

The background of the cover features a microscopic view of cells, likely showing nuclei and cytoplasm, in shades of purple and pink. Overlaid on this is a 3D molecular model of a protein, represented by a teal ribbon structure with various atoms shown as small spheres in white, red, and blue. The protein structure is complex, with several loops and helices, and is positioned diagonally across the cover.

The State of Innovation in  
Highly Prevalent Chronic Diseases

# Volume III: Type 2 Diabetes and Obesity Therapeutics

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by David Thomas, CFA and Chad Wessel  
BIO INDUSTRY ANALYSIS

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# The State of Innovation in Highly Prevalent Chronic Diseases

## Volume III: Type 2 Diabetes and Obesity Therapeutics

### Introduction

This is the third report in a series on the innovation landscape of highly prevalent, chronic diseases. In our previously published research, emerging company investment for drug development in many of these common diseases was shown to be declining over the last decade and is low relative to total healthcare costs of these diseases (**Figure 1**).<sup>1</sup> The persistence of this trend could have implications for the future output of innovative medicines in these disease areas. The cause for concern is magnified by the impact these chronic disease areas are having on the overall healthcare system in the US. Thus, it is important that barriers to therapeutic innovation are identified and removed.

This volume takes an in depth look at the state of innovation in diabetes mellitus type 2 and obesity therapeutics. Diabetes affects 30.3 million people in the U.S. alone, 95% of whom have type 2 diabetes, and costs the U.S. healthcare system \$237 billion annually.<sup>2</sup> Worldwide, the diabetes epidemic is growing and is expected to affect more than 600 million people by 2045.<sup>3</sup> Obesity affects 114 million people in the U.S. with a total healthcare cost estimated at nearly \$150 billion annually.<sup>4</sup> These two diseases are highly correlated, with 90% of adults with type 2 diabetes overweight or obese.<sup>5</sup>

Herein, we analyze all drugs approved for marketing in the U.S. for both type 2 diabetes and obesity, and potential future drugs that are progressing through the clinical pipeline to meet the urgent needs of patients suffering from type 2 diabetes or obesity. The pipeline analysis aims to assess the depth and breadth of innovation in both disease indications. Historical clinical success rates and failed mechanistic strategies are also identified, as well as trends in venture financing and investment into new clinical trials.

### Key Takeaways for Type 2 Diabetes

- **Marketed drugs:** There are currently 32 unique type 2 diabetes drugs sold in the U.S. that work via 11 different mechanistic strategies. Three new mechanistic strategies were introduced onto the market in the last decade.
- **Pipeline:** The 84 clinical programs for type 2 diabetes encompass 36 novel chemical drug programs with new mechanistic strategies. However, no Phase III programs with novel mechanisms were found.
- **R&D success rate:** Clinical success in type 2 diabetes drug development has been extremely difficult for novel drugs, with only a 4.8% probability of FDA approval from phase I (vs. 9.6% across all disease areas). Since 2008, a total of 217 clinical-stage type 2 diabetes programs have been suspended.
- **Clinical trial initiations:** There has been a 50% decrease in trial initiations for type 2 diabetes over the last decade.
- **Venture investment:** Venture capital funding of U.S. companies with novel lead stage programs in type 2 diabetes is 24 times below oncology funding (\$494 million vs. \$12.2 billion over the last decade).

<sup>1</sup> Thomas, D., Wessel, C. BIO Industry Analysis. Emerging Company Trend Report, (2018) ([www.bio.org/iareports](http://www.bio.org/iareports))

<sup>2</sup> American Diabetes Association (ADA) website, 2015 data accessed September 2018. <http://www.diabetes.org/diabetes-basics/statistics/>, and <http://www.diabetes.org/advocacy/news-events/cost-of-diabetes.html>

<sup>3</sup> Olokoba, A. et. al. Type 2 Diabetes Mellitus: A Review of Current Trends. Oman Med J. Vol 27(4) p. 269–273 (2012)

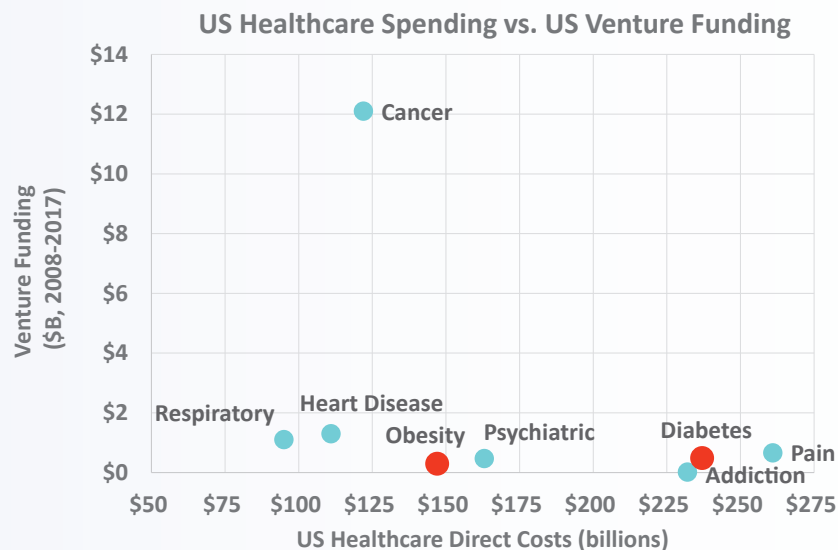
<sup>4</sup> Obesity defined here as BMI of 30 or higher. CDC website accessed August 2018, <https://www.cdc.gov/nchs/data/databriefs/db288.pdf>. Direct costs are 2008 numbers from Finkelstein E., et. al. Annual medical spending attributable to obesity: payer- and service-specific estimates. Health Affairs. 28: 822-831 (2009) and <https://www.cdc.gov/obesity/adult/causes.html>

<sup>5</sup> Public Health England. Adult obesity and type 2 diabetes (2014) and <http://tosconnect.obesity.org/obesity/content/weight-diabetes>

## Key Takeaways for Obesity

- **Marketed drugs:** There are currently 10 obesity drugs marketed in the U.S. These fall into eight mechanistic strategies, with four of the eight mechanistic classes entering the market within the last decade.
- **Pipeline:** The obesity clinical pipeline consists of 26 programs, 14 of which are novel chemical drug programs with new treatment approaches. There are no Phase III programs for non-rare indications of obesity and only two-phase II programs with novel mechanisms were found.
- **R&D success rate:** Clinical success in obesity novel drug development has been more difficult than type 2 diabetes, with only a 1.4% probability of FDA approval from phase I (vs. 9.6% across all disease areas). Since 2008, 57 clinical-stage obesity programs have been suspended.
- **Clinical trial initiations:** Trial initiations for obesity decreased by 37% from the five-year period 2008-2012 vs. 2013-2017.
- **Venture investment:** Venture capital funding of U.S. companies with novel lead stage programs in obesity is 40 times below oncology funding (\$304 million vs. 12.2 billion over the last decade).

### HEALTHCARE COST VS. VENTURE CAPITAL FUNDING OF NOVEL R&D FOR HIGHLY PREVALENT CHRONIC DISEASES



**Figure 1. Healthcare Cost vs. Venture Capital Funding into novel NCEs 2008-2018 for Oncology, and other highly prevalent, chronic diseases (Diabetes and Obesity are shaded red). Source for healthcare costs - Obesity: Health Affairs, 35, No. 6 (2016), Diabetes: March 2018 ADA report; Heart Disease, Respiratory, Oncology are based on 2013 data cited in Health Affairs, 35, No. 6 (2016); Pain: The Journal of Pain, 2012; Addiction: NIDA website 2018. Source for venture data: BIO Industry Analysis, Emerging Company Trend Report, 2008-2017 (June 2018, www.bio.org/iareports).]**

# Type II Diabetes

Type 2 diabetes is a complex chronic disease primarily characterized by poor regulation of blood sugar. Prolonged misregulation of blood sugar leads to disruption of cellular energy regulation in critical tissues through the body and can lead to organ failure and can be fatal if not addressed.<sup>6</sup> Early onset of type 2 diabetes is associated with a loss in tissue sensitivity to insulin, the peptide hormone with primary control over a cell's access to sugar. The disease can progress further with loss of insulin production itself or through further deterioration of its regulation and ability to function efficiently. Over time, various organs such as the heart, eyes, kidneys, and brain begin to deteriorate.

In this report, we review insulin as a treatment and the breakthroughs surrounding insulin through history, as well as the broader therapeutic options for type 2 diabetes. Unique formulations and combination products are included in the discussion. We exclude dietary supplements, and other non-FDA regulated drugs.

## FDA Approved Medicines for Type 2 Diabetes

Reviewing the history of type 2 diabetes drug development, we found 39 novel chemical entities (NCEs) approved for marketing in the U.S. over the last century. A total of 32 NCEs remain on the market today and are listed in **Figure 2** based on each drug's primary mechanistic strategy. Six of the 11 mechanistic classes entered the market beginning in 2000, three of which were introduced in the last decade.

The 11 mechanistic strategies shown in **Figure 2** are organized into four intervention strategies to control blood glucose. The first type of intervention, often the first-line therapy prescribed for type 2 diabetes, are oral drugs that sensitize the body's tissues to insulin. The second and third interventions are drugs that resupply insulin, either directly (insulin injections) or indirectly. The indirect acting drugs work by stimulating the pancreas to secrete insulin (for example, GLP-1 receptor agonists that behave similarly to natural peptide hormones released after meals). The fourth strategy involves the non-insulin pathway for the reduction of sugar circulating in the blood. For example, the newest class, SGLT2 inhibitors, work by increasing the export of sugar into the urine, thereby lowering blood sugar levels. All 11 mechanistic approaches are shown in **Figure 2** to provide historical context and shed light on the alternative mechanistic strategies found in the current clinical pipeline.

### Strategy #1 for Type 2 Diabetes – Drugs that Enhance Insulin Sensitivity

Sugar in the form of glucose is one of the basic stores of energy that the body relies on for normal functioning. Glucose spikes after a meal and is granted access into cells when insulin, released by pancreas beta cells, binds to insulin receptors on tissues throughout the body. The insulin binding on a cell's membrane triggers a cascade of molecular signaling events that result in the transport of glucose into the cell. However, binding of insulin to its receptor does not necessarily mean that the cell will allow glucose into the cell. The series of precise signaling events inside a cell must occur efficiently after insulin binds to ensure proper glucose usage. Failure to do so, is referred to as insulin resistance. This first group of diabetes drugs operates inside cells to repair that signaling mechanism that allows for sugar to enter the cell.

- **AMP kinase activators.** Drugs that activate AMP kinase can assist glucose transporter deployment to the plasma membrane, an essential part of the series of events described above for allowing cell access to glucose. One drug that activates the activity of AMP kinase, albeit indirectly, is metformin. However, there have been at least three other mechanisms that metformin may use to achieve its effect on insulin sensitization and lowering liver glucose production.<sup>7</sup> Metformin is currently recommended as a first-line treatment in type 2 diabetes by the American Diabetes Association (ADA), U.S. Department of Veterans Affairs, and other medical organizations.<sup>8</sup>
- **PPAR gamma receptor agonists.** Inside a cell's nucleus are proteins that can bind to DNA and turn on genes. One of these is a "nuclear receptor" called peroxisome proliferator-activated receptor gamma (PPAR gamma). PPAR gamma allows for the on/off regulation of more than 20 genes involved in sugar and fat metabolism and cell homeostasis.<sup>9</sup> Small molecules that bind to PPAR gamma and activate it were introduced in the late 1990s. The two drugs on the market, rosiglitazone (Avandia, 1999) and pioglitazone (Actos in 2000), are referred to as the thiazolidinedione, or "TZD", class of

<sup>6</sup> DeFronzo, F. From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. *Diabetes* Vol 58(4) p.773-795 (2009)

<sup>7</sup> The mechanisms of action of metformin. *Diabetologia* Vol 60 p.1577-1585 (2017)

<sup>8</sup> American Diabetes Association. *Diabetes Care* Vol 41 S73-S85 (2018)

<sup>9</sup> Ahmadian, M., et. al. PPAR signaling and metabolism: the good, the bad and the future. *Nature Medicine* Vol 19 (5) (2013)

insulin-sensitizing drugs. Rosiglitazone ran into a slowdown in usage as reports of higher risks of heart attacks surfaced in the 2000s and the FDA issued a warning and label change. In 2013, the FDA lifted rosiglitazone's label restrictions.<sup>10</sup> Pioglitazone is the more commonly prescribed TZD and is now available in generic form. The first TZD approved was troglitazone (Rezulin, 1997) but it was pulled from the market in 2000 due to findings related to elevated risk of liver failure.

## UNIQUE ACTIVE PHARMACEUTICAL COMPOUNDS MARKETED IN THE U.S. FOR DIABETES

Strategy	Target MOA	Description of MOA	Active Chemical Entity**	Brand Examples	# NCEs*	First Market Launch in US	
Insulin Sensitivity	1	AMP Kinase activation	Small molecule drug reduces liver gluconeogenesis, lowering glucose output and increases insulin sensitivity	metformin ("biguanides")	Glucophage, Riomet, Glumetza	1 (1)	1995
	2	PPAR gamma receptor agonists	Small molecule drug activates PPAR gamma nuclear receptor turning on genes regulating [Glucose] and sensitivity to insulin	pioglitazone, rosiglitazone (thiazolidinediones, "TZDs")	Actos, Avandia	2	1999
Insulin	3	Insulin receptor agonist	Peptide drug (insulin or analog) binds to insulin receptor in tissue and turns on glucose transport	human insulin, lispro, aspart, glargine, glulisine, detemir, degludec	Humulin, Novolin, Humalog, Novorapid, Lantus, Apidra, Levemir, Tresiba	6 (2)	1923 (animal) and 1982 (human)
Indirect Insulin secretion	4	ATP-sensitive K+ channel inhibition	Small molecule drug inhibits potassium channels in pancreas beta cells leading to insulin secretion	glimepiride, glipizide, glyburide, ("sulphonylureas"), nateglinide, repaglinide ("meglitinides")	Amaryl, Glipizide, Starlix, Prandin	4 (4)	1955 / 1984
	5	GLP-1 receptor agonists	Peptide drug (GLP-1 analogs) binds GLP-1 receptor in pancreas beta cells and assist in release of insulin	albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide	Victoza, Trulicity, Tanzeum, Bydureon, Ozempic, Adlyxin,	6	2005
	6	DPP IV inhibitors	Small molecule drug prevents degradation of GLP-1 allowing for higher [GLP-1] and thus insulin release	alogliptin, linagliptin, saxagliptin, sitagliptin	Januvia, Nesina, Tradjenta, Onglyza	4	2006
Non-insulin mediated glucose control	7	Alpha glucosidase inhibition	Small molecule drug inhibits the breakdown of large carbohydrates in the diet, thus prevents high [Glucose]	acarbose, miglitol	Precose, Glyset	2	1995
	8	Amylin receptor agonists	Peptide drug (amylin analog) activates amylin receptors (CTR/RAMP) leading to glycemic regulation	pramlintide	Symlin	1	2005
	9	Bile acid sequestrant	Polymer drug binds to bile acids in the intestine and thereby altering the gastric process and sugar uptake	colesevelam**	Welchol***	1	2008
	10	Monoamine receptor agonist	Small molecule agonist for dopamine and serotonin receptors	bromocriptine mesylate**	Cycloset***	1	2009
	11	SGLT2 inhibitors	Small molecule drug (transport inhibitor) blocks transport of glucose in kidney resulting in excretion of sugar to urine	canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Jardiance, Invokana, Farxiga, Steglatro	4	2013

Total unique chemicals: 32 (7)

**Figure 2. Unique FDA approved Active Pharmaceutical Ingredients (APIs) for Diabetes still active as of June 2018 (prescription or generic) categorized by four physiological strategies, primary mechanistic target strategy, then by date of first entry within each strategy. The list does not include herbal extracts and dietary supplements.**

\*The NCE count for discontinued chemicals is in parenthesis.

\*\*For mechanism 1, the biguanide analog phenformin was used in the 1950s and discontinued in the U.S. in 1978. Metformin was marketed in Europe in the 1950s but came to the U.S. market in 1995. Other biguanide analogs, buformin and the synthalins, were used and discontinued ex-U.S. Within mechanism 2, although Avandia (rosiglitazone) received FDA black box label restrictions based on evidence of heart related side effects (2010), it has not technically been withdrawn. Troglitazone (Rezulin) was the first approved in 1997 and withdrawn in 2000. For mechanism 3 (insulins), the various formulations and combinations are not shown. The discontinued insulin versions are pork and beef insulin (see figure 4). For mechanism 4, the first-generation sulfonylurea compounds (SUs) from the 1950's are no longer marketed (tolbutamide, carbutamide, chlorpropamide and gliclazide). Second generation SUs from 1980s' are listed. A third meglitinide entered the ex-U.S. market as of 2018.

\*\*\*These drugs are repurposed drugs that were originally approved for another indication decades before type 2 diabetes indication approval. Source: EvaluatePharma, Biomedtracker, fda.gov, company websites.<sup>11</sup>

<sup>10</sup> GSK press release, <https://us.gsk.com/en-us/media/press-releases/2014/fda-approves-avandia-rosiglitazone-label-update-lifts-restrictions-on-patient-access/>

<sup>11</sup> EvaluatePharma database ([www.evaluatepharma.com](http://www.evaluatepharma.com)) accessed June 2018, Biomedtracker ([biomedtracker.com](http://biomedtracker.com)) accessed June 2018.

## Strategy #2 for Type 2 Diabetes – Insulin Therapeutics

No other biologic drug has a history as long or as complex as insulin. Starting in 1923, animal insulin, isolated from either pig or cow pancreas, was marketed for diabetes. This early animal insulin was not reliably manufactured and required frequent dosing (due to short duration of action), making for a suboptimal experience for patients. Over the next nine decades of innovation in insulin protein and delivery science, the experience for diabetic patients has improved significantly.

In the 1930s, scientists figured out how to extend the duration of insulin's activity in the body using formulations of zinc and protamine protein isolated from fish semen. As described in **Figure 3**, this early formulation was known as "PZI" for protamine/zinc insulin and marketed throughout the 1940s. By the 1950s, the formulation was perfected through advances in protein crystallization procedures such that more stable versions could be manufactured (such as "NPH" insulin, with a duration in patient's blood of 12-18 hours), as well as insulin containing zinc but without exogenous protein (such as the "Lente" insulins, with a duration of 18-24 hours).<sup>12</sup> It should be noted that the NPH formulation technique is still used today for certain human insulin products while the zinc insulins were recently discontinued.<sup>13</sup> As will be described below, the capabilities of recombinant DNA technology have allowed for the innovation of longer acting insulins without the need for zinc or exogenous stabilizing proteins.

Over the next two decades (1960-1979), scientists perfected the purification of insulin from animals and tackled previously limiting obstacles such as issues of solubility, pH, and antigenicity for therapeutic use of insulin. The science advanced to the point where industry researchers could manufacture human insulin semi-synthetically by modifying highly purified pork insulin.<sup>14</sup> This required a single amino acid change from highly purified pork insulin (as pork insulin differs by one amino acid from the human protein sequence, see **Appendix A1**).

However, the first human insulin to make it to market was not this semi-synthetically manufactured version. In 1982, with the application of bacterial genetic engineering technology, the first human insulin was brought to market.<sup>15</sup> The semi-synthetically produced human insulin came to market shortly after, in 1983. It was a competitive race for the companies involved and although human insulin was sold from completely different manufacturing routes throughout the 1980s, recombinant DNA manufacturing would eventually win the race to generate more innovative insulin products.

By 1987, human insulin manufactured using genetically engineered yeast was brought to the market.<sup>16</sup> With the major manufacturers now heavily funding R&D of recombinant products, the stage was set for the next generation of insulins. To better understand these innovative insulin products that began to appear on the market in 1996, it is first useful to understand the complexity of administering insulin from both a mechanistic and patient need standpoint.

Manufactured insulin injected into a patient behaves differently than insulin endogenously secreted directly from the pancreas. In the pancreas, insulin hexamers are gently released via vesicles into the blood. With a syringe, injector pen, or even inhaled insulin, there is a bolus of insulin passing through physical barriers, and most manufactured insulins are not available in the same hexameric state as native insulin. This meant a 30-minute lag for insulin activity to appear followed by fairly fast disappearance (6 hours). For the long-acting formulations mentioned above, the onset of activity was slow (2 hours) and took 10-16 hours to reach peak activity.<sup>17</sup> This could make it complicated to time doses, requiring some patients to need an injection at meal time and another post-meal to maintain appropriate levels of insulin overnight. Industry's solution was to create "biphasic" mixtures containing a purified short-acting insulin with a longer acting form (NPH, lente, or ultralente).

FDA approved biphasic mixtures of human insulin combined with NPH human insulin in 1989. The development of these premixed solutions and the design of specialized injector pens and pump devices to deliver these mixed formulations, have provided patients with a variety of ways to receive medication that better matches personal needs and lifestyle. A list of these short and long acting insulin combination products is provided at the bottom of **Figure 4**.

In an effort to overcome slow onset and other imperfections in the first generation of human insulin, biochemical analogs of human insulin were developed. In 1996, the first insulin analog arrived onto the market, setting a new standard for fast-acting insulin providing with as little as 5 minutes onset. This product, lispro (Humalog), was generated by making a switch of the insulin DNA coding for two amino acids in the insulin sequence. This scientific advance paved the road for more insulin

<sup>12</sup> Hirsch, I., Insulin Analogues. NEJM Vol 352 p174-83 (2005)

<sup>13</sup> Eli Lilly discontinued old insulin in 2005 [ see ref ]

<sup>14</sup> The first human insulin derived by chemical conversion of pork insulin was developed by Nordisk Insulinlaboratorium in Denmark

<sup>15</sup> Originally developed at Genentech, Eli Lilly brought the first human insulin to market

<sup>16</sup> Human insulin from yeast was originally developed by Novo. In 1989, Novo Terapeutisk Laboratorium merged with Nordisk Insulinlaboratorium and became Novo Nordisk.

<sup>17</sup> Hirsch, I., Insulin Analogues. NEJM Vol 352 p174-83 (2005)

analogues (see **Appendix A1** for details). In total, three “rapid-acting” analogs have been approved by the FDA.

In 2000, the first “long-acting” insulin analog was approved by the FDA. A second long-acting form, insulin detemir (Levemir), was approved in 2005. Most recently, in 2015, an “ultra-long acting” form of insulin was approved by the FDA. This “ultra-long acting” form, insulin degludec (Tresiba), can last 42 hours.

In total, six insulin analogs have been approved by the FDA. Thus, if we include native forms of human, pork, and beef insulin there have been nine variations of insulin used by patients over the last century. (**Appendix A1**).

A small handful of emerging biotechs researched oral or inhaled insulin delivery through the 1990s and 2000s. In 2006, the first inhaled insulin came to market, but was discontinued in 2008 for lack of patient uptake.<sup>18</sup> Today a second inhaled insulin (Afrezza, FDA approved in 2014) is marketed. The second product uses a different technology for packaging monomeric human insulin into a more user-friendly inhaler.<sup>19</sup> Large companies have also invested heavily into developing new non-injectable delivery systems, but to date, no products have come to market as a result.<sup>20</sup>

### HISTORY OF MARKETED INSULIN

Year	Insulin Product Marketed in US	Duration of Activity	Notes
1920s	animal insulin (Iletin)	short-acting	Insulin, isolated from pork and beef pancreas, marketed in 1923, (Eli Lilly and more than 10 manufacturers ex-US)* Animal insulin manufacturing was not consistent and had many potential side effects and dosing limitations.
1930s	animal insulin in “PZI” formulation	intermediate-acting	Combined Protamine, Zinc, and Insulin, yielded “PZI” extended duration and more stable insulin products. (Novo)**
1950	animal insulin in “NPH” formulation	intermediate-acting and stable	‘NPH’ (Neutral Protamine Hagedorn) insulin is manufactured using a stoichiometric addition of protamine to mid-size crystalline zinc insulin, enhancing stability. (Novo)**
1953	animal insulin in “Lente” formulations	long-acting	The Lente, Semilente, and Ultralente insulins used zinc with large crystalline insulin, without protamine. First long-acting form allowed for once daily injection. (Novo)**
1982	human insulin (rDNA from bacteria, Humulin)	short-acting*	First human insulin on the market. (Originally produced in E. coli by Genentech in 1978 and later licensed and marketed by Eli Lilly.)
1983	human insulin (semisynthetic, Actrapid HM)	short-acting*	Although methods for changing pork into human were published in the 1970s prior to rDNA methods, it was not until 1983 that semisynthetic human insulin was launched. (Novo)**
1987	human insulin (rDNA from yeast, Novolin)	short-acting*	Third human insulin on the market (second rDNA insulin, with this version made in yeast). (Novo)**
1996	insulin lispro (Humalog)	rapid-acting*	First analog of human insulin on the market. (Eli Lilly)
2000	insulin aspart (NovoRapid)	rapid-acting*	Second analog of human insulin on the market. (Novo Nordisk)
2000	insulin glargine (Lantus)	long-acting	First “long-acting” analog of human insulin on the market. (Hoechst Marion Roussel, now Sanofi)
2004	insulin glulisine (Apidra)	rapid-acting	Third “rapid-acting” analog of human insulin on the market. (Sanofi)
2005	insulin detemir (Levemir)	long-acting	Second “long-acting” analog and first acylated version. (Novo Nordisk)
2006	inhaled hexameric insulin (Exubera)	short-acting	First approved inhaled human insulin. (Originally developed by Inhale, then Nektar, it was commercialized by Pfizer. Pfizer withdrew Exubera from the market in 2008.)
2014	inhaled monomeric insulin (Afrezza)	short-acting	Second approved inhaled human insulin. (Mannkind)
2015	insulin degludec (Tresiba)	ultra long-acting	First “Ultra-long acting” human analog, lasting up to 42 hours. (Novo Nordisk)

**Figure 3. Unique FDA approved insulins and unique, non-combination formulations as of June 2018.<sup>21</sup> The list does not include combination products, which are listed in Figure 4. \*Owens,D.R. Human Insulin: Clinical Pharmacological Studies in Normal Man (1986). \*\* “Novo” refers to Novo Terapeutisk Laboratorium and Nordisk Insulinlaboratorium prior to their merger and formation of Novo Nordisk in 1989.**

<sup>18</sup> Based on Pfizer press release and <https://www.diabetesselfmanagement.com/blog/exubera-inhaled-insulin-discontinued/> accessed September 2018

<sup>19</sup> Mohanty, R., et. al. Inhaled Insulin - Current Direction of Insulin Research. J Clin Diagn Res. 11 (4) p.1-2 (2017)

<sup>20</sup> In 2008, Lutz Heinemann regarded the billions invested into inhaled insulin alone: “probably one of the biggest product failures ever in the history of drug development”. The Failure of Exubera: Are We Beating a Dead Horse? J Diabetes Sci Technology. Vol 2( 3) p518–529 (2008)

<sup>21</sup> Marble, A., et.al. Crystalline Insulin. JAMA Vol 113(14), p1303-1309 (1939); Schmeltz, L., et.al. Comprehensive Medicinal Chemistry II, Vol 6, p417-458 (2007); Owens, D. Insulin preparations with prolonged effect. Diabetes Technol Ther. Vol 13 Suppl S5-14 (2011); Quianson, C., et.al. The History of Insulin. J Community Hosp Intern Med Perspect. Vol 2 (2012) EvaluatePharma database accessed June 2018, Bomedtracker accessed June 2018; fda.gov, company websites, drug package inserts.



## Strategy #3 for Type 2 Diabetes - Drugs that Indirectly Enhance Secretion of Insulin from the Pancreas

The *incretin* effect is a physiologic response activated after meals that augments the secretion of insulin.<sup>22</sup> This response consists primarily of two secreted peptides from the gut: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These two peptides regulate blood glucose by stimulating glucose-dependent insulin secretion, suppressing liver synthesis of glucose, appetite, and food absorption. In type 2 diabetes patients, GLP-1 receptor activity is believed to play the most important role in the incretin response, whereas GIP receptor activity is silent.<sup>23</sup>

As this incretin mechanism became better understood at the molecular level in the early 2000s, recombinant DNA based products and highly targeted small molecules were developed that sustained or elevated GLP-1 activity. Prior to this time period, going back to the 1950s, non-incretin drugs were marketed that had their own unique mechanism for stimulating the release of insulin from the pancreas.

It is important to note that for all of the drugs listed below that enhance insulin secretion, the patient's pancreas must be functioning well enough to produce insulin. Once the patient's beta cells within the pancreas are compromised, these drugs will not provide the desired effect on insulin production. Therapeutic options include:

- **ATP-sensitive potassium channel inhibition.** One of the earliest drug classes for treating diabetes through the induction of pancreas insulin release ("secretagogues") are the ATP-sensitive potassium channel inhibitors. These orally available small molecules block potassium (K<sup>+</sup>) channel efflux from the beta cells resulting in beta cell depolarization and release of insulin.<sup>24</sup> The first generation of these drugs, the sulphonylureas, were discovered in the 1940s and introduced on to the U.S. market in the 1950s. In 1980s, second generation sulphonylureas entered the market and after their success with patients, the older sulphonylureas were discontinued.<sup>25</sup> Their drawback is the potential for weight gain with long term use, hypoglycemia, and potential loss of beta cell function.<sup>26</sup> The prescribed drugs today from this class are generic versions of glimepiride and glipizide.

A second insulin secretagogue class using this mechanism, the meglitinide class, was introduced in the late 1990s. Both marketed drugs in this class, Repaglinide (Prandin) approved in 1997 and Nateglinide (Starlix) approved in 2000, are now off-patent.

- **GLP-1 receptor agonists.** All six glucagon-like peptide-1 (GLP-1) agonists marketed to date are either analogs of the native human protein or analogs of the reptilian protein version (exenatide and lixisenatide). The changes made in the biologic drugs derived from the native human GLP-1 protein allow for enhanced stability (preventing DPP IV peptidase cleavage) and/or greater duration of activity in the blood (for example, adding lipids or other proteins to the GLP-1 core sequence).<sup>27</sup> The longer half-life allows these to be dosed once weekly to once every two weeks. The first to market was the Gila Monster derived version in 2006 (Byetta), which was later reformulated for once weekly dosing (Bydureon). In 2017, the first oral GLP-1 agonist was FDA approved (semaglutide, Ozempic).
- **DPP IV inhibitors.** The dipeptidyl peptidase (DPP IV) inhibitor class of compounds increase the incretin duration by allowing GLP-1 to circulate in the blood longer. They do this by slowing the natural degradation of GLP-1 by peptidase enzymes.<sup>28</sup> The net effect is sustained insulin secretion from the pancreas, lower glucagon secretion, resulting in lower blood glucose. In addition to activity of the GLP-1 agonist class of drugs, DPP IV inhibitors can also prevent the breakdown of other blood proteins, such as glucose-dependent insulinotropic polypeptide (GIP) which further stimulates the incretin process. As of August 2018, four of these small molecule drugs have been approved, with the first (sitagliptin, Januvia) entering the market in 2006.

<sup>22</sup> Deacon, C. et. al. Physiology of Incretins in Health and Disease. Rev Diabet Stud. Vol 8 (3) p.293–306 (2011)

<sup>23</sup> Kim, W. The Role of Incretins in Glucose Homeostasis and Diabetes Treatment. Pharmacol Rev. Vol 60 (4) p.470–512 (2008)

<sup>24</sup> This mimics what happens naturally when ATP builds up as a result of high glucose metabolic turnover within cells. As more and more glucose is used up during glycolysis, more ATP is made. The ATP inhibits potassium efflux from the beta cell, hence the term "ATP-sensitive" channels. This build up of potassium (positively charged ions) depolarizes the membrane which then causes an opening of calcium channels, and calcium influx activity. This calcium build up in the cell in turn causes the insulin vesicles to migrate to the membrane for secretion and release.

<sup>25</sup> Celest, C. et. al. History of current non-insulin medications for diabetes mellitus

<sup>26</sup> Sola, D., et al. Sulphonylureas and their use in clinical practice. Arch Med Sci Vol 12; 11(4): 840–848.

<sup>27</sup> Lingjet Tran, K., et. al. Overview of Glucagon-Like Peptide-1 Receptor Agonists for the Treatment of Patients with Type 2 Diabetes. Am Health Drug Benefits. Vol 10(4): 178–188 (2017). Human GLP-1 derived: liraglutide (Victoza) is the acylated form of human GLP-1 (7-37) and is used once daily; albiglutide (Tanzeum) is a fusion protein of two GLP-1 sequences (each with a single amino acid change) and albumin on the C-terminus for extended half-life; dulaglutide (Trulicity) is also made with two GLP-1 sequences but with IgG4 heavy chain on the C-terminus to create a once-weekly injection; semaglutide (Ozempic, Novo Nordisk) is the first oral GLP-1 agonist, has two substitutions (aa8 with 2-aminoisobutyric acid and aa34 to arginine) and LYS26 is acylated. Gila Monster derived: exenatide is naturally more resistant to DPP IV and is available in a once weekly extended release formulation; lixisenatide (Sanofi) is similar but has a modified C-terminus with 6 ARG additions and one PRO deletion.

<sup>28</sup> Vella, A. Mechanism of Action of DPP-4 Inhibitors—New Insights. The Journal of Clinical Endocrinology & Metabolism, Vol 97 (8) p2626–2628 (2012)

## Strategy #4 for Type 2 Diabetes - Drugs with Non-Insulin Mediated Glucose Control

Multiple non-insulin approaches to sugar control have been developed. Some of these involve direct removal of sugar from the blood (such as altering kidney reabsorption) and others are more indirect neurological approaches (working through neurotransmitter receptors or hormones).

- **Alpha glucosidase inhibition.** These drugs directly block the production of simple sugars in the gut by inhibiting alpha glucosidase digestive enzyme. Without alpha glucosidase, the body does not digest complex carbohydrates into simple sugars quickly, thus less glucose enters the blood. The net effect of inhibiting this enzyme with a drug is lower blood glucose levels after eating. The two drugs acarbose and miglitol were approved in the 1990s. Both are dosed with meals.<sup>29</sup>
- **Amylin receptor agonists.** Native human amylin peptide is co-secreted with insulin from the pancreas beta cells working synergistically with insulin to regulate blood sugar levels. Due to its inhibitory mechanism on glucagon, gastric digestive functions, and hunger, amylin helps lower blood glucose and can reduce the amount of insulin required in the clinical setting. The first amylin mimetic, Pramlintide, originally developed by a small biotech, was approved in 2005 for use with insulin.<sup>30</sup>
- **Monoamine receptor agonists.** In 2009, the FDA approved the ergot-derived bromocriptine mesylate (Cycloset) for glycemic control in type 2 diabetes. It acts as an agonist of various monoamine receptors, in particular the dopamine and serotonin receptors found on neurons in the hypothalamus, a key brain region for the regulation of overall plasma glucose and fat. It is the only monoamine receptor agonist indicated for type 2 diabetes, and the only drug to work via a resetting of the circadian neuroendocrine cycle. Although generic for some time, as it had been FDA approved for various non-diabetic indications since 1978, a small company led the repurposing clinical development for the type 2 diabetes indication. Cycloset was the first drug to be approved subsequent to the FDA's new guidelines that require studies demonstrating that diabetes drugs do not increase cardiovascular risk.<sup>31</sup>
- **Bile acid binding agents.** Colesevelam is a modified amino polymer that binds to bile acids in the gut, reducing the gastric effects of intestinal bile acid.<sup>32</sup> Colesevelam was first approved for hypercholesterolemia in 2000, eight years before the type 2 diabetes approval (marketed as Welchol). As in the case of bromocriptine, the drug is not widely prescribed and not mentioned in the prescribing decision tree for physicians published in the 2018 consensus report from American Diabetes Association (ADA) and the European Association for the Study of Diabetes ADA and EASD.<sup>33</sup>
- **SGLT2 inhibitors.** The sodium-glucose cotransporter 2 inhibitors act on the kidney directly to block glucose reabsorption. With reabsorption blocked, more glucose is secreted in the urine and blood glucose lowers. The first oral SGLT2 inhibitor approved was Invokana in 2013.<sup>34</sup>

<sup>29</sup> Aleskow Stein, S. A review of the efficacy and safety of oral antidiabetic drugs. *Expert Opin Drug Saf.* Vol 12(2) p.153-175 (2013)

<sup>30</sup> The small biotech that developed amylin, was Amylin Pharmaceuticals (acquired by BMS in 2005 and now part of AstraZeneca). Informa strategic transactions database.

<sup>31</sup> Shivaprasad, C. and Kalra, S. Bromocriptine in type 2 diabetes mellitus. *Indian J Endocrinol Metab.* Vol 15(Suppl1): S17-S24 (2011). NDA approval letter: [http://www.accessdata.fda.gov/drugsatfda\\_docs/appletter/2009/020866s000ltr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/020866s000ltr.pdf) (VeroScience, in collaboration with S2 Therapeutics)

<sup>32</sup> US Patent 5,607,66. GelTex (acquired by Genzyme in 2000) and collaborator Daichi Sankyo sponsored the R&D.

<sup>33</sup> Davies, M. et. al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (2018)

<sup>34</sup> The National Institute of Diabetes and Digestive and Kidney Diseases, 2016: <https://www.niddk.nih.gov/news/archive/2016/story-discovery-sglit2-inhibitors-harnessing-kidneys-help-treat-diabetes>

## Management of Type 2 Diabetes and Combination Products

Heterogeneity in the type 2 diabetes patient population demands multiple therapeutic options and combinations of those options. Prior to the re-introduction of metformin in 1995, type 2 diabetes patients often relied on one injectable (insulin) and one oral drug (sulphonylureas) for managing sugar levels. There are now eight oral therapies classes in the hands of the primary care physicians, most of which can be used in combination with the three injectable classes (insulins, GLP-1s, and amylin), that provide options for treatment that take into account the severity, progression of the disease and idiosyncratic issues (such as pregnancy, allergies, other medications, etc.).

According to the 2018 American Diabetes Association (ADA) recommendations, metformin (as an oral generic tablet) is used as first-line therapy.<sup>35</sup> It has a low risk of hypoglycemia and can be combined with additional therapies if it alone is not reducing blood glucose to normal levels. In addition to metformin, a second therapy from a different mechanistic class can be added or new combination formulations can be taken orally. Companies have spent significant development time and investment to create oral combination products optimized for efficacy. For example, as shown in **Figure 4**, metformin combo drugs are available with ATP potassium inhibitors, PPAR gamma agonists, and DPP IV inhibitors. In certain cases of sustained high glucose levels, three or four therapies can be utilized at the same time.

Insulin can be used at any stage, and with the most combinations. Note in **Figure 4** the recent combinations of GLP-1 and insulin. Also shown in **Figure 4** are the biphasic mixtures of different insulins. All of these mixtures combine a fast-acting with a longer duration insulin. These new formulations serve patient's needs during both meal time and post-meal time settings.

### UNIQUE COMBINATIONS MARKETED IN THE U.S. FOR DIABETES

Unique Combinations (with at least one non-insulin drug)

Target combos	Generic Names	Brand names (examples)	Company	FDA Approval	Patent Status
AMPK + ATPK Channel	Metformin and glyburide or glipizide	Glucovance, Metaglip	BMS	2002, 2005	off patent
AMPK + PPAR gamma	metformin + pioglitazone (or rosiglitazone)	Actoplus Met, (and XR), (Avandamet)	GSK, Takeda, Mylan	2002, 2005	off patent
ATPK Channel + PPAR gamma	glimepiride + pioglitazone or rosiglitazone	Avandaryl, Duetact	GSK, Takeda	2005, 2006	off patent
AMPK + DPP IV	metformin + sitagliptin	Janumet	Merck & Co	2007	on patent
GLP-1 + insulin	liraglutide + insulin degludec	Xultophy	Novo Nordisk	2016	on patent
	lixisenatide + insulin glargine	Soliqua 100/33	Sanofi	2016	on patent
SGLT2 + DPP IV	empagliflozin + linagliptin	Glyxambi	Boehringer Ingelheim	2015	on patent
	ertugliflozin + sitagliptin	Steglujan	Merck & Co	2017	on patent
	dapagliflozin + saxagliptin	Qtern	AstraZeneca	2017	on patent

Complex Biphasic Mixtures of Insulins

Insulin Type	Generic Names	Brand names (examples)	Company	FDA Approval	Market Status
insulin (fast + intermediate acting)	human insulin (30%) + human insulin NPH (70%)	Humulin 70/30; Novolin 70/30	Eli Lilly, Novo Nordisk	19,891,991	off patent
	Insulin lispro (50% or 25%) + insulin lispro protamine (50% or 75%)	Humalog MIX 50/50, Humalog MIX 75/25	Eli Lilly	1999	off patent
	insulin aspart (30%) + insulin aspart protamine (70%)	NovoMix 70/30	Novo Nordisk	2001	off patent
insulin (fast + long-acting)	insulin aspart (30%) + insulin degludec (70%)	Ryzodeg 70/30	Novo Nordisk	2015	on patent

**Figure 4. Unique FDA approved combination products (listed as APIs) for Diabetes, active as of August 2018, categorized by primary mechanistic. Source: EvaluatePharma database accessed June 2018, Bomedtracker accessed June 2018; fda.gov, company websites, drug package inserts.<sup>36</sup>**

<sup>35</sup> American Diabetes Association. Diabetes Care Vol 41, S73-S85 (2018)

<sup>36</sup> EvaluatePharma database (www.evaluategroup.com) accessed June 2018, Bomedtracker (biomedtracker.com) accessed June 2018.

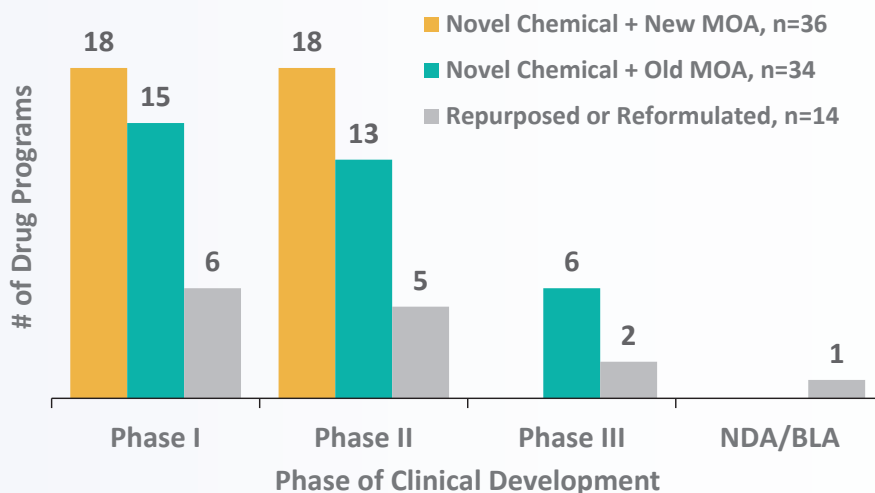
## Current Clinical Pipeline in Type 2 Diabetes

There has been stable progress over the last few decades in advancing our understanding of the biologic mechanisms underlying diabetes. As mentioned above, the SGLT2 inhibitors were a turn of the century example of newly defined targets spawned out of basic biological research, followed by industrial breakthroughs in biochemical specificity.

The current clinical pipeline includes 84 ongoing clinical programs for type 2 diabetes. Of these 84 programs, 70 are considered NCEs (novel chemical entities), 36 of which have drugs with completely novel targets. There are 14 programs that are either repurposing previously approved drugs or are new formulations of existing drugs. The breakdown of novel drug programs can be found in **Figure 5**.

It is noteworthy that there are more clinical programs in a single sub-indication in oncology than in the entire type 2 diabetes pipeline. For example, breast cancer has 158 active clinical development programs, lung cancer 180, and leukemias 211 – each well above the total of 84 found in the type 2 diabetes clinical pipeline.<sup>37</sup>

### 2018 CLINICAL PIPELINE FOR TYPE 2 DIABETES

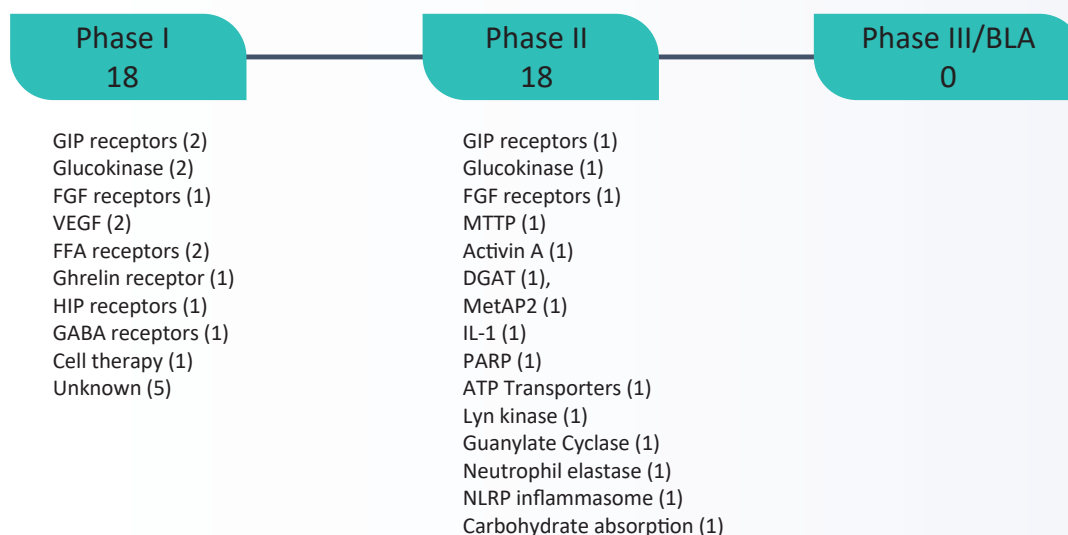


**Figure 5. The currently active type 2 diabetes clinical pipeline (September 2018), based on Biomedtracker’s classification methodology by phase of development. Clinical programs were categorized into three groups: 1) Clinical programs with novel chemical entities (NME or biologic) and a target (or mechanism of action, MOA) with no approval history, 2) those with novel chemical entities pursuing an MOA with a prior approval history and 3) non-NME drugs that are reformulated or repurposed products. For combination drugs, only the novel active component is used to categorize as novel. If no novel compound is present in the combination drug, the Non-NME label is used.**

<sup>37</sup> Data for oncology R&D pipeline is taken from the Biomedtracker database, and current as of January 2018. A total count by disease area can be found in Thomas, D., Wessel, C. BIO Industry Analysis. Emerging Company Trend Report, (2017) ([www.bio.org/iareports](http://www.bio.org/iareports))

The clinical pipeline can be described as early-stage given that not a single novel program exists in Phase III. Most of the 36 highly novel programs are split between Phase I (18) and Phase II (18). However, there does seem to be a fair number of drug candidates with novel mechanistic strategies - the 36 clinical programs in type 2 diabetes with novel targets can be grouped into 23 mechanistic strategies, as shown in **Figure 6**.

### TYPE 2 DIABETES PIPELINE FOR NOVEL APPROACHES 36 NCES WITH 23 NOVEL TARGETS



**Figure 6. The breadth of completely new target strategies in the current type 2 diabetes pipeline. Only novel approaches with no prior FDA approval history in type 2 diabetes are shown. The drug targeting strategy listed is based on the primary target of the novel compound under development. For combination drugs, only the novel active component's target is listed. Pipeline data by phase of development was obtained from Biomedracker.**

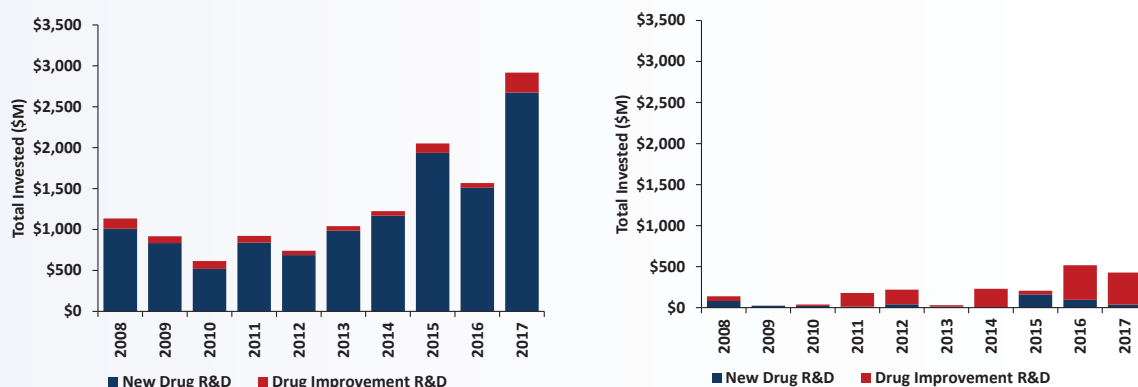
The mechanistic strategies are quite varied with 23 new targets listed in **Figure 6** that can be categorized into four groups. The first, and most advanced group, are the GIP receptor agonists that have insulin secretagogue functionality as well as satiation effects. The second group consists of the centrally acting drug candidates targeting the ghrelin receptor and GABA receptors. Third, new insulin sensitization via Lyn kinase activation. The fourth group of drug candidates aim to modulate inflammatory effects that might be behind beta cell deficiency or insulin resistance. Examples include interleukin-1 (IL-1), the NLRP inflammasome, and neutrophil elastase. The fifth group targets growth factors receptors, such as fibroblast growth factor (FGF), vascular epithelial growth factor (VEGF), and Actavin A (TGF beta pathway). Finally, there are new direct metabolic targets in the pipeline, such as a diacylglycerol acyltransferase (DGAT), MetAp2, glucokinase, and microsomal triglyceride transfer protein (MTTP).

To predict what may enter the clinical pipeline in the near future, we examined novel preclinical type 2 diabetes programs in the Biomedracker databases and recently published literature. We found that 20 of the 75 preclinical programs listed had unique targets not currently in the clinic or previously approved, indicating further advances may be on the horizon.

## Trends in Venture Investment and R&D Activity (Clinical Trial Initiations) in Type 2 Diabetes

For small private companies, we identified companies with lead compounds in type 2 diabetes and assess venture funding over the last decade. A more comprehensive method for assessing investment across the industry, based on quantifying the number of clinical trials starts by phase over time, is also presented below.

### 2008-2017 VENTURE INVESTMENT INTO U.S. COMPANIES WITH LEAD PROGRAMS IN ONCOLOGY VS. TYPE 2 DIABETES



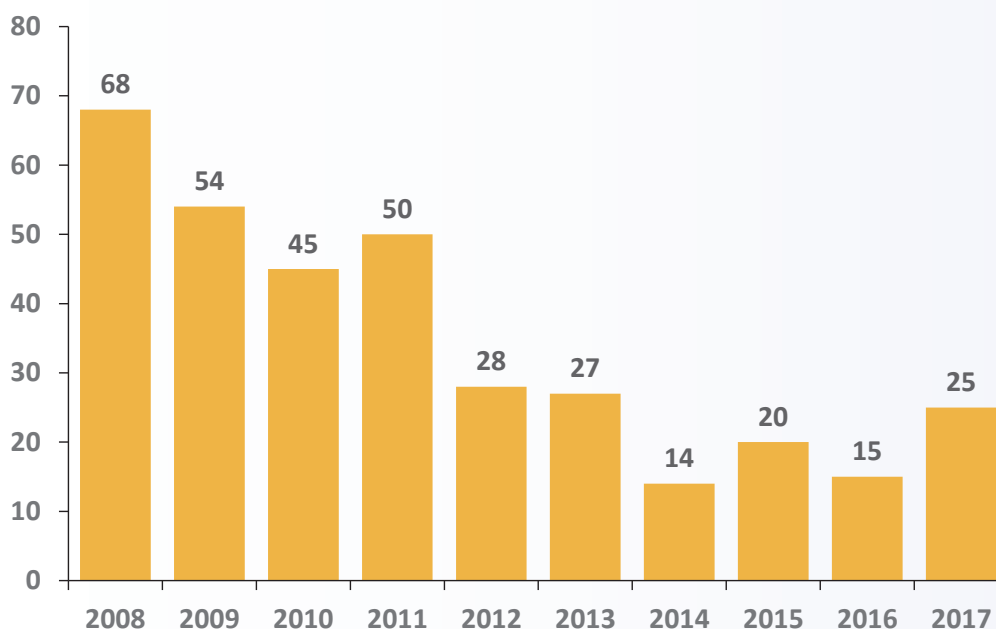
**Figure 7. Left: Venture funding of companies with lead products in oncology, 2008-2017. Right: Venture funding of companies with lead products in type 2 diabetes, 2008-2017. Blue bars denote investment in novel drug for the lead asset under development. Red bars indicate investment in drug improvement (reformulation, repurposing) for the lead asset under development.**

As can be seen in **Figure 7**, venture investment into U.S. companies with lead type 2 diabetes products from 2008 to 2017 totaled \$2 billion. However, much of this funding (\$1.5 billion) went to companies developing reformulated/repurposed products over truly novel drug candidates, as shown in red in **Figure 7**. Accounting for truly novel lead drug candidates only, the total was \$500 million. This is 24x times less than the funding received for novel oncology drugs (\$12.2 billion) during the period from 2008 to 2017.

Eight companies with lead drugs in type 2 diabetes were financed each year, on average. By comparison, there were 78 oncology companies financed each year, suggesting that early-stage investors currently prioritize other disease areas, such as oncology, over type 2 diabetes.

The above methodology, whereby lead asset is used as a proxy for private investment, tends to underestimate venture dollars ultimately used for diabetes R&D in small companies, as some companies have broad pipelines. Although most capital will tend to be used for the lead asset, this is not always the case. For example, a company with a lead candidate drug in Phase III trials for obesity may also have portfolio products in Phase II for type 2 diabetes. This would understate the type 2 diabetes investment. Unfortunately, private companies do not report R&D expenses by project or indication. Using the broader endocrine disease area, which includes all endocrine disease such as growth hormone deficiency, type 1 diabetes, and osteoporosis, we still find a large difference (\$1.5 billion for novel endocrine diseases versus \$12.2 billion for cancer).

## 2008-2017 CLINICAL TRIAL STARTS FOR TYPE 2 DIABETES DRUG INTERVENTION TRIALS



**Figure 8. Clinical trial starts for novel drugs for type 2 diabetes, 2008-2017. TrialTrove data accessed June 2018. A total of 2090 clinical trial starts were retrieved from TrialTrove. Trials were individually assessed for novelty of drug (no prior approval history of the active compound) and trial phase cohorts de-duplicated. A total of 346 novel drug intervention trials including add on therapy trials with new drugs) were initiated during this time period.**

We also use a method for approximating broader industry R&D investment activity (combining small, midsize, and large public companies and private biopharmaceutical companies) and the annual level of funding for private emerging biotech companies. This requires the use of the TrialTrove database, which tracks clinical trial start dates by indication. From 2,090 trial starts, we categorized trials for novel drugs, vs. nonintervention trials, reformulations, combinations of older drugs and other duplicate trials per phase, identifying 346 novel drug intervention trial starts over the 10-year period.

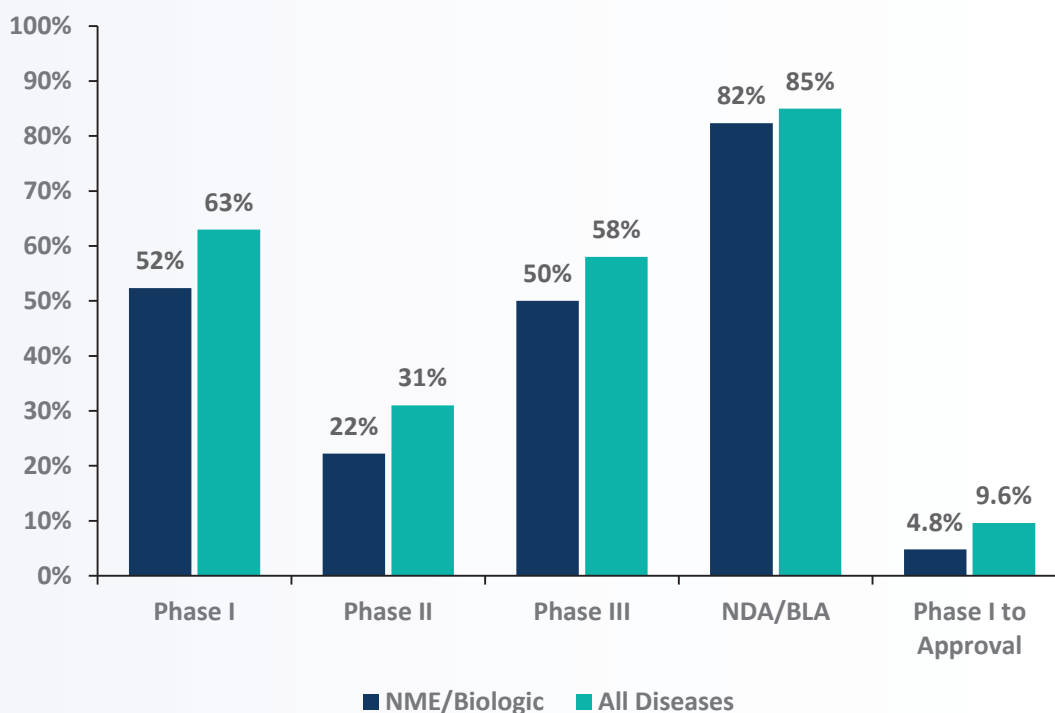
Clinical trial starts involving novel type 2 diabetes drugs over the last decade declined by more than 50%. The lowest years of trial initiation were in 2014 and 2016, as shown in **Figure 8**. Trials were also individually assessed for whether or not they were new insulin or GLP-1 therapies. Only a few of these were found in the data set.

## Clinical Development Success Rates for Novel Diabetes Drugs

The clinical trial success rates for new type 2 diabetes drug candidates were found to be lower than what is observed across all disease areas. Looking at new molecular entities and new biologics, we calculated a 4.8% success rate from Phase I to FDA approval (N=289 transitions 2006-2015) compared to 9.6% for across all disease areas (N = 9985 transitions 2006-2015).<sup>38</sup> As shown in **Figure 9**, novel type 2 diabetes drug development programs in Phase I had a 52% chance of success in transitioning to Phase II, and only a 22% chance of transitioning from Phase II to Phase III. These lower Phase I and II success rates were major contributors to the low overall probability of success.

Analyzing the R&D programs that were active at any point during January 2016 to September 2018, we found that 217 clinical programs have been suspended. Examples of failed strategies are numerous and include targets such as Cannabinoid-1 (CB1), Interleukin-1 (IL-1), Chemokine Receptor 2 (CCR2), and other programs.

### CLINICAL DEVELOPMENT SUCCESS RATES FOR NOVEL DIABETES DRUGS 2006-2015



**Figure 9. Clinical success rates for all diabetes indications compared to overall industry probabilities, 2006-2015. Data is based on approximately 10,000 drug programs in the Biomedtracker database. (Thomas, D., et al. BIO, BioMedtracker, Amplion. Clinical Development Success Rates 2006-2015 (2016) (Accessed at [www.bio.org/iareports](http://www.bio.org/iareports))**

<sup>38</sup> The low success rate for novel drugs was not observed for the non-NME pain drugs (those that are mostly reformulations of older APIs). The non-NME drugs had an overall 25% success rate.



# Obesity

Most definitions of obesity describe a certain weight range for a given height that correlates with increased risk of various medical conditions, such as type 2 diabetes or cardiovascular disease. The World Health Organization utilizes body mass index (BMI) to categorize obesity into three levels of severity. However, the location of the excess weight has also been used to define persons more at risk of developing specific diseases.<sup>39</sup> Using BMI as a baseline definition, it has been estimated that more than 2 billion people are “overweight” and 600 million are considered to be obese worldwide. Some medical organizations are requesting the term “obesity” be renamed to “adiposity-based chronic disease” or ABCD. The rationale being that a more descriptive name will give recognition to the severity of the disease and help advocacy and awareness leading to increased diagnosis and treatment in the primary care setting.<sup>40</sup> What options are available for this population and what is on the horizon? This section of the report examines currently available therapeutic options in the U.S. and the current pipeline for highly prevalent indications of obesity.

## FDA Approved Medicines for Obesity

FDA approved obesity drugs are categorized based on their primary strategy for weight reduction in **Figure 10**. There are three primary strategies: drugs targeting the brain to suppress appetite, 2) a combination of neurologically and metabolically acting drugs, and 3) direct metabolically acting drugs. Within each broad strategy are more target-based mechanistic categories for the drugs, each listed in **Figure 10** by the year each class entered the U.S. market.

Although a total of 16 chemical entities (12 active and four discontinued) have been approved in the U.S. (listed in **Figure 10**), there have been 13 drugs approved ex-U.S. and not marketed in the U.S. All but one of the ex-U.S. drugs marketed for weight loss in the 1900s were neurologically acting compounds, such as amphetamine and its many derivatives, and 10 of the 13 have since been withdrawn (due to side effects such as addiction or cardiovascular complications). More recently, Rimonabant (a cannabinoid CB1 receptor inverse agonist, approved in Europe in 2005), was withdrawn in 2009. A few others, such as Cetilistat, a lipase inhibitor, remain on the market ex-U.S. All 13 ex-U.S. approvals are listed in the description below **Figure 10**.

Prior to 1999, most of the U.S. marketed drugs for weight loss worked by modulating synaptic concentrations of norepinephrine, epinephrine, and dopamine (the monoamine class of neurotransmitters). The only exception to this is the very first drug marketed broadly for weight loss, dinitrophenol (DNP). This drug, marketed only briefly from 1933-1937, acted peripherally by enhancing overall metabolic rate, which at high doses was found to be lethal.<sup>41,42</sup> It was not until 1999 that a new non-neurologically acting agent was approved, orlistat (Xenical). Since that year, three mechanistically distinct classes have been introduced for the obesity indication. SGLT2 targeting drugs used for type 2 diabetes have shown weight loss in clinical studies but have not received a direct indication approval.<sup>43</sup> Each FDA approved obesity drug is described below.

<sup>39</sup> Weaver, J. Practical guide to Obesity Medicine. Elsevier (2018)

<sup>40</sup> Mechanick, J., et. al. Adiposity-Based Chronic Disease as a new diagnostic term. Endocrinology Practice Vol 23 (3) p.372-378 (2017)

<sup>41</sup> This is excluding thyroid hormone (extracted from animals) and analogues of thyroxine, and later levothyroxine, used to treat hypothyroidism. Weaver, J. Practical guide to Obesity Medicine. Elsevier (2018)

<sup>42</sup> Hendricks, E. Off-label drugs for weight management. Diabetes Metab Syndr Obes. Vol 10 p223–234. (2017) <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5473499/>

<sup>43</sup> Nauck, M. Update on developments with SGLT2 inhibitors in the management of type 2 diabetes. Drug Des Devel Ther. Vol 8: p1335–1380 (2014)

## UNIQUE ACTIVE PHARMACEUTICAL COMPOUNDS MARKETED IN THE U.S. FOR OBESITY

Broad Strategy	Mechanistic Strategy	Generic Name	Brand Names	# unique NCEs Active (discontinued)	1st Year Marketed in U.S.	
Neurologic	1	Adrenergic and trace amine-associated receptor 1 (TAAR-1) agonists (NOR/DOP pathway)	methamphetamine, phentermine (Phen), phendimetrazine, benzphetamine (amphetamine)	Desoxyn, Ionamin, Plegine, Didrex (Benzadrine)	4 (1)	1947
	2	Monoamine transporter reuptake inhibitors	diethylpropion, (fenfluramine (Fen), sibutramine)	Tenuate, (Pondimin, Meridia)	1 (2)	1959
	3	Serotonin 5-HT <sub>2C</sub> receptor agonist	lorcaserin	Belviq	1	2012
	4	GABA modulator + Adrenergic agonist	topiramate + phentermine	Qsymia	2	2012
	5	Opioid receptor antagonist + Monoamine reuptake inhibitor	naltrexone + bupropion	Contrave	2	2014
Metabolic and Neuro.	6	GLP-1 receptor agonist	liraglutide	Saxenda	1	2014
Metabolic	7	Protonophores	(2,4 dinitrophenol)	(DNP)	0 (1)	1933
	8	Lipase inhibitor	orlistat	Xenical	1	1999

Total NCEs: 12 (4)

**Figure 10. Unique active ingredients for obesity, marketed in the U.S., categorized by primary mechanistic target strategy and physiological strategy. See text for details on the above 12 active NCEs. Note that two drugs listed are combinations, and each NCE is listed and counted as a unique chemical entity approved for obesity. (Source: EvaluatePharma, Biomedtracker, fda.gov, company websites.) U.S. drugs that are not listed are OTC products (such as the 2011 launch of fortetropin (Myo T-12), phenylpropanolamine/norpseudoephedrine, and pipradrol/methylphenethylamine), off-label agents (such as Mazindol (an NRI)), and drugs for rare diseases or non-chronic indications (deoxycholic acid (Kybella) primarily used for cosmetic purposes (reduce chin fat), and drugs for Cushing's syndrome, a rare disease resulting in weight gain from high cortisol levels, were not included (e.g. Korlym/RU-486). Thyroxine analogues for treatment of hypothyroidism reduce weight but are not prescribed for the broader chronic obesity context, and thus are not listed. Not in the table are 13 ex-U.S. marketed compounds (most of them withdrawn): phenmetrazine (withdrawn in 1965), aminorex fumarate (withdrawn in 1968), chlorphentermine (withdrawn in 1974), cyclovalone (withdrawn 1988), benfluorex (withdrawn in 1997), mefenorex (withdrawn in 1999), fenproporex (withdrawn in 1999), clobenzorex (withdrawn in 2000), and Rimonabant (cannabinoid CB1 receptor inverse agonist, approved in Europe in 2005 and withdrawn in 2009), pyrovalerone (withdrawn in some countries); Three active: cloforex (Oberex), fenbutrazate (Cafilon), Cetilistat (lipase inhibitor).[see reference 44, Onakpoya, I (2016).]**

## Strategy #1 for Obesity – Drugs with Neurologic Targets

Historically, the largest class of drugs for treating obesity target the brain act by suppressing appetite by either agonizing neuronal receptors or inhibiting transport proteins to elevate levels of monoamine neurotransmitter. One exception to this, is the fairly recent approval of a combination drug that includes an opioid receptor antagonist with a monoamine modulator. Unfortunately, a high percentage (83% according to one study) of neurologically acting drugs have been withdrawn from the market due to adverse psychiatric properties, drug abuse, or cardiovascular complications.<sup>44</sup> Below, we describe the five mechanistic strategies that target the brain for treating obesity.

**Adrenergic and trace amine-associated receptor (TAAR) agonists:** When amphetamine was first marketed in 1947, the mechanism was not known. Today, amphetamine is known to act as a stimulant due to its influence on monoamine activity in the brain, and norepinephrine and dopamine in particular. Unfortunately, amphetamine has addictive properties and must be used with care and in extreme cases of obesity. Today, methamphetamine (the active compound in street “crystal meth”) is prescribed for treatment-resistant obesity. The close relative of methamphetamine, phentermine, is also prescribed for treating obesity and has been on the market since 1959. Although approved only for short-term use, U.S. physicians have used phentermine for long-term use for decades.

**Monoamine reuptake inhibitors:** This class of compounds increases monoamine concentrations causing a reduction in hunger. This action is mediated by inhibiting monoamine transporters such that the extracellular (synaptic) concentration of monoamines increases. Such a mechanistic strategy has been used for mood enhancing drugs (such as SSRIs for depression) for decades. For influencing appetite and eating behavior, diethylpropion was the first of this reuptake inhibitor class to be approved by the FDA (1959). A closely related compound, bupropion came to market in 1985 to treat depression. Both of these drugs have particularly influence on noradrenaline levels in the hypothalamus. In contrast, fenfluramine, approved in 1973 acts primarily on serotonin. Sibutramine, approved in 1997, works on both serotonin and noradrenaline but has been withdrawn due to cardiovascular side effects. In the 1990s, fenfluramine and sibutramine were used off label in combination (known as “Fen/Phen”) until the 1997 marketing withdrawal request from FDA for fenfluramine (and dexfenfluramine) based on documented reports of heart valve damage in patients.<sup>45</sup>

**Selective serotonin receptor agonists:** A new monoamine approach that gained approval in 2012, specifically targets and acts as antagonists to the serotonin receptor 5HT<sub>2C</sub>. Lorcaserin is the first and only 5HT<sub>2C</sub> drug to reach the market for obesity.

**GABA modulators:** Topiramate, a drug approved in the late 1990s, is an antiepileptic and anticonvulsive agent believed to work through a GABA neurotransmitter modulation pathway. This same mechanism has anti-addictive properties and the drug has been used to help people recover from alcoholism and drug addiction. In 2012, the combination of topiramate with phentermine (the generic adrenergic and trace amine receptor agonist) was approved for obesity.

**Opioid receptor antagonists:** Naltrexone, is an opioid receptor antagonist used to treat addiction for decades. Combined with bupropion (the generic NDRI mentioned above) a combination drug with the brand name Contrave was approved in 2014 (as a non-NME classified drug for reformulation and repurposing).<sup>46</sup>

<sup>44</sup> Onakpoya, I. Post-marketing withdrawal of anti-obesity medicinal products because of adverse drug reactions: a systematic review. *BMC Medicine* Vol 14 p. 191 (2016)

<sup>45</sup> FDA press release 1997, accessed October 2018: <https://wayback.archive-it.org/7993/20170723090512/https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm179871.htm>

<sup>46</sup> Roddy, E. Bupropion and other non-nicotine pharmacotherapies. *BMJ*, 328 (7438): 509–511. (2004). Bupropion, originally approved for depression (as Wellbutrin in the 1980s), was approved in 1997 for smoking cessation (renamed Zyban for this indication). Bupropion is known to decrease appetite cravings and elevate dopamine levels but may have other relevant activity such as antagonizing acetylcholine receptors

## Strategy #2 for Obesity – Drugs with Combined Neurologic and Metabolic Targeting

The group of drugs listed under Metabolic and Neurologic strategy in **Figure 10** act both in the brain and at other tissue sites in the body. As with the natural peptides they mimic, multiple physiological pathways are involved.

**Leptin receptor agonists:** In the late 1990s, the protein leptin was regarded as a promising potential therapy for general obesity. Leptin was found to be secreted by adipose cells but act on receptors in the brain to regulate the body's energy balance and hunger state. However, when the protein was used as a therapy it was found that obese people have a decreased sensitivity to leptin, or "leptin resistance". Reducing the body's ability to respond when they are full despite the abundance of high energy stores and leptin levels in the body.<sup>47</sup> Metreleptin, a synthetic analog of the hormone leptin, was approved for treatment of congenital or acquired generalized lipodystrophy in 2014 (Myalept). It is not included in **Figure 10** as this indication is not a highly prevalent form of obesity, but rather a rare form of abnormal distribution of fat in the body due to a lack of leptin.

**GLP-1 receptor agonists:** As described above in the section on type 2 diabetes, GLP-1 agonists were first approved in 2005 for diabetes. During the development of these peptide drugs and the basic research surrounding the incretin system, researchers found that GLP-1 has a role in neurological control of appetite and satiety. The first approval of a GLP-1 receptor agonist for an obesity indication was in 2014.

## Strategy #3 for Obesity – Drugs with Direct Metabolic Targeting

Excluding common laxatives that have been used throughout history for decreasing food absorption, and therefore partially preventing weight gain, this last strategy of targeting metabolic pathways has only one prescription product on the market.

**Dinitrophenol:** The first obesity drug, launched in 1933, was in fact a metabolically acting compound that ramped up cell energy usage. Dinitrophenol (DNP) acts on the electron transport energy chain in mitochondria (the system responsible for a cell's energy production) and drives thermogenesis (heat production). Unfortunately, if large quantities are consumed the thermogenesis effects can be so powerful that body temperatures can rise to 111 °F and be fatal.<sup>48</sup> The drug was pulled from the market in 1937. However, DNP has recently been sold illegally on the internet and reported fatalities from overdose have returned.<sup>49</sup>

**Lipase Inhibitors:** The lipase enzyme is the first step in the metabolism and storage of fat. Orlistat is the only lipase Inhibitor approved in the U.S.. Another is approved for use in Europe.

<sup>47</sup> Pan H, et. al. Advances in understanding the interrelations between leptin resistance and obesity. *Physiology & Behavior*. 130 p.157–69 (2014)

<sup>48</sup> Weaver, J. *Practical guide to Obesity Medicine*. Elsevier (2018)

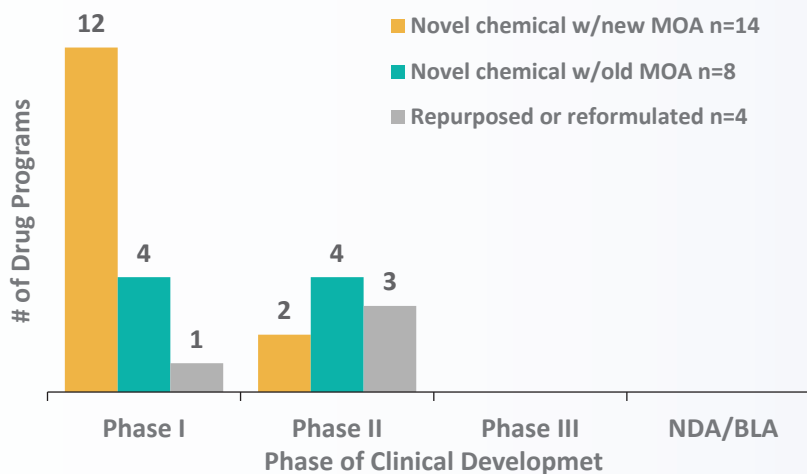
<sup>49</sup> Grundlingh J. 2,4-dinitrophenol (DNP): a weight loss agent with significant acute toxicity and risk of death. *J Med Toxicol*. Vol. 7 (3) (2011)

## Current Clinical Pipeline in Obesity

There are 26 programs in the clinical-stage obesity pipeline according to data obtained from the Biomedtracker database. As shown in **Figure 11**, the majority (24) are novel molecules and four are programs with repurposed or reformulated drugs. However, only 14 of the novel molecules have a new mechanism of action that has not been approved previously for obesity.

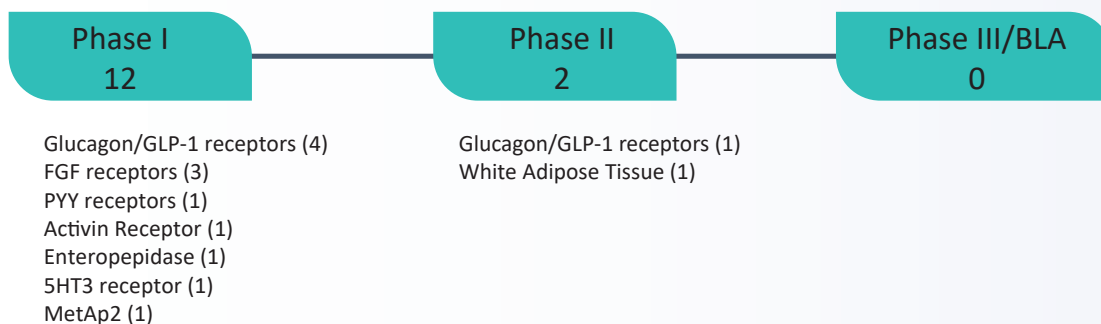
Like the type 2 diabetes pipeline, the obesity pipeline is biased to early-stage, with no Phase III programs found for highly prevalent obesity. It should be mentioned that there is one ongoing Phase III for a rare obesity disorder not included in this analysis of highly prevalent indications. This drug works by agonism the melanocortin 4 receptor (MC4R), a target that has been under development by multiple companies but no approvals to date.

### 2018 CLINICAL PIPELINE FOR OBESITY



**Figure 11. Clinical pipeline for obesity based on Biomedtracker database, September 2018. Novelty criteria: Novel drugs that do not have an approval history and non-NME drugs that are reformulated or repurposed products. For combination drugs, only the novel active component is used to categorize as novel. If no novel compound is present in the combination drug, the “Non-NME” label is used.**

### OBESITY PIPELINE FOR NOVEL APPROACHES 14 NCES WITH 8 NOVEL TARGETS



**Figure 12. New MOAs in development, by Phase, for obesity. \*Only novel approaches with no prior FDA approval history in obesity are shown.<sup>50</sup> \*\*These are dual agonists (“GG”), but 1 is a triple “GG + GIP” (Glucagon receptor has no prior FDA approval history specifically for obesity.) This table is for highly prevalent forms of obesity. A Phase III MC4R agonist program is ongoing for a rare obesity disease.**

<sup>50</sup> Phase of product and target information in this section are based on Biomedtracker and company websites accessed January 2018.

Investigating the new mechanisms of the NCEs in clinical development, 10 biological targets were found. Most abundant in this set, with five ongoing programs, are glucagon targeting agonists. Although glucagon is used to treat hypoglycemia, there have not been glucagon activating drugs approved in obesity. The new programs have dual or even triple agonizing properties in that they agonize GIP and/or GLP-1 in addition to glucagon. Also in Phase II is a new targeted thermogenesis agent that acts to convert white fat to brown fat, the fat cell type associated with higher energy burn.<sup>51</sup>

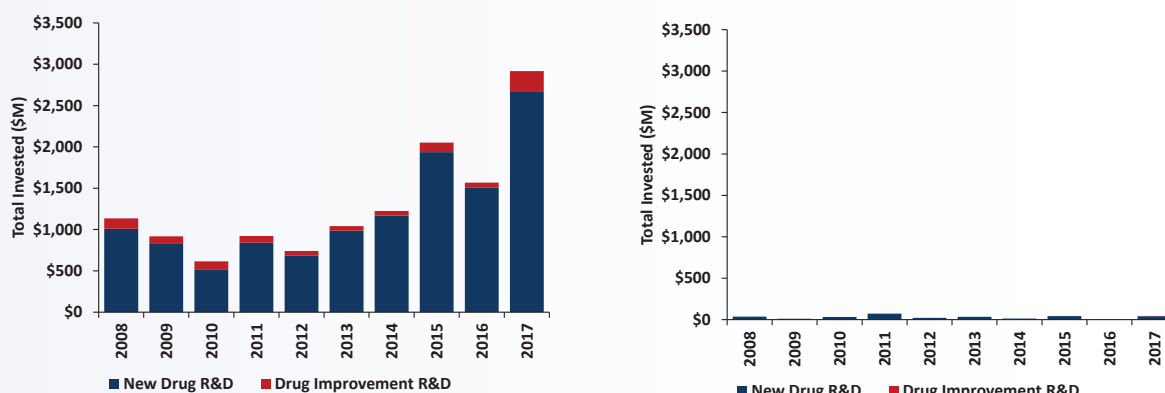
Fibroblast growth factor receptors (FGF21 and FGF23 in particular) feature prominently as Phase I clinical targets, as well as drugs that target activin receptors (TGF pathway), enteropeptidase, and two brain receptors: peptide YY (PYY 3-36) receptors, serotonin receptor 5HT3.

A search for Preclinical phase programs yielded six programs in the Biomedtracker database. Targets not found among the current clinical programs, include acetyl-CoA carboxylase (ACC), an enzyme with a central role in fatty acid metabolism, GDNF Receptor Alpha-Like (GFRAL), free fatty acid receptors, melanocortin (MC) receptors. Other known targets for drug development found in the literature include growth/differentiation factor GDF-15, recently found to be elevated in obese animals, chemokine receptors (CCRs), cholecystokinin (CCK) receptors, bradykinin, as well as beta-hydroxysteroid dehydrogenase.

## Trends in Venture Investment and R&D Activity (Clinical Trial Initiations) in Obesity

Venture investment into U.S. companies with lead products in obesity has been relatively low over the past 10 years. Venture capital funding of U.S. companies with novel lead stage programs in obesity is 40 times below oncology funding (\$304 million vs. 12.2 billion over the last decade, as shown in **figure 13**). Although using the “lead product only” methodology underestimates investment, as it only takes into account lead program disease indication, the picture is nonetheless bleak. We only identified \$304 million invested across nine obesity-focused companies over the last decade.

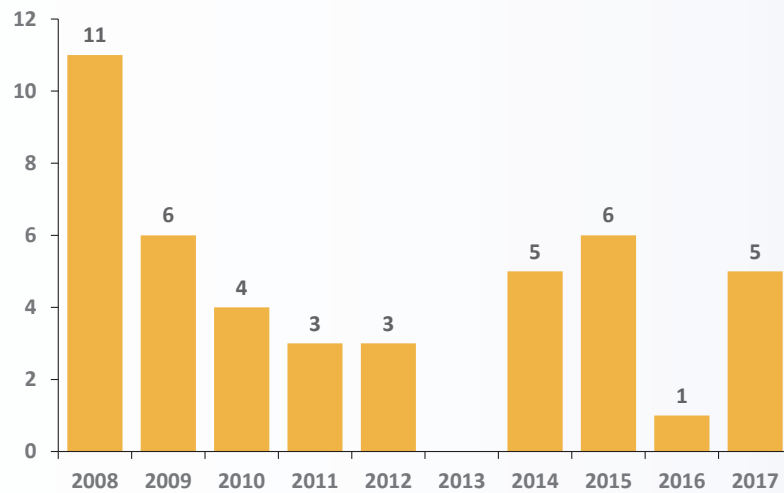
### 2008-2017 VENTURE INVESTMENT INTO U.S. COMPANIES WITH LEAD PROGRAMS IN ONCOLOGY VS. OBESITY



**Figure 13. Left: Venture funding of companies with lead products in oncology and obesity, 2008-2017. Right: Venture funding of companies with lead products in obesity, 2008-2017. Blue bars denote investment in novel drug for the lead asset under development. Red bars indicate investment in drug improvement (reformulation, repurposing) for the lead asset under development.**

<sup>51</sup> Clinicaltrials.gov accessed Oct 2018: <https://clinicaltrials.gov/ct2/show/NCT03171415>

## 2008-2017 CLINICAL TRIAL STARTS FOR OBESITY DRUG INTERVENTION TRIALS



**Figure 14. Clinical trial starts for obesity, 2008-2017. TrialTrove data accessed June 2018. A total of 197 clinical trial starts were retrieved from TrialTrove. Trials were individually assessed for novelty of drug (no prior approval history of the active compound) and trial phase cohorts de-duplicated. A total of 44 novel drug intervention trials (including add on therapy trials with new drugs) were initiated during this time period.**

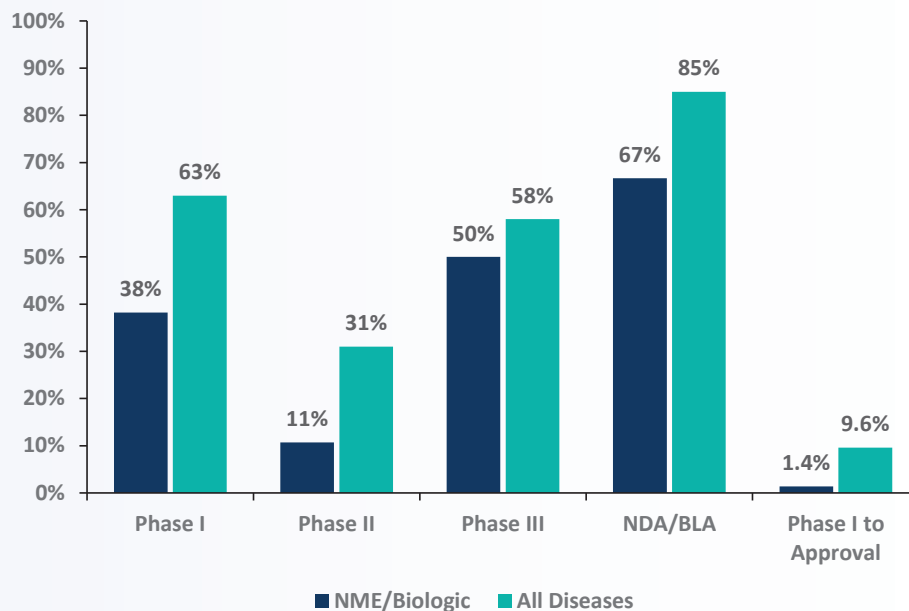
Looking more broadly at clinical trial starts, a very limited number of trials are initiated per year as shown in **Figure 14**. Trial initiations for obesity decreased by 37% from the five-year period 2008-2012 vs. 2013-2017, from 27 to 17 trial starts. Out of the 44 novel trial initiations over the 10-year period, only five were for programs starting a phase 3 trial. Most of the trial starts were for phase 1 trials with 23 trial initiations over the same period.

# Clinical Development Success Rates for Novel Obesity Therapeutics

The clinical development success rates for new obesity drug candidates is lower than what is observed overall for drugs developed in other indications. Looking at new molecular entities and new biologics, we calculated a 1.4% probability for a drug program to move from Phase I all the way to FDA approval (N=69 transitions 2006-2015). This compares to the overall probability of 9.6% for all drug programs, across all disease areas.<sup>52</sup> As shown in **Figure 15**, obesity drug development programs in Phase I had only a 38% chance of success in transitioning to Phase II, and only a 11% chance of transitioning from Phase II to Phase III. Phase III success was closer to average success rates seen in other indications for NMEs. Both obesity and type 2 diabetes had a 50% success rate in moving from Phase III to NDA/BLA filing, which is on par with the 49% for NMEs across all indications, but below 58% for all categories of drugs (biologics, non-NMEs, and NMEs combined). However, unlike with type 2 diabetes, the FDA approval rate of filed NDAs or BLAs is one of the lowest in the disease areas studied, with only 67% success vs. 85% across all disease areas. The low Phase II success rates (which is half of that seen in type 2 diabetes) and the low FDA filing success were major contributors to the 1.4% chance of success from first in man in the obesity space.

Analyzing the R&D programs that were active at any point during January 2016 to September 2018, we found that 86 clinical programs have been suspended. Examples of failed strategies are numerous and include targets such as PTP-1b, PYY receptors, CB1 receptors, histamine receptors, CCK receptors, 5HT6 receptors, CNTF receptors, PPAR delta, growth hormone receptors, melanocortin receptors, MTPP, gastric lipase. Ongoing clinical programs that have mechanistic strategies with a history of failures include MetAP2, DGAT, FGF receptors, leptin receptors.

## CLINICAL DEVELOPMENT SUCCESS RATES FOR NOVEL OBESITY DRUGS 2006-2015



**Figure 15. Clinical success rates for all obesity indications compared to overall industry probabilities, 2006-2015. Data is based on approximately 10,000 drug programs in the Biomedtracker database. (Thomas, D., et al. BIO, Biomedtracker, Amplion. Clinical Development Success Rates 2006-2015 (2016) (Accessed at [www.bio.org/iareports](http://www.bio.org/iareports))**

<sup>52</sup> The low success rate for novel drugs was not observed for the non-NME pain drugs (those that are mostly reformulations of older APIs). The non-NME drugs had an overall 25% success rate.



# Discussion

Type 2 diabetes and obesity are highly correlated in populations of both developed and developing nations. There are hundreds of millions of people considered either diabetic or obese in the world today. The simultaneous rise of both indications is staggering and the total economic costs to nations should be front and center of addressable issues. At the forefront of remedies is the widespread push for optimal diet and exercise, a prescription for a modern world awash in carbohydrate heavy food and sedentary lifestyles. However, shifts in cultural norms are hard to predict or influence. Thus, therapeutic interventions are a necessary component for addressing the rising incidence of type 2 diabetes and obesity and the comorbidities that accompany them.

New drug approvals over the last decade for type 2 diabetes and obesity have provided more options for patients. Using new first-in-class drugs approved by FDA as a proxy, significantly more innovation has made it to the market in these two areas than for the other chronic diseases we have reported on this year combined (depression, pain, and addiction). However, it should also be noted that a number of these products with new mechanisms have not seen broad uptake in populations with high unmet need.

Unfortunately, the funding does not seem to match the rising unmet need. With venture investment a tiny fraction of what goes into oncology and declines found in the broader industry's clinical trial commitment, for both indications there is concern for future innovation. This is also evident in the fact that not a single new mechanistic approach is found in Phase III in the current industry pipeline. Looking at obesity Phase I/II programs, only eight new mechanistic approaches can be identified. However, with success rates well below rates seen in other disease areas, more shots on goal are needed.

Policies supporting efficient and effective regulatory environments will encourage investments into new treatments. Funding basic research to advance our understanding of the biology of diabetes and obesity will enable modern approaches to drug development and regulatory review. For example, utilization of innovative clinical trial designs and digital technologies, as well as, more sophisticated utilization of biomarkers to stratify patient populations to better predict what treatments work best and for whom, would serve to incentivize innovation and change the paradigm of how we treat these widespread diseases.

Additionally, barriers to access to and coverage of innovative medicines have a strong negative impact on investment. This is true even when there are very large patient populations to treat. However, few have access to new therapeutic options and are left with generic medicines. Recent drug launches in chronic, highly prevalent indications, even launches of highly innovative drugs, have faced challenges to coverage and access, creating uncertainty in the investor community. As we enter a period of patent expiration on newer insulin and GLP-1 analogs, more pressure will be placed on coverage of newer innovative medicines that may dissuade early-stage investors from entering the space.

The Biotechnology Innovation Organization (BIO) and member companies view innovation as the key to changing the paradigm for the treatment of type 2 diabetes and obesity. Advancements in science, more choices for patients and a policy environment that stimulates investment in R&D are necessary to achieve this goal.

# Appendix

## VARIATION OF THERAPEUTIC INSULIN PROTEIN SEQUENCE THROUGH HISTORY

#	Year Marketed	Sequence name	Amino Acid Sequence Differences (N) from Human
1	1923	beef insulin	N=3 A8 THR-->ALA, A10 ILE-->VAL, B30 THR-->ALA
2	1923	pork insulin	N=1: B30 THR-->ALA
3	1982	human insulin	N=0, Equivalent
4	1996	insulin lispro (Humalog)	N=2: B28,B29 PRO-LYS--> LYS-PRO
5	2000	insulin aspart (NovoRapid)	N=1: B28,PRO --> ASP
6	2000	insulin glargine (Lantus)	N=3: B31,32 added as ARG-ARG + A-21 LYS-->Gly
7	2004	insulin glulisine (Apidra)	N=1: B29,LYS --> GLU
8	2005	insulin detemir (Levemir)	N=2: B29 LYS-->LYS-C14 + B30 deletion of THR
9	2015	insulin degludec (Tresiba)	N=2: B29 LYS-->gamma + B30 deletion of THR

**A1. Unique insulin sequences of APIs FDA approved for type 2 diabetes 1923-2018. Source: [fda.gov](http://fda.gov), company websites and drug package inserts. Animal insulins are no longer commercially available for clinical use.<sup>53</sup>**

<sup>53</sup> EvaluatePharma database ([www.evaluategroup.com](http://www.evaluategroup.com)) accessed June 2018, Bomedtracker ([biomedtracker.com](http://biomedtracker.com)) accessed June 2018.



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