctors providing it despite it not being approved for weight loss by the FDA, a legal practice known as off-labeling), there has been an Ozempic shortage that began in April of 2022 and is predicted to continue throughout 2024. What exactly does this mean for the average consumer? Ozempic is a prescription drug that is essential for many type-2 diabetics, as it lowers blood sugar by increasing insulin secretion, therefore allowing patients to properly manage their diabetes symptoms, as well as lose weight—an essential factor as obesity reduces insulin sensitivity [1]. Because of the shortage, the price of the Ozempic that remains on the market has

skyrocketed and its scarcity puts many patients at risk, especially if they cannot afford it.

According to the CDC, approximately 11.6% of Americans suffer from diabetes, and 90-95% of these patients are diagnosed with type 2 diabetes [2]. This study details the common causes, demographics, symptoms, testing procedures, and treatments of type 2 diabetes with a focus on Ozempic (semaglutide) in order to propose alternative medications that may prove to be as, or even more effective, both from a physical perspective as well as a financial one.

2. Type 2 Diabetes

What is Type 2 Diabetes? — Type 2 diabetes mellitus (T2DM) is a disease in which the patient's body is unable to adequately regulate and utilize glucose for one of two reasons: the production of insulin, a glucose-regulating hormone, decreases, or the body's resistance to insulin increases. Unfortunately, diabetes can also result from a combination of both insulin resistance and decreased production. Insulin is a hormone that manages blood sugar levels by moving glucose from the bloodstream and into the cells that need it as a source of energy. When a patient's insulin production decreases, this results in high blood glucose (hyperglycemia), energy shortage, dehydration, etc. because there is no insulin to move glucose into the cells. For patients with insulin resistance, this leads to the proliferation of insulin and in turn, a high risk of acute hypoglycemia as the increase of insulin allows cells to absorb glucose, depleting that of the bloodstream.

Now, T2DM is not to be confused with type-1 diabetes (T1DM), as T1DM is an autoimmune disease where the immune system attacks the pancreas and prevents the creation of insulin. T2DM, on the other hand, is not autoimmune and is rather characterized by either the reduction of insulin production, the resistance of insulin, or a combination thereof.

Common Causes and Possible Risk Factors — According to the CDC [3], individuals over the age of forty-five are more at risk of developing type-2 diabetes, as well as those who suffer from obesity and lead a life of inactivity [3]. Some other risk factors include pre-existing conditions such as polycystic ovary syndrome (PCOS), heart disease, hypertension, and depression. Those with a history of diabetes should also be cautious, from prediabetes or gestational diabetes to genetic predispositions such as GCGR, a glucagon hormone involved in glucose regulation, or CAPN10, associated with type 2 diabetes in Mexican Americans [4].

Demographics — Compared to other ethnic groups, Type 2 diabetes is most prevalent in Hispanic, African American, and Asian American individuals — in part because of genetics and in part due to the health inequities in marginalized communities. The prevalence of diagnosed type 2 diabetes by racial/ethnic group is as follows: Asians 9.0%, African Americans 13.2%, Hispanic 12.8%, and non-Hispanic whites 7.6%. There is a wide variation in prevalence in the Native American population (e.g., 6.0% in Alaskan Natives and 24.1% in southern Arizona Native American groups) and among Hispanics (e.g., 8.5% in Central/South Americans, 9.3% in Cubans, 13.9% in Mexican Americans, and 14.8% in Puerto Ricans [5].

Physical Symptoms— Physical symptoms of type 2 diabetes commonly include but are not limited to: frequent urination, thirstiness, unintentional weight loss, increased hunger,

blurred vision, Acanthosis nigricans (darkening of the skin), fatigue due to the lack of glucose stores within the body or the inability of insulin to provide glucose to working cells, and hyperglycemia [6].

Acute hyperglycemia is particularly dangerous as it damages blood vessels in the brain, impairing the brain's regulation of the body in some of the following ways: memory and learning difficulties, lack of emotional regulation, and weight gain. Among the most concerning effects of hyperglycemia are certain types of dementia, including Alzheimer's Disease [7].

Psychological Symptoms — Like most diseases, type 2 diabetes is not only limited to physical symptoms. Diabetes distress is a psychological state induced by the burden of managing and having diabetes which, according to the CDC, "In any 18-month period, 33% to 50% of people with diabetes have diabetes distress" [8]. It is not considered to be a form of clinical depression, but rather, it is often thought of as an emotional/mental reaction due to the high stress placed on a victim of diabetes and therefore not a mental illness. That does not mean that there is not a correlation between diabetes and depression. Both type 1 and type 2 diabetes increase the risk of developing depression, and in general, people with diabetes are twice as likely to have depression [9]. It is interesting to note that due to type 1 being an autoimmune disorder, depression is only considered a risk factor for type 2 diabetes.

Another significant mental symptom that can occur is the development of eating disorders. According to the NIDDK, "anorexia nervosa, bulimia nervosa, and binge eating disorder may affect up to 20% of people who have diabetes", a reasonable statistic when you take into consideration the necessity of tracking food combined with managing diabetes [10]. With self-managed diabetes comes the risk of a lesser-known eating disorder, orthorexia nervosa, characterized by an obsession with healthy eating. Now, there is a "healthy orthorexia" in which restrictive eating is based on health concerns rather than weight, but it can be different to differentiate between the two, especially because "obesity rates are high in patients with type 2 diabetes mellitus (T2DM)" [11].

Testing and Treatment — Testing for diabetes type 2 is done through several means, and individuals are usually screened when providers take note of anything abnormal with one's BMI, family history, blood pressure, cholesterol levels, and most importantly, blood sugar levels. There are four common tests administered: an A1C test, a random blood sugar test, a fasting blood sugar test, and a glucose tolerance test. For the A1C test, below 5.7% is normal, 5.7% to 6.4% is diagnosed as prediabetes, and 6.5% or higher on two separate tests indicates diabetes [12].

There are several available treatments for T2DM, ranging from holistic to medicinal, and this study will focus on three receptor agonists, "drugs that bind to a receptor inside a cell or on its surface and cause the same action as the substance that normally binds to the receptor [13]. The three drugs that will be covered are Metformin, the only biguanide used to treat diabetes, tirzepatide, commonly known as Mounjaro, and semaglutide, which is more popularly known as Ozempic.

3. Ozempic

The advancement of Ozempic began after the exploration of venom derived from the Gila monster, a venomous lizard. This exploration yielded exendin-4, a peptide

that's similar to human's glucagon-like peptide-1 (GLP-1), a hormone that stimulates insulin secretion. Subsequently, this discovery led to the creation of the first GLP-1 agonist–exenatide. Since then, other GLP-1 agonists, including Ozempic, have been developed [14].

Specifically, Ozempic is an aqueous, clear, and colorless solution that contains semaglutide, a GLP-1 receptor agonist, which mimics the GLP-1 hormone that is released to prompt the body to produce more insulin in the lower gastrointestinal tract, which in turn lowers glucose levels. Disodium phosphate dihydrate (Na_2HPO_4) is added as a buffer to keep the medication potent and Propylene glycol ($C_3H_8O_2$) as an isotonic agent to lessen pain and reduce clogging. Additionally, phenol (C_6H_6O), a preservative, water (H_2O), an injection vehicle, as well as sodium bicarbonate ($NaHCO_3$), to adjust the acidity, is added [15].

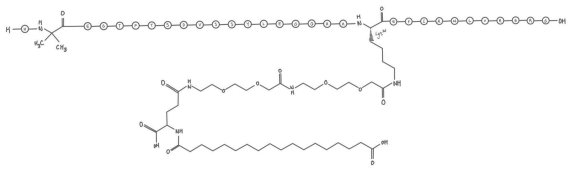

Fig. 1 Chemical Structure of Ozempic
The circular peptide backbone is produced by yeast fermentation and protracted using albumin binding, facilitated by modification of position 26 lysine with a hydrophilic spacer and a C18 fatty di-acid. The molecular formula is $C_{187}H_{291}N_{45}O_{59}$, and its molecular weight is 4113.58 g/mol [15].

Method of Storage
Prior to first use, store in the refrigerator between 36 and 46 ˚F (2 to 8 ˚C). After first use, it can be stored in the refrigerator at the same temperature as previously stated, or at room temperature between 59 and 86 ˚F (15 to 30˚C) [16]

Semaglutide (injection)
Semaglutide, the active ingredient in the aforementioned Ozempic, is a medication used for patients with type 2 diabetes to lower blood sugar levels and reduce the risk of major cardiovascular events. Additionally, it is also used for weight loss purposes amongst the nontype 2 diabetes patients leading to multiple societal issues. These occur as semaglutide is a GLP-1 agonist, which means it mimics the action of the hormone GLP-1. Mimicking this hormone allows the body to increase insulin release without taking artificial injections, lower the amount of glucagon released, and delay gastric emptying, which leads to reduced appetite [17].

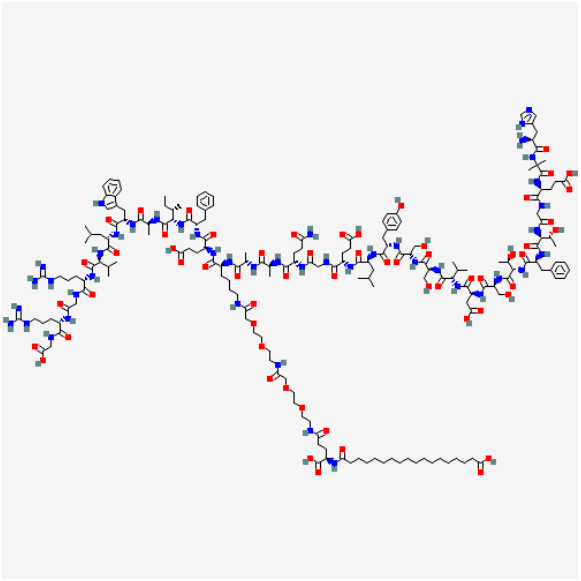

Fig. 2 Chemical Structure of Semaglutide $C_{187}H_{291}N_{45}O_{59}$ [18]

Ozempic offers several advantages: substantial weight loss ranging from 5% to 20% of body weight; improvements in blood sugar levels, blood pressure, and cholesterol profiles; low risk of hypoglycemia compared to insulin therapy.

However, it exhibits a range of potential adverse effects: gastrointestinal disturbances, nausea, diarrhea, abdominal pain, vomiting, and constipation. Moreover, it increases the risk of suicidal ideation, emotional disturbances, altered taste perception, diabetic retinopathy, gallbladder disease, kidney complications, pancreatitis, allergic reactions, and possible hypoglycemia if consumed with other medications. Furthermore, Ozempic's lack of FDA approval as a weight loss medication underscores potential challenges related to long-term weight maintenance [19].

Due to the above downfalls and chemical compounds that may attack certain individuals, several contraindications limit the use of semaglutide therapy. Patients with a personal or family history of medullary thyroid cancer (MTC) or Multiple Endocrine Neoplasia Type 2 are advised against its use. Individuals under 18 years of age, pregnant or breastfeeding women, those with diabetic retinopathy, and patients with type 1 diabetes or a history of pancreatitis should also avoid semaglutide therapy [20].

The financial implications of semaglutide therapy vary significantly depending on insurance coverage. With insurance, the monthly cost typically goes around $281. However, without insurance coverage, the annual expense can rise to approximately $11,229, averaging $936 per month [21].

Ozempic, a prominent brand of semaglutide-based medication, is experiencing a multifaceted challenge in recent society. Its perceived advantage in facilitating weight loss, coupled with endorsements from public figures, may contribute to limited accessibility for certain demographics. Furthermore, the psychological aspect of diabetes management, including issues such as Diabetes Distress, warrants consideration in assessing the broader societal impact of Ozempic and similar medications.

4. Alternatives

Tirzepatide – *Mounjaro* (injection)

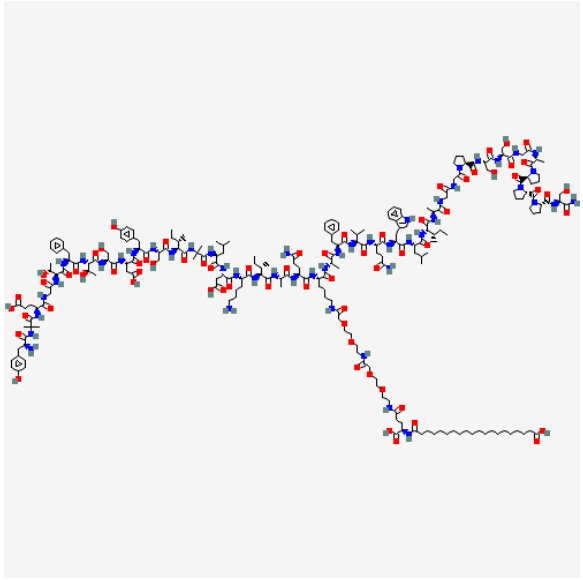

Fig. 3 Chemical Structure of Tirzepatide
Tirzepatide is a synthetic linear peptide molecule containing 39 amino acids. Its molecular formula is $C_{225}H_{348}N_{48}O_{68}$ with a molecular weight of 4813.45 Da [22].

Tirzepatide is a dual-GIP and GLP-1 receptor agonist, which triggers both GIP and GLP-1 receptors to initiate insulin release [23].

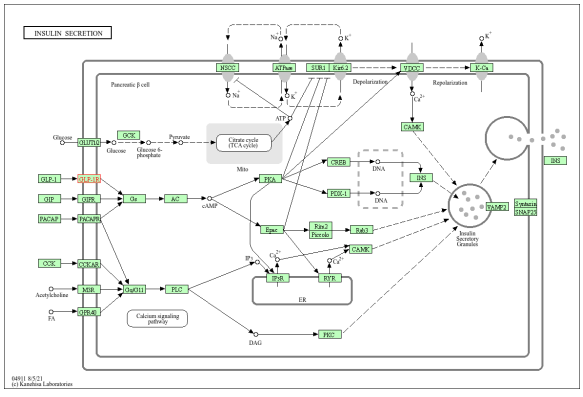

Fig. 4 Insulin Secretion Pathway [24]

Tirzepatide is involved in the Insulin secretion pathway, and as it is shown in the pathway, GLP-1 and GIP are triggered, which then activates GLP-1R and GIPR respectively. Then, they arrive at the GNAS complex locus (Gs), which regulates the Insulin secretion process. The activated Gs alpha from the Gs subunit binds to and activates an enzyme called adenylyl cyclase, which, in turn, catalyzes the conversion of ATP into cyclic adenosine monophosphate (cAMP). This cAMP signaling activates the cAMP-responsive element binding protein 3, which binds to a DNA sequence called cAMP response elements (CRE), thereby increasing or decreasing the transcription of the genes. In the end, the DNA sequence produces the INS gene, which is located on chromosome 11 and is in charge of producing human insulin. Here, the semaglutide only triggers GLP-1, which is the reason why it has a slower weight loss process than tirzepatide medications.

To continue on the comparison between semaglutide and tirzepatide, a comparative study for type 2 diabetes showed that semaglutide lowered A1C levels by 1% to 2%, while tirzepatide lowered A1C by 2% to 2.5%. In an additional study, weight loss with semaglutide ranged from 6 to 10 kg (13.2 to 22 lb), and with tirzepatide, weight loss ranged from 7 to 13 kg (15.4 to 28.6 lb) [25]. These reveal that tirzepatide may have a better effect to help lower blood sugar and lead to weight loss but may be associated with more stomach side effects at higher dosages.

Study	SURPASS-2, 40 weeks			
Agent	Tirzepatide			Sema[1]
Dose	5 mg	10 mg	15 gm	1 mg
Patient num. per arm	470	469	470	469
Effectiveness				
HbA_{1c} reduction vs. baseline [%]	-2.0	-2.2	-2.3	-1.9
Body weight reduction vs. baseline [kg]	-7.8	-10.3	-12.4	-7.8
Adverse events				
Nausea	17.4	19.2	22.1	17.9
Vomiting	5.7	8.5	9.8	8.3
Diarrhea	13.2	16.4	13.8	11.5
Constipation	6.8	4.5	4.5	5.8
Any “gastro-intestinal” adverse event	40.0	46.1	44.9	41.2
Adverse event leading to treatment discontinuation	6.0	8.5	8.5	4.1

Table 1. “Gastro-intestinal” adverse events reported in clinical trials comparing tirzepatide (5, 10, and 15 mg per week) with selective GLP-1 receptor agonist, semaglutide (1 mg per week) [26]
Sema[1]: Semaglutide

Cost-wise, utilizing tirzepatide (*Mounjaro*) was found to offer a better value for money when compared to semaglutide (Ozempic) for body weight reduction in T2DM patients over 68 to 72 weeks – The total cost of 72 weeks of tirzepatide medication was estimated at $17,527 compared with $22,878 for 68 weeks of semaglutide medication [27]. Now, this information may seem contradictory; on a dose-by-dose basis, Mounjaro is more expensive than Ozempic. However, when isolating weight reduction, because tirzepatide is so much more effective than semaglutide, Mounjaro achieves more cost-effectiveness, leading to quicker treatment.

Accessibility-wise, unlike semaglutide medication (Ozempic) which is expected to have a global shortage throughout 2024, *Mounjaro* (tirzepatide) is accessible at retail and mail-order pharmacies in the U.S., E.U., and Japan after receiving approval from the U.S. Food and Drug Administration (FDA) on November 8, 2023. [28, 29, 30]

Unfortunately, you may not take Mounjaro while you are pregnant, and this applies the same to Ozempic as semaglutide should not be taken during pregnancy [31].

Biguanide – Metformin (oral)

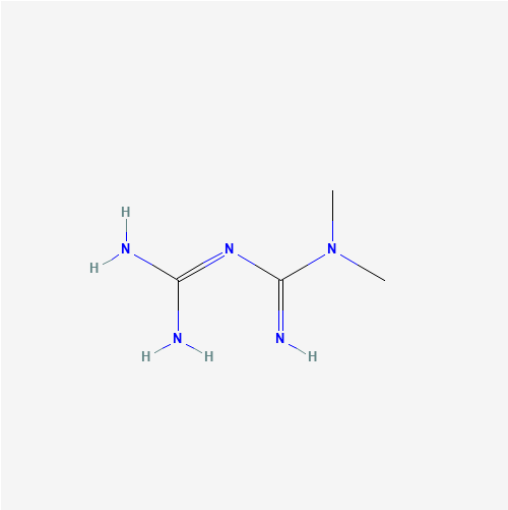

Fig. 5 Chemical Structure of Biguanide $C_4H_{11}N_5$ [32]

Biguanide medications are oral diabetes medications that stimulate insulin sensitivity by controlling the glucose production in the liver, resulting in the intestines absorbing smaller amounts of sugar [33].

Patients take either 50mg twice daily or 85mg once daily; then, gradually increase the dosage to 500mg weekly or 850mg over 2 weeks. When maintaining, patients take 2000mg/day; the maximum dosage is 2500mg/day [34].

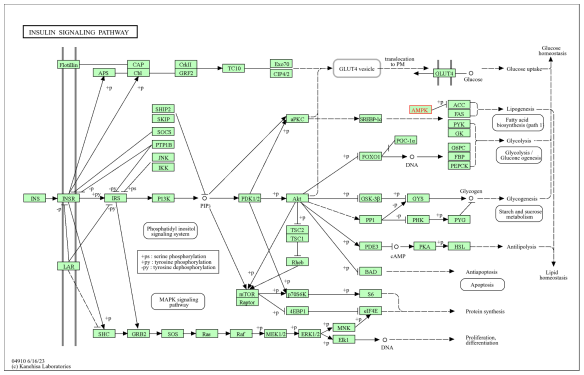

Fig. 6 Insulin Signalling Pathway [35]
Biguanide is involved in the Insulin signaling pathway glucose homeostasis, one of the outputs of the pathway, is visualized, meaning that Biguanide helps reduce the glucose level produced during digestion to maintain a stable blood sugar level.

Different from semaglutide or tirzepatide, which causes the pancreas to release insulin and block the liver from making extra glucose, biguanide helps your body use its own insulin more effectively by decreasing the amount of glucose made and absorbed [36].

The greatest advantages of biguanide medications are that they are inexpensive, safe, and accessible. Metformin (biguanide) is sold for as low as $16 per month without

insurance and around $240 per year while it is around $11,229 per year for Ozempic [42, 41].

Amongst the medications discussed in this paper, Metformin (biguanide) is the only option that is safe, effective, and rational enough to use for reducing insulin resistance in pregnant women with type 2 diabetes [39]. Last but not least, after receiving approval for type 2 diabetes by the FDA in 1994, Metformin quickly spread across the globe and is now publicly available in 94% of the countries worldwide, making it one of the most accessible type 2 diabetes medications on the planet [40].

5. Conclusion and Discussion

T2DM is a widespread, expensive disease, and as more and more people are finding themselves susceptible to it, it is important to do what we can to combat and treat it. Lifestyle changes can be a good start, but often they are not enough, and medical intervention is necessary. Although there are several alternative treatments to Ozempic (semaglutide), it is important to understand the significance of these alternatives and how they can prove to be a better investment, both physically and financially. Ozempic's rise to prominence was not without reason, but after examining Mounjaro (tirzepatide) and Metformin (biguanide), we have concluded that these drugs can not only replace Ozempic for certain patients but even surpass its benefits.

One concern for many patients is how medications can interact with pregnancy, and while Ozempic and Mounjaro are not to be used, Metformin is a safe alternative. Not only is it cheaper than the other options, but it is also very thoroughly researched and consistently available. While it does lead to some weight loss, when compared to semaglutide and tirzepatide, biguanide is not as strong a contender, but frankly, metformin is not intended for weight loss. Metformin is ideal for a patient whose main focus is controlling blood sugar and weight is not a significant concern.

Mounjaro is more expensive than Ozempic, which may lead to some apprehension on the consumer's part, but some benefits could possibly allay one's concerns. When compared to semaglutide, tirzepatide is more effective when it comes to losing weight, and it is also significantly more accessible, especially because of its direct-to-patient platform launched by Eli Lilly in January of 2024. It is ideal for patients who struggle with obesity or weight gain.

Medication	Ozempic	Mounjaro	Metformin
On Average Without Insurance			
Cost per Month (in USD)	$936 [41]	$1,069	$16-25 [42]
Cost per Year (in USD)	$11,229	$12,829	$240
On Average With Insurance			
Cost per Month (in USD)	$281 [41]	$321	N/A*
Cost per Year (in USD)	$3,369	$3,849	N/A*

Table 2. Cost Comparison between Ozempic and its Two Alternatives – Mounjaro and Metformin
*there was no available information on the average cost of Metformin on an insurance plan.

In order for Ozempic to regain its place as an effective and available treatment, researchers should look into weight loss

alternatives that will not put pressure on diabetes treatment production, policymakers should pass laws regarding off-labeling for specific diseases and medications in instances such as the Ozempic shortage, and doctors should be supported by the health infrastructure to focus on preventative care as well as diabetes treatment, effectively lowering the need for these medications.

The Novo Nordisk company can invest a healthy amount of its 2023 profit ($28.5 billion) into not only increasing its manufacturing capacity but also by streamlining distribution channels to ensure that Ozempic reaches patients promptly (perhaps following a direct-to-consumer model like Eli Lilly). Collaborating with logistics partners and optimizing supply chains will help distribute the medication more efficiently and prevent such a shortage in the future. The company can also invest in in-depth clinical trials and research to minimize side effects, making it a stronger contender in the T2DM medication market.

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