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Zacks Small-Cap Research

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Brian Marckx, CFA
bmarckx@zacks.com
Ph (312) 265-9474
Anita Dushyanth, PhD
adushyanth@zacks.com

scr.zacks.com

10 S. Riverside Plaza, Chicago, IL 60606

MannKind Corp (MNKD-NASDAQ)

MNKD: Initiating Coverage. Market Is Underestimating Value of Afrezza and Technosphere Technology

LLY and NVO trade at an average of ~5.5x forward sales. Given MNKD's much more rapid estimated percentage revenue growth, we apply that same multiple to our forecasted 2021 Afrezza sales of $106M, which values the Afrezza portion at approximately $3.65/share. Our 10-year DCF uses a 15% discount and values the TreT collaboration at approximately $98M, or ~$0.60/share. Our sum-of-the-parts calculation puts total value of the company at ~$4.25/share.

Current Price (12/10/18)	$1.74
Valuation	**$4.25**

OUTLOOK

MannKind is engaged in the development and commercialization of inhaled biopharmaceutical products for chronic diseases such as diabetes and pulmonary arterial hypertension. Afrezza, a rapid-acting dry powder inhaled insulin approved for use in managing both type 1 and type 2 diabetes, launched in the U.S. in early 2015. It is built around MannKind's proprietary platform drug delivery technology, called Technosphere. We think the general investor sentiment implied by MNKD's current market capitalization is underestimating the long-term potential of Afrezza and is mistakenly categorizing it as a perennial niche product. While Afrezza is currently the company's only commercial product, MNKD is actively engaged at building out their commercial portfolio. The focus of their product development strategy is on leveraging the versatility of their Technospehere platform drug delivery technology and expanding into other disease areas. Our sum-of-the-parts methodology values MNKD at $4.25/share. Our model and valuation are subject to updating, including incorporating other collaboration candidates, if and when we feel there is enough information with which to base reasonably-confident assumptions – which could provide upside to our current target price.

SUMMARY DATA

52-Week High	**$4.05**
52-Week Low	**$0.98**
One-Year Return (%)	**-44.79**
Beta	**2.13**
Average Daily Volume (sh)	**2,569,384**
Shares Outstanding (mil)	**160**
Market Capitalization ($mil)	**$279**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**23**
Insider Ownership (%)	**9**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2018 Estimate	**N/A**
P/E using 2019 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**High,**
Type of Stock	**N/A**
Industry	**Medical Technology**

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	3 A	2 A	2 A	5 A	12 A
2018	3 A	4 A	5 A	5 E	17 E
2019					35 E
2020					71 E

Earnings Per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	-$0.22 A	-$0.35 A	-$0.31 A	-$0.28 A	-$1.13 A
2018	-$0.25 A	-$0.16 A	-$0.16 A	-$0.17 E	-$0.71 E
2019					-$0.63 E
2020					-$0.68 E

Zacks Projected EPS Growth Rate - Next 5 Years % **N/A**

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SNAPSHOT

MannKind Corporation (MNKD) was founded in the early 2000's by the late Alfred Mann, a physicist by training, Mann was a pioneer in several fields including aerospace, electronics and medical devices. Among his successes prior to MannKind was development of the first rechargeable pacemaker and MiniMed, a revolutionary miniaturized insulin pump that was sold to Medtronic in 2001 for more than $3B.

MannKind is engaged in the development and commercialization of inhaled biopharmaceutical products for chronic diseases such as diabetes and pulmonary arterial hypertension. Afrezza, a rapid-acting dry powder inhaled (human) insulin approved for use in managing both type 1 and type 2 diabetes, launched in the U.S. in early 2015 and is expected to make its international debut in the near-term. It is built around MannKind's proprietary platform drug delivery technology, called Technosphere.

While Afrezza is currently the company's only commercial product, MNKD is actively engaged at building out their commercial portfolio. The focus of their product development strategy is on leveraging the versatility of their Technospehere platform drug delivery technology and expanding into other disease areas. In early September they announced a collaboration with United Therapeutics (UTHR) related to development and commercialization of a dry powder formulation of treprostinil for the treatment of pulmonary arterial hypertension (PAH). This is a significant market. Drug therapies approved to treat PAH via the prostacyclin deficient pathway generated nearly $2 billion in sales in the U.S. in 2016, of which, treprostinil contributed the bulk.

This follows a January 2016 announced collaboration with Receptor Life Sciences (RLS) related to development and commercialization of (potentially) multiple inhaled therapeutic products – the first of which could be an inhalable cannabinoid for cancer pain. Other programs, collaborations and partnerships could follow.

In addition to expanding the pipeline and opportunities for long-term value creation, collaborations, partnerships and licensing agreements have brought significant non-dilutive funding which MNKD has put to work in the form of cleaning up their balance sheet, product development and commercialization of Afrezza. The RLS agreement included $1M upfront and another potential $100M+ in development and commercialization milestones, while the UTH deal brings $45M upfront and another $50M in possible back-end payments. These follow more than $200M received from Sanofi-Aventis for commercialization rights to Afrezza.

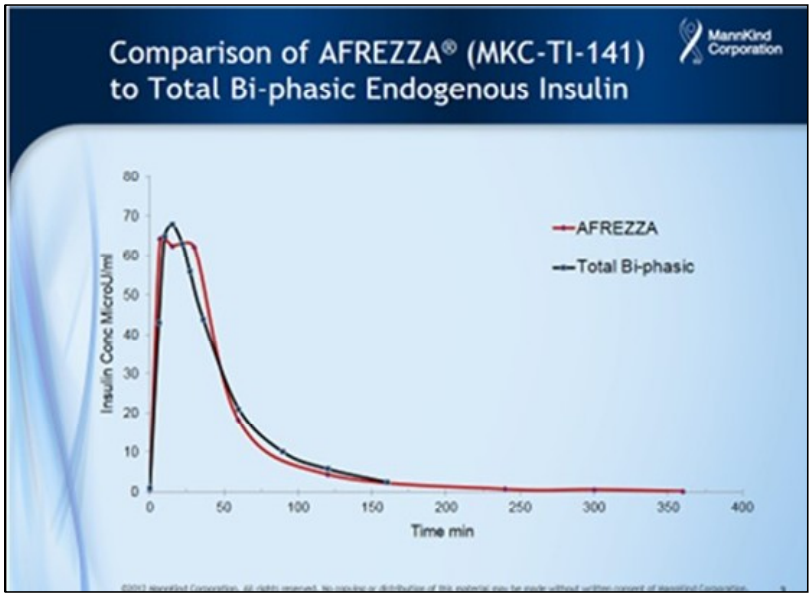
Technological advancements in injected insulin have not resulted in better patient outcomes…
Diabetes is an epidemic in the U.S. and getting worse. Prevalence in the U.S. is on the rise, having grown at a CAGR of approximately 4% since 1980. Approximately 30M Americans have diabetes (22M of which have been diagnosed) and nearly 2M new cases are diagnosed each year. Prediabetes affects another 86M people, or approximately 37% U.S. adults. If not sufficiently controlled, blood glucose peaks and valleys can have serious consequences and result in organ and nerve damage, cardiovascular disease, loss of eyesight and death.

Approximately 96% of the six million diabetic insulin users in the U.S. use injected insulin (from a needle, pen, patch or pump). Despite the feverish pace of technological advancements in diabetic care, including introduction of 'novel' rapid and long-acting injectable insulin, personal mini-pumps and continuous glucose monitoring, there has been no significant change in the percentage of diabetics (~50%) that regularly reach their A1c goals. In fact, some studies (Carls et al., Casagrande et al.) indicate that among diabetics that use injected insulin, fewer are actually reaching recommended the HbA1c target of <7% today as compared to a decade (or more) ago. This highlights the unmet need for a new class of insulin therapy that can increase compliance, increase the proportion of diabetics reaching goal and improve patient outcomes – as we discuss below, we think Afrezza represents that therapy.

Technosphere and the importance of natural action profile…
While oral administration is practical for small molecule drugs, parenteral routes, such as intravenous, subcutaneous or intramuscular injection, are used to deliver therapeutic peptides and proteins (i.e. biologics) which cannot survive the harsh environment of the gut. MannKind's Technosphere technology allows for the delivery of a dry powder formula of certain drugs through inhalation into the lungs. Unlike traditional administration, inhaled drugs bypass the liver, thereby improving systemic exposure. Technosphere's powders are dissolved extremely rapidly following inhalation and are delivered directly into the arterial circulation. Clinical studies have shown that this translates into a much more natural physiologic profile as well as dose-to-dose consistency. Technosphere insulin (i.e. Afrezza) represents a new class of insulin therapy that has the potential to provide incremental clinical benefit to injected insulin and result in a greater number of diabetics reaching A1c targets.

Inhaled insulin's novel time-action profile translates into better patient outcomes…
This 'fast-on-fast-off' profile means Afrezza begins to decrease sugars faster and return serum insulin levels to baseline sooner than injected insulins. In October 2017 Afrezza's label was updated to include its rapid time-action profile. Clinical trials have shown that this duration of effect which closely mimics physiological insulin results in lower rates of hypoglycemia (i.e. too low glucose levels), a significant drawback (and contributor to lack of adherence) of insulin treatment. As optimal hypoglycemia control can improve patient compliance and lack of compliance is the most significant contributor to insufficient glucose control (which eventually results in serious complications), Afrezza's unique time-action profile has demonstrated the ability to improve patient outcomes. The convenience benefits, such as pain-free administration and related stigma of injecting in public, also lend themselves to improving upon adherence to treatment guidelines.

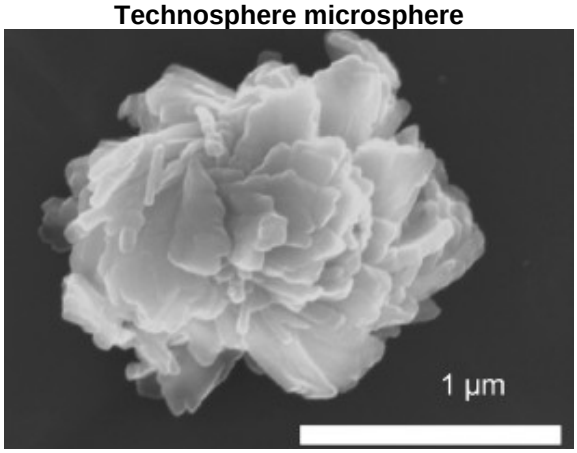
Afrezza mimics endogenous insulin



INVESTMENT THESIS

Technosphere technology
MannKind's Technosphere drug delivery technology is built around a proprietary excipient called fumaryl diketopiperazine. FDKP is a pH-sensitive organic molecule that, when exposed to acidic conditions, self-assembles into small particles (i.e. 'microparticles') through a hydrogen bonding process. These microparticles have a large surface area and high porosity (~60% - 80%), allowing for the absorption of a variety of therapeutic substances. Certain therapeutic peptides and proteins, such as human insulin, can be combined with FDKP and encapsulated within the microspheres. These microparticles (with a median diameter of ~2.0mcm to 2.5mcm) are then freeze-dried into a powder formulation suitable for pulmonary inhalation.

Technosphere microsphere



Inhaled drug delivery…

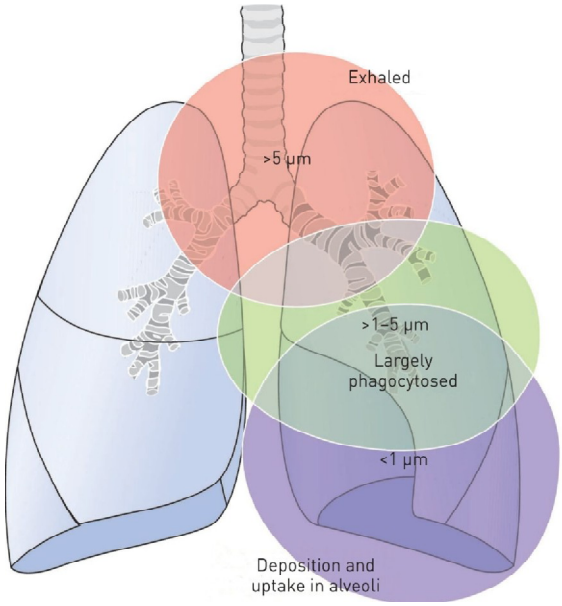
Inhalation not only represents an alternative to traditional drug delivery, but offers significant advantages to both oral and injected (i.e. subcutaneous, or sc) administration. Delivery into the lung circumvents the harsh environment of the gastrointestinal tract and, given that levels of metabolism are much lower in the lung, inhaled delivery avoids hepatic first-pass metabolism. User-friendliness including ease of self-administration and pain-free dosing are attractive features as compared to subcutaneous and intravenous methods. But inhalation's benefits go beyond patient convenience and can also include significant clinical advantages – much of which is possible due to the extraordinary gas-exchange efficiency of the lungs.

Keep in mind that while inhalation avoids certain difficulties that other forms of administration must overcome (such as hepatic metabolism), that they face an environment riddled with it its own challenges and characterized by the likes of mucus, macrophages, lung volume, air flow, absorption and coughing, among others.

Unique properties of Technosphere Insulin…

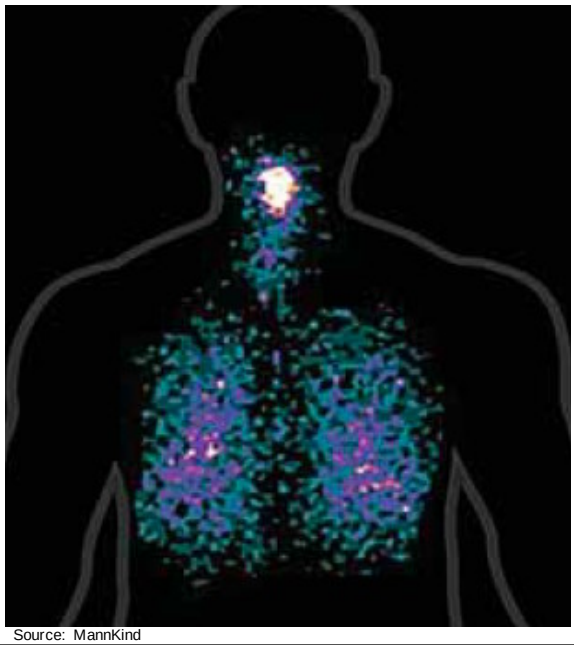
It is the unique properties of Technosphere that separate it from other inhaled delivery medium's (such as that used for Exubera) and which make it such a particularly effective and versatile inhaled therapeutic platform. The size and aerodynamic shape of Technosphere microparticles allows for fast and efficient travel through the air and into the lungs. And with more than 90% of the microparticles in the respiratory range (i.e. >0.5 µm and <5.8 µm), Technosphere technology is optimized for deep inhalation into, and uniform dispersion throughout, the lungs. Additionally, Technosphere pH-activated powders are quickly dissolved in the interstitial fluid immediately after inhalation and coming into contact with the characteristically neutral pH conditions of the lung. This results in ultra-rapid absorption into the circulatory system, avoidance of peripheral circulatory degradation and high bioavailability.

Technosphere particles have an average diameter of~2.5 µm, well within the 1 µm to 5 µm range that is necessary for inhaled therapies to reach the deep lungs



Source: Sabine H. van Rijt et al. Eur Respir J 2014;44:765-774

Image of technetium-labeled Technosphere insulin particles shows deep penetration into and uniform dispersion throughout the lungs

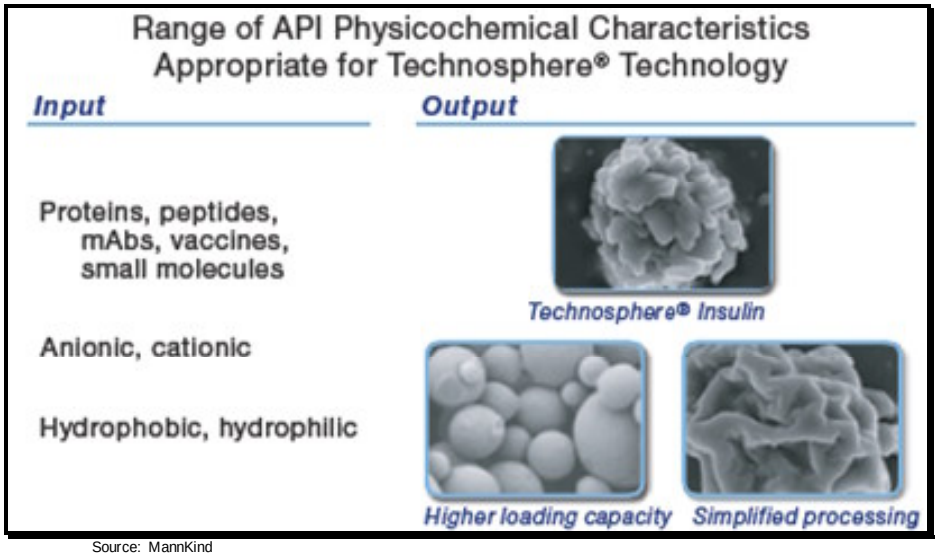


Source: MannKind

Technosphere is a platform technology…

Technosphere was developed as a platform technology applicable to a large assortment of various therapeutic biologics. While peptides and proteins (most notably insulin and, more recently, treprostinil) have been the most significant focus for MannKind, Technosphere has shown to be capable of absorbing molecules of various types and sizes. In addition to peptides and proteins, this includes anionic and cationic drugs, hydrophobic and hydrophilic drugs and small molecules and ranging in molecular weight from 500 to 140k Da.

Technosphere Platform Has Wide-Ranging Utility



Source: MannKind

Afrezza…

Afrezza, built on the Technosphere platform technology, is a prescription rapid-acting dry powder form of human insulin. Unlike traditional insulin therapy, which is administered by subcutaneous injection, Afrezza dry powder insulin is inhaled into the lungs through the use of a proprietary small portable inhaler. It is the only inhaled insulin available in the U.S. Afrezza, received FDA approval in June 2014 to control high blood sugar in adults with both type 1 and type 2 diabetes and became available in U.S. retail pharmacies in February 2015.

Afrezza is protected by more than 566 issued patents in the U.S. and elsewhere and is the subject of over 200 pending patent applications. Among these are composition patents and inhaler and cartridge patents which expire at various dates through the year 2032. Method of treatment patents extend out to 2031.

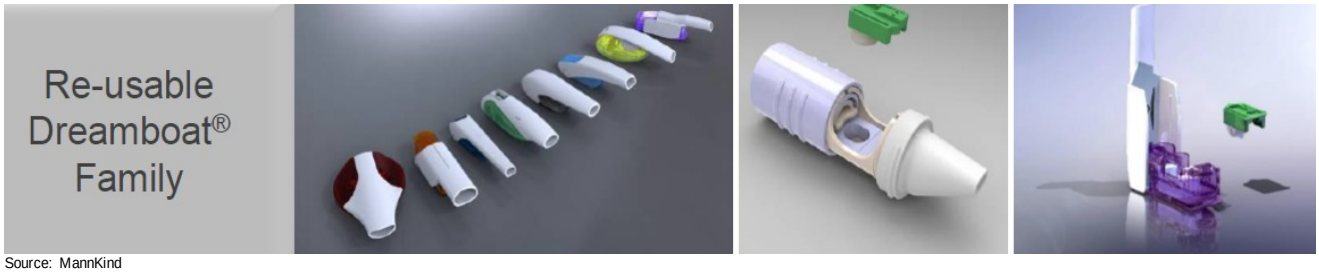
The dry powder is packaged in single-use cartridges and color-coded for three different starting doses. A supplied conversion table (below) allows users to estimate the appropriate Afrezza starting dose based on corresponding injected insulin dose (note that Afrezza's label was recently updated to include language on adjusting dosing).

Converting from injected mealtime insulin

INJECTED MEALTIME INSULIN DOSE	AFREZZA DOSE	# OF CARTRIDGES NEEDED		
		4 UNIT (BLUE)	8 UNIT (GREEN)	12 UNIT (YELLOW)
UP TO 4 UNITS	4 UNITS			
5-8 UNITS	8 UNITS			
9-12 UNITS	12 UNITS	+		OR
13-16 UNITS	16 UNITS			
17-20 UNITS	20 UNITS			+
21-24 UNITS	24 UNITS			

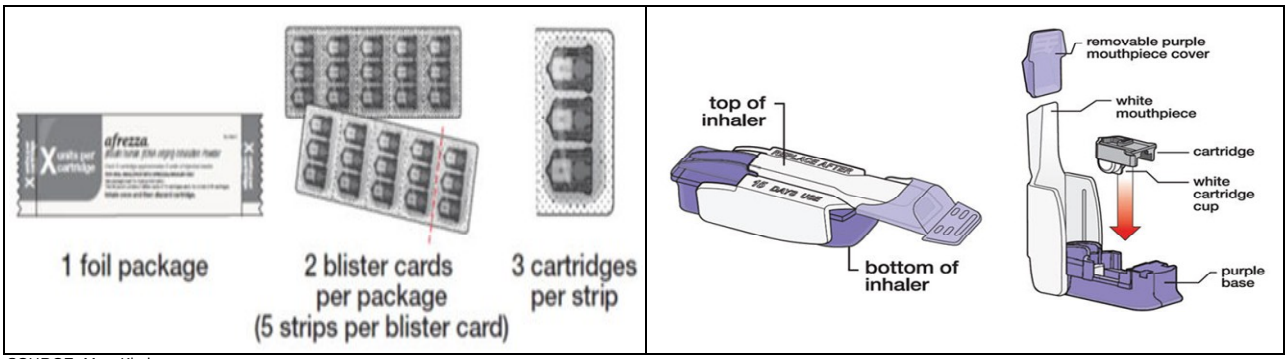
Source: MannKind

Two (Dreamboat) reusable (for up to 15 days) inhalers are included in each Afrezza package. MNKD's proprietary inhalers were designed to be inexpensive, efficient and simple to use – all attributes that are important for driving patient compliance. MNKD's marketing literature notes that their Dreamboat inhalers deliver more than 90% of powder formulations to the patient with approximately 70% of that in the respirable range. This, again, speaks to the unique properties and related benefits of the Technosphere technology including the size and shape of the microparticles and their ph-activation.



Source: MannKind

Each foil package of Afrezza insulin contains a total of 30 cartridges (3 cartridges per blister strip x 5 blister strips per card x 2 blister cards). Afrezza insulin has a minimum shelf life of 24 months if refrigerated and 10 days if stored at room temperature. To administer, a patient simply removes a dose-appropriate number of cartridges from their package and, with the mouthpiece lifted to a vertical position, loads a cartridge into the inhaler. After the mouthpiece is closed, the user exhales, places their lips around the mouthpiece, then inhales deeply and holds their breath. The spent cartridge is discarded and, depending on an individual's particular prescription, the process is repeated.



SOURCE: MannKind

Primer on blood glucose and insulin glucose control

The benefits of inhaled insulin (as compared to subcutaneous insulin) are largely two-fold; more user-friendly administration and clinically-proven 'superior glucose control'. While we cover Afrezza's action profile in more detail later in this report, a quick primer of what we characterize as 'superior glucose control' might be helpful to fully understand the benefits of Afrezza in the context of managing diabetes and in improving diabetics' quality of life.

Glucose is created when the body breaks down carbohydrates. In healthy individuals, excess glucose is stored in the liver, which it then releases into the blood as-needed. Insulin and glucagon are hormones that regulate how much and when glucose is stored and how much and when glucose is released into the blood. Diabetics have compromised insulin function, which means if not controlled with exogenous insulin, their blood glucose will rise to unhealthy levels (hyperglycemia).

Fear of hypoglycemia increases risk of severe health outcomes associated with hyperglycemia…

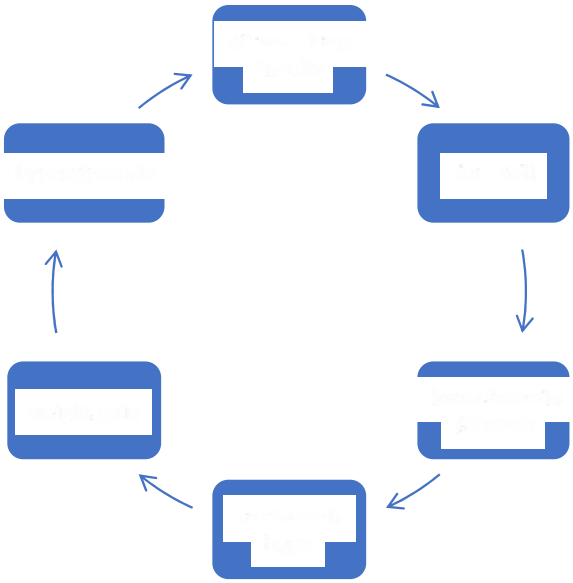
Hyper- and hypoglycemia result if a diabetic's blood sugar is not properly controlled. Hypoglycemia is when blood glucose has become too low – generally considered 70 md/dl or lower. Initial symptoms include hunger, tiredness, sweating, nausea and irritability. If not addressed, hypoglycemia can result in severe confusion, seizures and unconsciousness. Unfortunately, 'addressing' hypoglycemia for diabetics usually means eating and eating, of course, results in weight gain and risk of hyperglycemia.

When glucose rises above 180 mg/dl a person has become hyperglycemic (frequently referred to as 'high blood sugar'). Initial symptoms may not be noticeable and if they are, are mostly confined to annoyances or slight discomfort – such as frequent urination, increased thirst and headaches. Chronic hyperglycemia, which insulin-using diabetics are at-risk of if the disease is not properly controlled, can be much more serious and result in severe weakness, chronic wounds, nerve and organ damage, blindness and even death.

In the context of this report, the important take-aways relative to these two potential outcomes is that hypoglycemia is largely confined to being an unpleasant side effect of exogenous insulin – as a result, diabetics often either skip mealtime insulin in order to avoid hypoglycemia (risking serious hyperglycemia outcomes) or take their mealtime insulin and then eat more (often 1 to 2 hours after a meal), often resulting in weight gain. Neither choice is a

healthy option. As such, if an exogenous insulin were shown to significantly reduce the risk of hypoglycemia, diabetics would be less prone to skipping mealtime dosing and, by extension, would not be exposed to the serious health risks associated with hyperglycemia or the never-ending cycle of fighting high blood sugar with (too-long tailed) mealtime insulin and the resultant hypoglycemia with food.

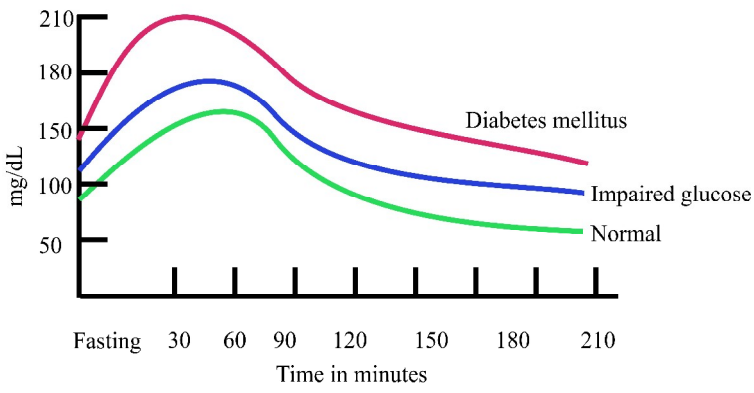
Viscious Cycle of Injected Insulin



The most common risk of meal-time insulin (as disclosed on the labels of each product) is hypoglycemia which is a significant contributor to lack of adherence to treatment guidelines. Despite the feverish pace of technological advancements in diabetic care, including introduction of 'novel' rapid and long-acting injectable insulin, personal mini-pumps and continuous glucose monitoring, there has been no significant change in the percentage of diabetics (~50%) that regularly reach their A1c goals. In fact, some studies (Carls et al., Casagrande et al.) indicate that among diabetics that use injected insulin, fewer are actually reaching recommended the HbA1c target of <7% today as compared to a decade (or more) ago. Much of the reason why so many diabetics do not reach their A1c goals has to do with them skipping mealtime insulin – and, as discussed, much of skipping mealtime insulin has to do with fear of hypoglycemia. This is what makes Afrezza such a compelling product – as detailed below, Afrezza's time-action-profile directly addresses the issues of hypoglycemia and resultant health risks of hyperglycemia.

Insulin functioning: healthy versus diabetic…

The chart below illustrates blood glucose curves of a healthy individual compared to that of someone with impaired insulin function and with that of a diabetic. As the graph illustrates, blood glucose spikes to peak levels within 30 minutes after a meal and, in the case of diabetics, can rapidly exceed the recommended maximum of 180 md/dl. However, even the impaired and diabetic insulin curves, while elevated, begin to return to baseline within 60 minutes and have nearly returned to baseline within two hours. Below, compare these to how Afrezza and subcutaneous insulin control blood glucose.



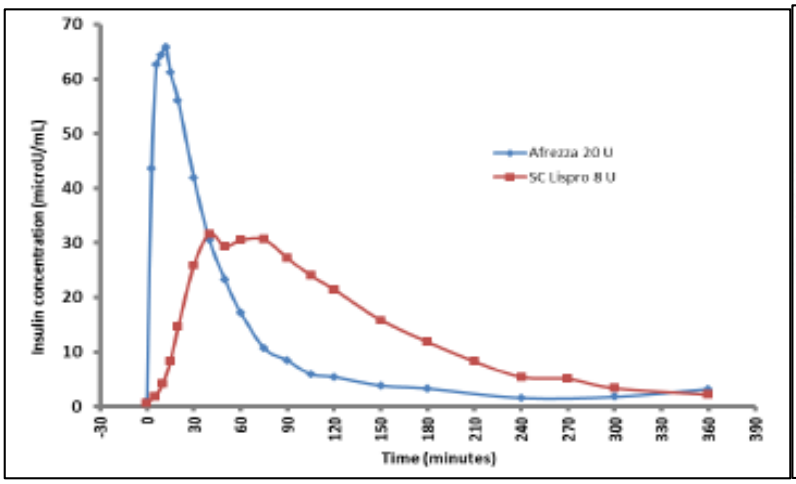
Source: labpedia.net

The graphs below compare Afrezza (at different doses) to subcutaneously-delivered insulin on two of the most significant parameters related to how well insulin manages blood glucose and, by extension, how it effects a diabetics' quality of life. These graphs (dose-ranging study vs human insulin) were included as supportive documentation in the regulatory filing seeking FDA approval of Afrezza in 2013.

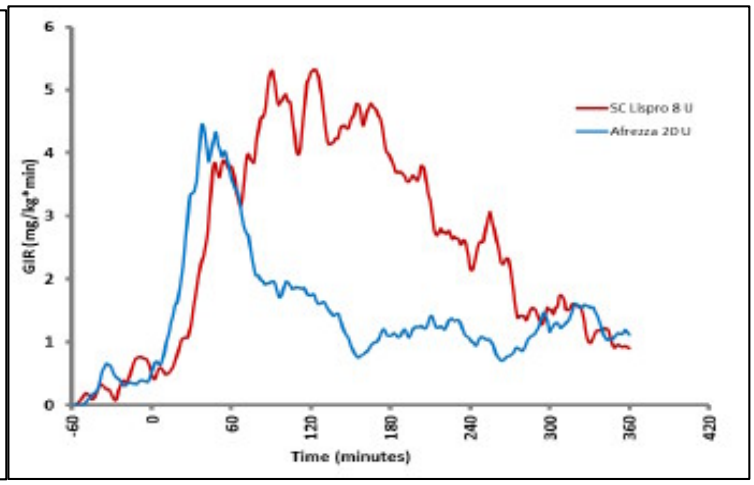
The graph on the left depicts insulin concentration in the blood following administration while the graph on the right depicts the ability of each therapy to control glucose. As illustrated (L), Afrezza reaches maximum insulin concentration very rapidly, corresponding almost exactly to the near-immediate timeframe of the increase in blood glucose following a meal. Meanwhile, the subcutaneous insulin curve shows that peak concentration is reached between approximately 30 and 60 minutes, or not until the diabetic glucose curve (red line above) is well into the unhealthy zone – resulting in hyperglycemia.

Both charts below also depict Afrezza's more rapid dissipation from the blood. This is important as too much insulin over too long will result in hypoglycemia, a significant drawback (and contributor to lack of adherence) of traditional endogenous insulin therapy. Hypoglycemia, characterized by fatigue, sweating, irritability, shakiness and other unpleasant symptoms, is a major contributor to lack of patient compliance. As many diabetics would rather skip mealtime insulin than risk feeling nauseous, hypoglycemia is implicated as one of the most significant contributors to ~50% of diabetics not meeting their A1c targets.

Afrezza Quickly Knocks Down Glucose, Reducing Hyper Risk



Afrezza Rapidly Dissipates, Reducing Hypo Risk



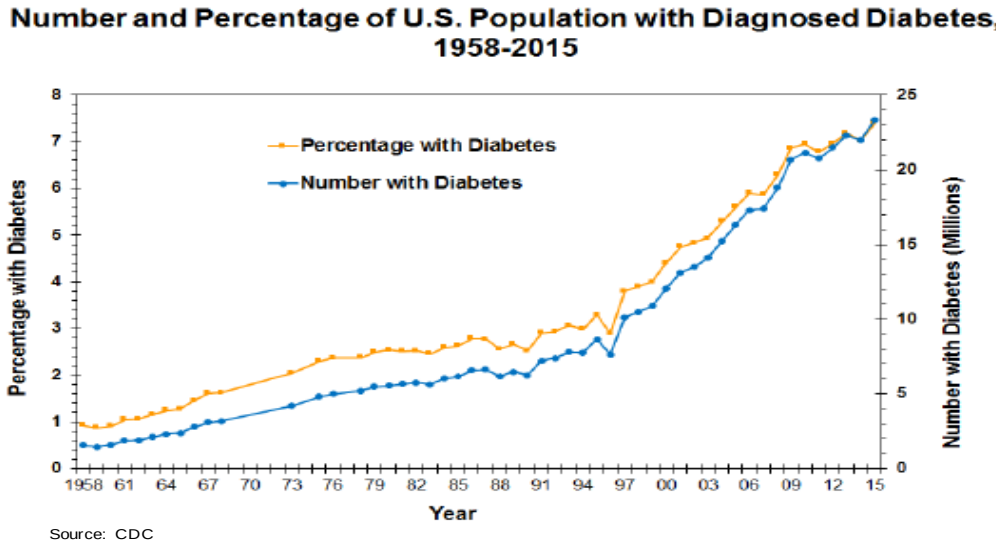
Diabetes

Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose levels as a result of problems with insulin - where either the body is not making enough of this hormone or it is not effectively utilizing it. Chronically elevated blood sugar (i.e. glucose) can cause serious complications and increase the risk of heart disease, eye problems including blindness, kidney disease, nerve damage (i.e. diabetic neuropathy) and dental diseases, among other potential problems. It is also the seventh leading cause of death.

Statistics

According to the International Diabetes Federation, 415M people are currently affected by the disease worldwide and this is expected to grow to 642M people by 2040. About one-half of those with the disease are unaware that they have it.

The CDC estimates that approximately 30M Americans, or about 9.5% of the total population, have diabetes. Of the 22M+ which are currently diagnosed with the disease, over 20M have type 2 and ~1.25M have type 1. Prevalence of diabetes in the U.S. is on the rise, having grown at a CAGR of approximately 4% since 1980. Almost 2M new cases are diagnosed each year in the U.S. Prediabetes, in which blood sugar is abnormally high but not at a level to be considered diabetes, affects another 37% of American adults, or 86M people.



Type 1 diabetes, which is often referred to as juvenile diabetes as it typically develops early in life, is characterized by autoimmune destruction of beta cells in the pancreas which are responsible for insulin production. It is well-established that tight glucose control is critical for type 1 diabetics (T1D) as excursions can significantly increase the risk of long-term health complications. T1D's insulin regimen typically includes use of a long-acting insulin as well as a short or rapid-acting insulin, also called mealtime insulin. Glucose monitoring must be done regularly throughout the day to determine whether a T1D is within recommended blood sugar ranges. Traditionally accomplished with a finger prick, test strips and reader, blood sugar testing technology now includes non-invasive and continuous glucose monitors that can eliminate the need for regular and painful blood testing and provide constant readings (and highs and lows) to better manage the disease.

Type 2 accounts for approximately 90% of all diabetes cases. Obesity is a significant risk factor for developing the disease, which is characterized by hyperglycemia (uncontrolled spikes in blood sugar) due to the body's inability to properly use insulin. This is a result of a combination of resistance to, as well as insufficient production of, insulin. Unlike type 1 diabetics, most individuals with type 2 are typically able to produce some insulin and oftentimes can control the disease with oral drugs such as sulfonylureas and meglitinides (to stimulate insulin secretion), biguanides (to decrease glucose production), thiazolidinediones (to improve insulin action) and DPP-4 and SGLT2 inhibitors (which directly lower A1C). In fact, only about 29% of diagnosed T2Ds regularly use exogenous insulin. Type 2 diabetes, however, is a chronic condition that can get progressively worse if not properly controlled.

Insulin

Insulin has been used to treat diabetes since the 1920's when it was first isolated from the pancreas of a dog. Evolution of therapeutic insulin over the following years largely related to optimizing its sourcing, purity, immunogenicity and pharmacokinetics. The overlying goal has been to develop an exogenous insulin therapy that acts identical to that of endogenous insulin (of a healthy person) in maintaining glucose homeostasis and without any side effects. While advances have been made, most of the recent innovation has focused on novel ways to deliver liquid insulin. Meanwhile, the last several decades have witnessed only very incremental improvements of rapid-acting injectable insulin as it relates to glucose control.

Insulin comes in several different forms, based on their function, and is typically delivered subcutaneously via syringe, pens, pumps and patches. For type 1 and some type 2 diabetics, two or more different types of insulin may be used; rapid-acting, regular (or short)-acting, intermediate-acting, long-acting or a combination (pre-mixed) of these. The intermediate and long-acting insulin are basal doses used for maintenance of energy throughout the day with onset and duration of effect as long as 4 hours and 12 hours, respectively. These longer-acting insulins are designed to maintain 'fasting plasma glucose' (FPG) within a specified range (see below). FPG is blood sugar level when a person has not eaten for at least 8 hours.

Rapid-acting and short-acting insulin, also known as meal-time insulins, are taken at the same time and within 30-60 minutes of eating, respectively. These faster-acting insulins are designed to maintain 'postprandial plasma glucose' (PPG) within a specified range. PPG is blood sugar level measurement one to two hours following a meal.

Recommended Glucose Ranges

	ADA	AACE
FPG	80 - 130 mg/dl	<110 mg/dl
PPG	<180 mg/dl	<140 mg/dl
A1c	**<7%**	**<6.5%**

Exogenous **meal-time insulin** helps to control the extra glucose that enters the blood as a result of the breakdown of carbohydrates following a meal. In addition to Afrezza, other rapid-acting insulins include Lispro (Humalog) from Eli Lilly (LLY), Aspart (Novolog) from Novo Nordisk (NVO) and Glulisine (Apidra) from Sanofi-Aventis (SNY). Humulin R, regular insulin, is also marketed by Lilly. Together these four injected meal-time insulins generate more than $7.5B in annual sales, including ~$4.4B in the U.S.

Rapid-acting insulin sales

2017 Revenue (millions)				
	U.S.	**Europe**	**ROW**	**Total**
NovoLog	$1,632	$660	$799	$3,091
Humalog	$1,718	NA*	$1,147	$2,865
Apidra	$117	$157	$160	$434
Humulin R	$885	NA*	$450	$1,335
Total	**$4,352**	**NA***	**$2,556**	**$7,725**

*LLY does not disclose European sales

Importance of meal-time insulin…

Optimally, meal-time insulin will be able to do two things well; quickly knock down glucose as it rapidly rises following eating and then rapidly dissipate, allowing for glucose levels to stabilize back within recommended guidelines. The risk of not coming on quick enough is that glucose will rise above recommended ranges (i.e. experience hyperglycemia) while not dissipating fast enough risks falling bellow recommended ranges (hypoglycemia).

How well a particular meal-time insulin performs these two functions largely depends on its 'time-action profile.' That is, how quickly does it get into the bloodstream, how quickly does it begin knocking down the spiking glucose and how effectively does it bring glucose back to pre-prandial (i.e. before eating) levels (without overshooting).

Afrezza's Pharmacodynamics and Pharmacokinetics Profile

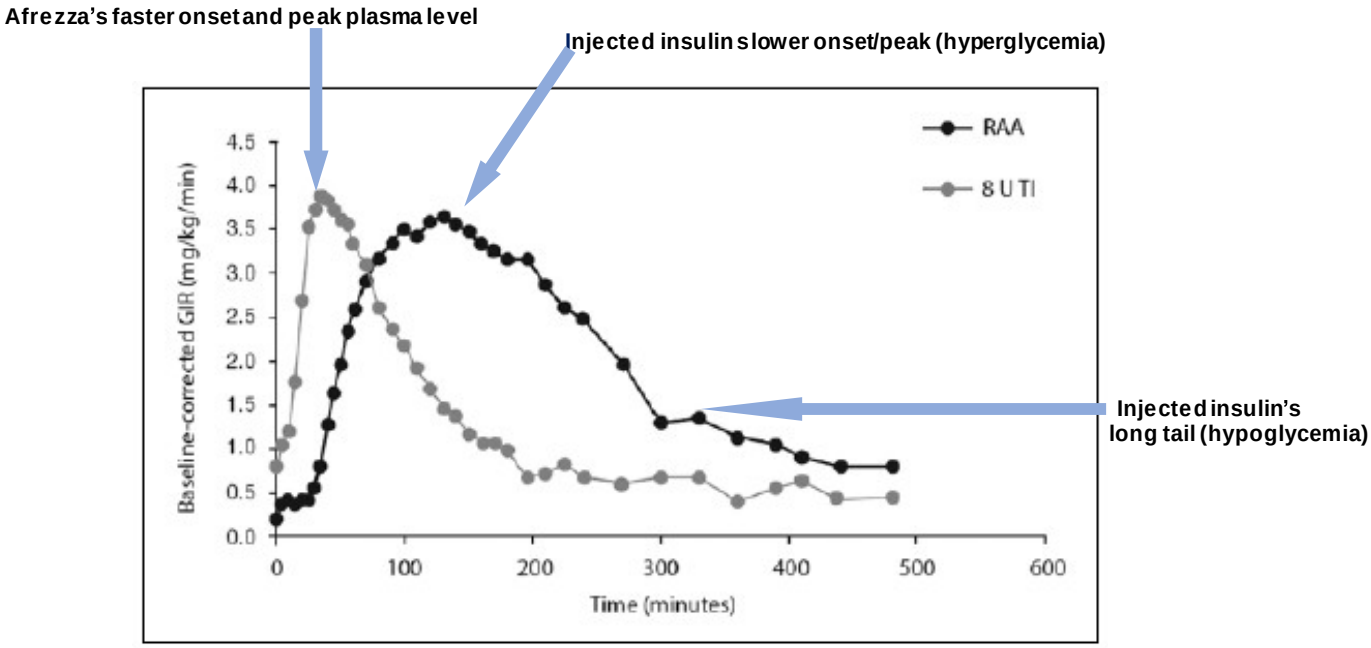
Studies have firmly established that Afrezza comes on much quicker and reaches peak insulin concentration faster than its subcutaneous counterparts. It also eliminates from the body similar to regular human insulin. As explained earlier, its faster onset of action and more rapid dispersion means that Afrezza controls blood glucose better and reduces risk of hypoglycemia. And it's not just subcutaneous insulin that Afrezza outperforms on these measures. It also has a superior on/off profile to that of Exubera, the first inhaled insulin to make it to the U.S. market (see our Appendix for a comparison between Afrezza and Exubera).

Afrezza's onset of action is approximately 12 minutes, it reaches peak plasma insulin concentration (i.e. T_{max}) in about 50 minutes and has duration of around two hours. While rapid-acting injectable insulin also has a rapid onset – in about 10 to 15 minutes – studies have shown that it may not reach peak plasma concentration until two or more hours after administration - much later than that of Afrezza, and risks hyperglycemia. Additionally, subcutaneous insulin has a notoriously 'long tail' – that is, it lingers too long, combating blood glucose which is now in-range and, hence, results in hypoglycemia.

Glucose clamp studies illustrates Afrezza's rapid on/off compared to lispro…

Glucose clamp studies are used to evaluate PD profiles of exogenous insulin therapy. In these studies, glucose is artificially infused into the bloodstream at a rate that maintains (i.e. 'clamps') blood sugar at a preset level. Continuous glucose monitoring is used to determine glucose infusion rates throughout the duration of the study. Effectiveness of insulin therapy is measured by the amount and timing of glucose infusion required (i.e. glucose infusion rate, or GIR) to clamp it at the preset level. The superiority of Afrezza's PD profile is demonstrated in a glucose clamp study comparing it to injected insulin lispro in 25 patients with type 1 diabetes.

Results showed that among patients receiving Afrezza, the glucose infusion rate (which, again, is a proxy for glucose-controlling efficacy) peaked at 30 minutes after administration. By contrast, the GIR among patients receiving subcutaneous rapid-acting insulin peaked at an average of 150 minutes following administration. Moreover, the time to 50% of maximum effect was 19 minutes among Afrezza patients and 50 minutes among those receiving injected insulin. The long-tail of injected insulin is illustrated by the fact that GIR baseline was not reached until about 300 minutes after administration – by contrast, GIR baseline was reached within approximately 180 minutes among those receiving Afrezza. Additionally, at 120 minutes after administration, 60% of Afrezza's total glucose lowering effect had been delivered but only 33% of lispro's had.



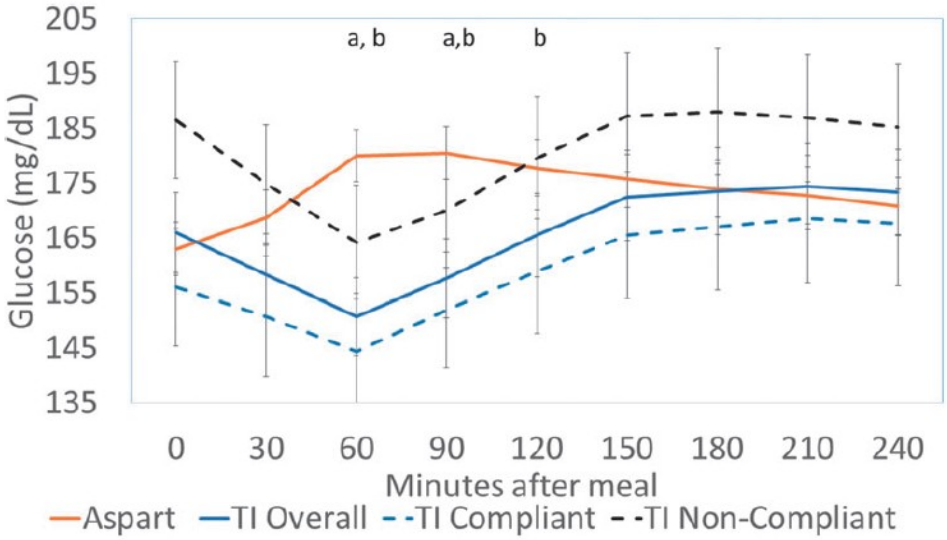
Source: Heimemann, et al. Journal Diab Science & Tech 2016

STAT Study Highlights Afrezza's Dosing Flexibility, Results in Less Hypoglycemia, Superior TIR
Traditional mealtime insulin is taken within 30 minutes of a meal and, due to the risk of hypoglycemia, is not typically supplemented with additional dosing. However, unlike traditional mealtime insulin therapy, Afrezza's quick peak onset and shorter duration allows for supplemental dosing without the same risk of hypoglycemia.

The STAT study, published in November 2018 in Diabetes Technology & Therapeutics, showed that the greater flexibility afforded by Afrezza's rapid on/off action which allows for supplemental dosing resulted in superior time-in-range (i.e. less hypo and hyperglycemia), and even less weight gain, as compared to injected insulin. The primary outcomes were time-in-range (TIR: 70–180 mg/dL) and post-prandial glucose excursions (PPGE) in 1 to 4 hours after eating. Glucose was measured with continuous glucose monitoring (CGM).

Patients in the open label, multicenter study were randomized to either Afrezza (n=26) or insulin aspart (n=34). Of the 26 Afrezza patients, evaluable data were available on 22 (i.e. intent-to-treat). Patients in the Afrezza cohort were instructed to take supplemental inhalations at one and two hours after meals if CGM values showed glucose excursions above goal. Not all Afrezza patients ended up complying with instructions to take supplemental doses. As a result, at the end of the study, investigators assessed what ended up being three cohorts; Afrezza total intent-to-treat (n=22), Afrezza non-compliant (n=15) and aspart.

STAT Study: Afrezza associated w/ significantly longer Time-In-Range

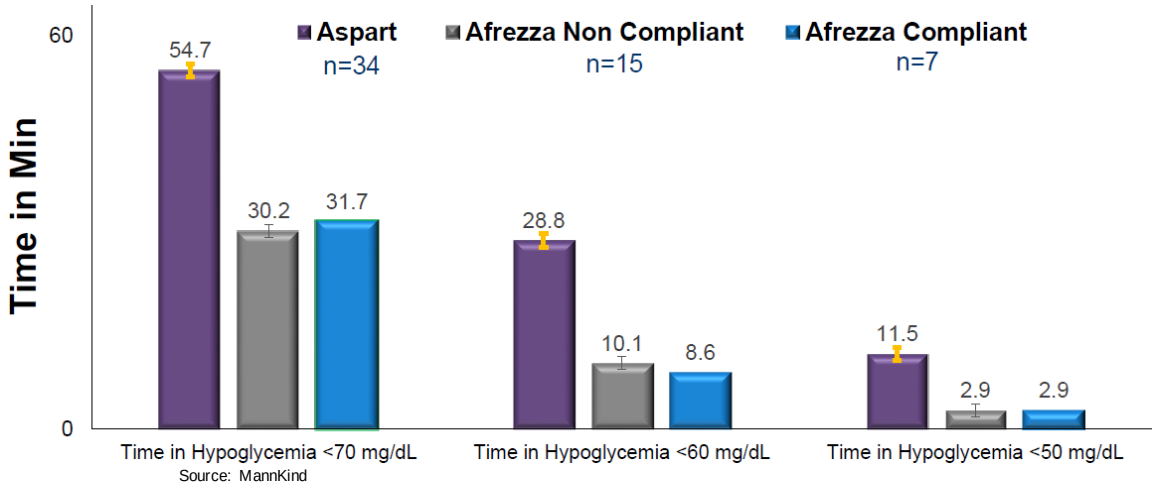


a, p<0.05 for TI Overall vs. Aspart; b, p<0.05 for TI Compliant vs. Aspart

Source: Halis Kaan Akturk, et al., 2018 Diabetes Tech&Ther

Results showed that while time-in-range (TIR) was similar between both the Afrezza total and aspart cohorts, Afrezza total patients spent significantly less time in hypoglycemia (<60 and <50 mg/dl, p<0.05). Afrezza-compliant patients fared even better. In the Afrezza-compliant group, TIR was significantly greater (63% vs 54%, p=0.009) and time in hyperglycemia (i.e. >180 mg/dl) was significantly less (34% vs 41%, p=0.045) than the aspart cohort.

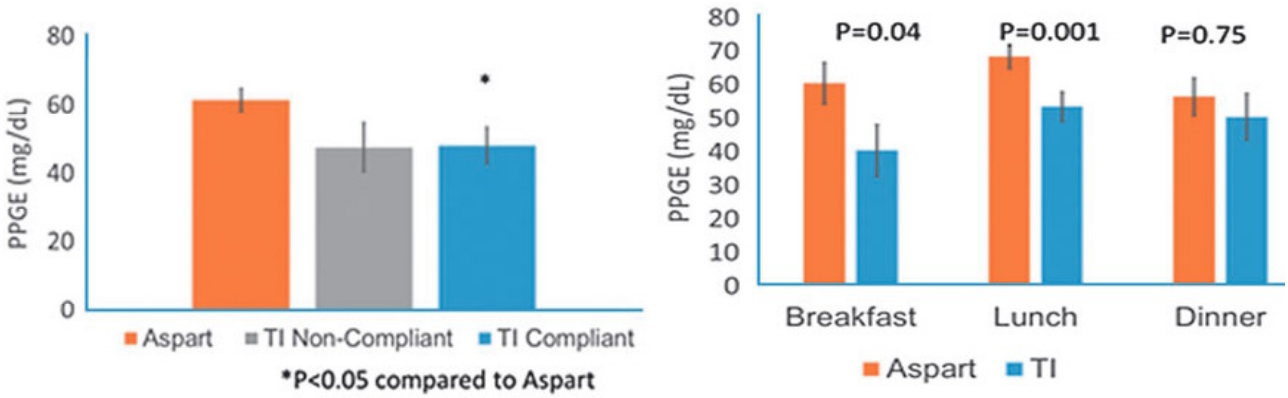
STAT Study: Afrezza associated w/ significantly less hypoglycemia



Source: MannKind

In addition, PPG was significantly lower in the total Afrezza cohort at both 60 and 90 minutes after a meal and PPGE was lower in the Afrezza-compliant group over 1 to 4 hours post-meal (p<0.05). PPGE-control is arguably one of the most telling measures when comparing one mealtime insulin to another as, as the name implies, it's post-meal efficacy that is most important. On this measure Afrezza was not only significantly superior to aspart on average over three meals, but was also superior at both breakfast and lunch (although not dinner).

STAT Study: Afrezza associated with significantly less post-prandial excursions (PPGE)



Source: Halis Kaan Akturk, et al., 2018 Diabetes Tech&Ther

Afrezza patients also did better when it came to weight gain. While aspart patients gained weight, the total Afrezza group actually lost weight (p=0.006). The difference on the weight measure is compelling given that Afrezza patients administered higher prandial doses - which typically, with subcutaneous insulin, will cause overeating due to hypoglycemia, which in- turn results in weight gain.

Key takeways were that Afrezza's rapid onset and short duration allows for supplemental dosing shortly after a meal – something that is considered antithetical to how subcutaneous rapid-insulin therapy is used (given resultant hypoglycemia – and this supplemental dosing significantly increases time-in-range (i.e. reduces hyper and hypoglycemia), reduces post-prandial excursions (which is the true test of a mealtime insulin) and reduces weight gain as compared to subcutaneous insulin. This, in our opinion, provides substantive additional evidence of Afrezza's superior time-action profile as well as bolstering the case that inhaled insulin is indeed a much different class than its subcutaneously administered counterparts.

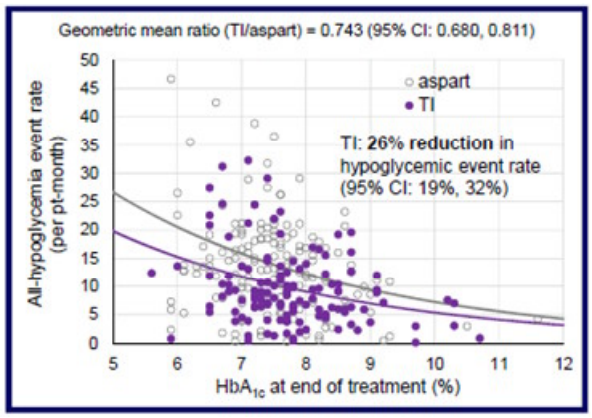
AFFINITY-1 Subset Data Further Supports Afrezza's Superior Hypoglycemia Profile

For background, the AFFINITY studies (AFFINITY-1 in T1D, AFFINITY-2 in T2D) were used as primary support for MNKD's regulatory application seeking FDA approval of Afrezza with use of the Dreamboat inhalers. Earlier in 2018 MNKD presented data (poster session at ADA 78th, June 22 – 26th) from a subset of patients from AFFINITY-1 study.

This subset study evaluated the overall and severity of hypoglycemic event rates in patients treated with Technosphere Insulin (TI, i.e. Afrezza) relative to sc insulin. The results revealed that Afrezza allows for better HbA1c control and significantly lower rates of hypoglycemic. Rates of hypoglycemia associated with Afrezza were 26% lower across all levels of HbA1c. For some patients, HbA1c levels could be reduced by 1.2% from 8% at baseline with no increase in hypoglycemic rates while for others, who were already at or below 7% HbA1c levels, would expect to experience four fewer hypoglycemia events per month.

AFFINITY-1 Subset: Further supports Afrezza superior hypoglycemia profile

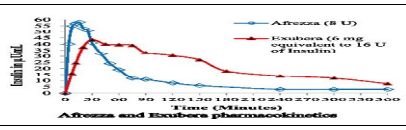
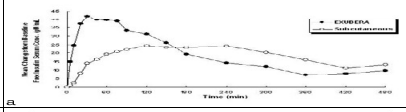
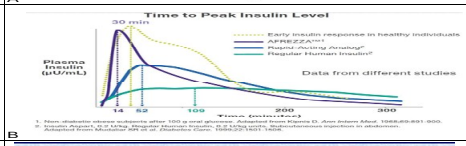
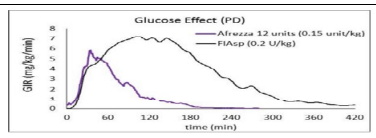
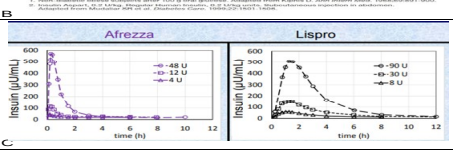
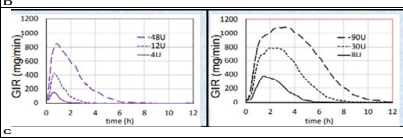
	Parameter	Aspart	TI	*P* value
	N	150	129	
All hypoglycemia	Incidence, n (%)	150 (100)	129 (100)	1
	Events	11,723	6983	<0.001
	Events per patient	78.2	54.1	
Severe hypoglycemia	Incidence, n (%)	47 (31.3)	28 (21.7)	0.071
	Events	127	59	0.114
	Events per patient reporting at least 1 severe hypoglycemic event	2.7	2.1	



Source: Blonde L. et al. MannKind. ADA 78th Poster Presentation

For more information on how Afrezza compares to injected insulins: See our Appendix near the end of this report (which includes a larger version of this chart) where we compare Afrezza to currently available subcutaneously administered insulins, as well as to how Afrezza stacked up against Exubera

Comparison of Rapid-Acting Mealtime Insulins

Company	Drug (Brand Name)	Active Substnce	FDA approval date	Route of admin.	Onset of Action (mins)	Time to Peak (mins)	Duration (hrs)	Comparative PK profile	GIR profile
Mannkind	Afrezzaa	Human Insulin	2015	Inhaled	12 to 15	53	2.5 to 3		
Pfizer	Exubera	Human Insulin	2006	Inhaled	10 to 20	30 to 90	6		
Novo Nordisk	Fiasp	Insulin Aspart, B3 (niacinamide)	2017	Subq (sc)	20	63	5		
Eli Lilly	Humalog	Insulin Lispro	1996	Subq (sc)	15 to 30	30 to 150	3 to 6.5		
Sanofi-Aventis	Apidra	Insulin Glulisine	2004	Subq (sc)	10 to 15	60 to 90	3 to 5		
Novo Nordisk	Novolog	Insulin Aspart	2000	Subq (sc)	10 to 20	40 to 50	3 to 5		

A. J Control Release. 2015 Oct 10;215:25-38
B. http://ocdiabetesconference.org/presentations/bhangoo-research-t1dm-and-t2dm/
C. http://www.mannkindcorp.com/assets/Baughman-2016-TI-displays-earlier-onset-and-shorter-duration-than-insulin-lispro-ADA-100-LB.pdf
a. https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=4e25a881-dfc3-44a2-9ede-49f7443776d8&type=display
b. http://files.shareholder.com/downloads/AMDA-22AJB/5936705050x0x969834/34160268-2B2F-4FBA-ADBA-98310CF45943/MannKind_NobleCon_2018_FINAL.pdf
c. http://www.mannkindcorp.com/assets/Baughman-2016-TI-displays-earlier-onset-and-shorter-duration-than-insulin-lispro-ADA-100-LB.pdf

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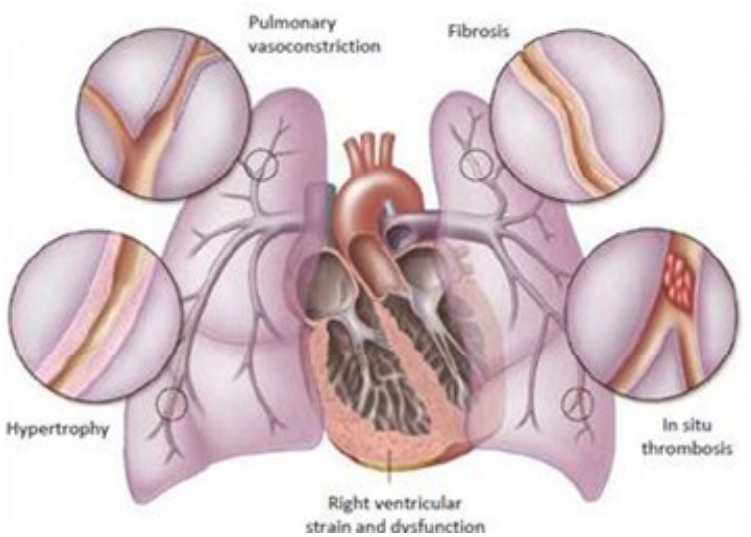
MannKind's Pipeline

Low hanging fruit: TreT

Inhaled treprostinil (Tyvaso), a drug-device combination for the treatment of pulmonary arterial hypertension, was approved by the FDA in 2009 and is the most widely prescribed product for that condition since its launch. United Therapeutics has relentlessly worked on improving the system's design to improve patient compliance. In October 2017, the FDA approved a third-generation device which was designed around feedback from both physicians and patients. Focused on user-friendliness, it has an ergonomic design with single button operation, an intuitive user interface as well as a graphical display that helps patients follow the correct inhalation procedure. The new device also allows patients to keep track of their last treatment and is equipped with an internal, rechargeable battery.

United had significantly strengthened the patent protection surrounding Tyvaso, although some of its U.S. patents expire between November 2018 and December 2028. Since payers encourage patients to use generic versions of branded drugs, United was fending off ANDAs referencing Tyvaso for several years. Eventually, United Therapeutics settled their litigation with Watson Laboratories and granted them rights to manufacture and commercialize the generic version of Tyvaso in the U.S. from 2026 onwards. This allows United to maintain their monopoly over the inhaled treprostinil market through to end of 2025.

Pulmonary Arterial Hypertension (PAH): The CDC describes PAH, a rare, progressive disease, as having high blood pressure in the pulmonary arteries. Under normal conditions, blood flows from the right ventricle of the heart to the lungs for oxygenating blood. The blood pressure in the lungs is much lower than the systolic or diastolic pressure since pulmonary vascular resistance (PVR) is low. However, abnormal changes in the pulmonary arteries such as vasoconstriction, cell proliferation, and thrombosis (platelet activation and aggregation) cause the arterial walls within the lungs to become non-compliant (stiff and narrow). This leads to restrictions in the blood flow to the lungs. The resulting increase in blood pressure in the lungs leads to remodeling of the right ventricle, followed by decreased ability of the heart to pump blood. This results in volume overload, right ventricular adaptation, and death. Multiple factors including heart or lung diseases, metabolic, hematologic, or systemic disorders are associated with PAH. It has been shown that early intervention may be beneficial in improving clinical outcome for PAH patients.



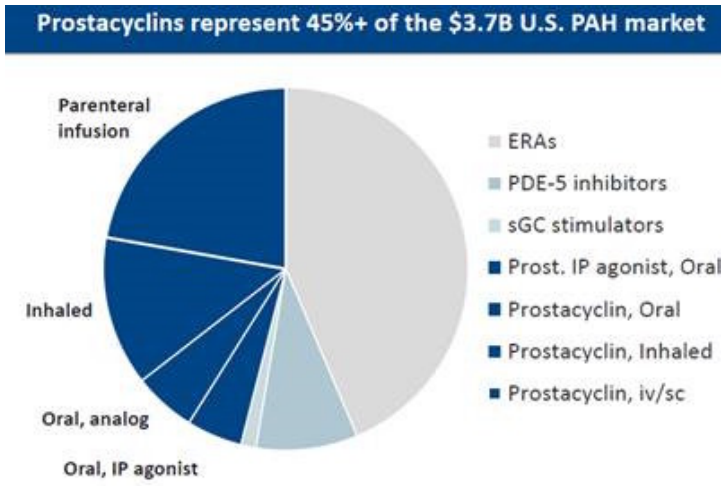
Source: Liquidia August 2018 Presentation

PAH Market size

Despite PAH being categorized as a rare disease, the FDA has granted marketing approval for more than ten drugs to provide multiple therapeutic options for managing the disease. The types of drugs, which address PAH-specific pathways, include

1. endothelin receptor antagonists (ERAs; bosentan, ambrisentan, macitentan),
2. phosphodiesterase type-5 inhibitors (PDE5Is; sildenafil, tadalafil),
3. soluble guanylate cyclase stimulators (sGCs; riociguat),
4. prostacyclins (epoprostenol, iloprost, treprostinil) and
5. prostacyclin receptor agonists (selexipag).

ERAs and PDE5Is are typically recommended for patients classified under WHO patient Class II and III while prostacyclin therapy is generally advised for patients falling under WHO Class II-IV[1,2].



Source: Liquidia August 2018

Role of Prostacyclin:

Prostacyclin (prostaglandin I2) has been identified as a vasodilator, an anti-proliferative agent, and an anti-thrombotic agent. Evidence indicates that prostacyclin is dysregulated (body does not produce sufficient

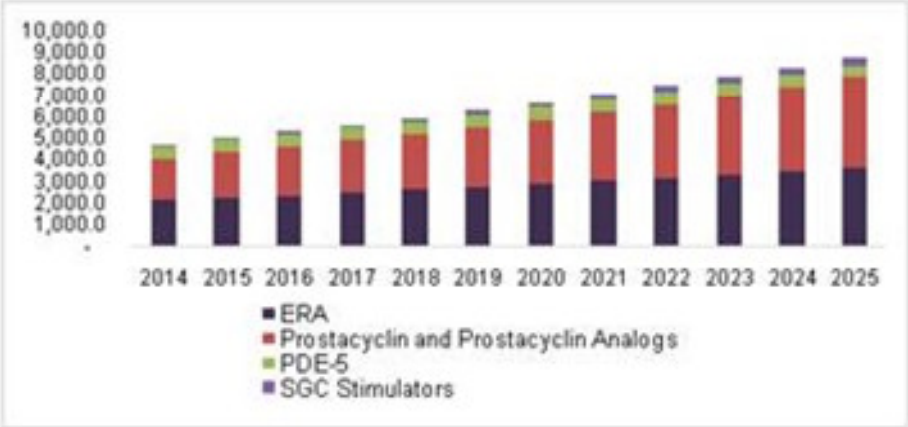
[1] Harrison W. Farber, Wendy Gin-Sing, Practical considerations for therapies targeting the prostacyclin pathway, European Respiratory Review 2016, 25: 418-430;

[2] Zamanian R.T., et al, An observational study of inhaled-treprostinil respiratory-related safety in patients with pulmonary arterial hypertension, Pulmonary Circulation. 2016, 6(3): 329–337.

prostacyclin) in PAH[3]. As mentioned earlier, one of the synthetic analogs of prostacyclin, treprostinil, has been approved by the FDA for the treatment of PAH.

Grand View Research estimates the global PAH market size to be ~$8 billion by 2025. Research conducted by the consulting company, Decision Resources Group, indicated that sales for all major PAH drugs in 2016 amounted to more than $6 billion globally.

Pulmonary Arterial Hypertension market, by drug class, 2014 - 2025 (USD Million)



Source: Grandview Research

Decision Resources Group valued the U.S. market for PAH drug therapies at approximately $4 billion as of 2016. The company also assessed that more than 50% of patients with PAH in the U.S. were prescribed treprostinil (oral, inhaled, and parenteral infusion). Drug therapies approved to treat PAH via the prostacyclin deficient pathway generated close to $2 billion in sales in the U.S. in 2016, of which, treprostinil contributed to the bulk of total sales. The drug Tyvaso (treprostinil inhalation solution), accounted for more than 80% of the U.S. market for PAH inhaled treatments in 2016[4].

Despite having positive risk-benefit profile and a long history of being in the market, prostacyclin analogs have relatively under-performed in this continuously evolving and growing marketplace. One of the reasons for clinical under-use is the requirement for dosage up-titration based on a patient's response to the initial dose. Adding to this hurdle is the idea that higher doses result in greater pain at the injection site when administered subcutaneously.

Is inhaled treprostinil better than traditional (injectable) version?

Inhaled prostacyclin analogs have demonstrated clinical benefits such as decreased frequency in dosing and shorter duration of inhalation. The inhaled drug reaches the target directly, reduces ventilation/perfusion mismatch in the lungs, minimizes systemic hypotension, circumvents site pain/allergic reaction from IV/SC route of administration, and could be potentially used in critical care. However, duration of inhalation and device maintenance, which are time intensive for the patient, have compromised patient compliance and resulted in slower than expected adoption.

Inhaled prostacyclin analog therapies in the market…

Two inhaled formulations of prostacyclin are available in the U.S. Ventavis (inhaled iloprost) has been available since 2005. It uses the I-neb adaptive aerosol delivery system. Ventavis is indicated for patients with PAH with NYHA Functional Class III-IV symptoms. Inhaled iloprost (5µg of prostacyclin analog per breath) has a short half-life (20–30 min) and hemodynamic effect (30 to 60 min) demanding up to nine inhalation exercises /day with a minimum of two hours between doses. This cumbersome procedure combined with the unavoidable break during the night is regarded as the major drawback of inhaled iloprost therapy[5].

Tyvaso (inhaled treprostinil) has been available since 2009. It uses the TD-100 ultrasonic pulmonary delivery device. Tyvaso is indicated for patients with severe PAH who are categorized as WHO functional class IV. Tyvaso

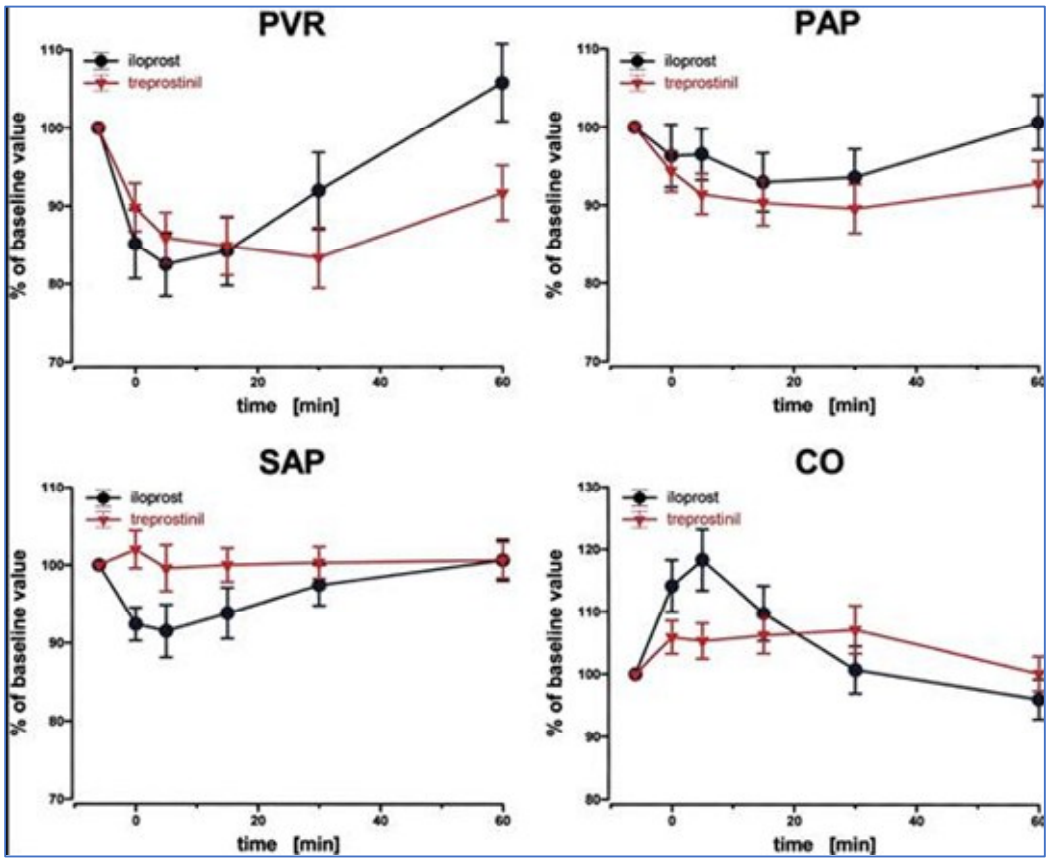
[3] Chan SY, Loscalzo J. Pathogenic Mechanisms of Pulmonary Arterial Hypertension. Journal of molecular and cellular cardiology. 2008;44(1):14-30. doi:10.1016/j.yjmcc.2007.09.006.
[4] Liquidia SEC filings
[5] Newman SP1, Chan HK,In vitro/in vivo comparisons in pulmonary drug delivery, Journal of Aerosol Medicine and Pulmonary Drug Delivery. 2008 Mar;21(1):1-12

offered a more favorable administration exercise with the initial dose being three breaths (18µg), four times daily with a minimum of four hours between doses[6]. Doses up to 60µg could be safely delivered in one single inhalation. Tyvaso has a half-life of approximately 44-52 minutes and hemodynamic effect lasting up to three hours[7].

Clinical studies with inhaled prostacyclin analog therapies for PAH:

- ***Study 1(Iloprost Vs. Treprostinil):*** A randomized, open-label, single-blinded, crossover study with 44 PAH patients was conducted in 2006 in Germany to compare the acute hemodynamic and systemic side effects of inhaled treprostinil with inhaled iloprost at similar doses. Iloprost was inhaled at a concentration of 4µg/ml (6 min inhalation time; n = 44) and treprostinil was inhaled at concentrations of 4µg/ml (6 min inhalation; n = 14), 8µg/ml (6 min inhalation; n = 14) or 16µg/ml (3 min inhalation; n = 16).

The inhalation of both drugs was done using the Optineb ultrasonic nebulizer (Nebutec, Elsenfeld, Germany). Data from the 44 patients who had inhaled both drugs in randomized order, revealed a rapid decrease in PVR and pulmonary arterial pressure (PAP). A more sustained effect on PVR and increase in cardiac output was recorded after treprostinil inhalation. The results revealed a prolonged drug effect of treprostinil compared with iloprost.



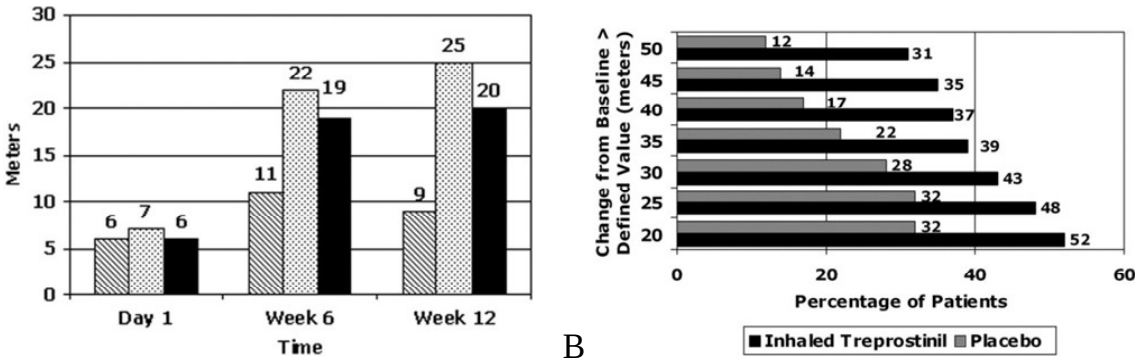
Source: JAMC Volume 48(8), 2006, P1672-1681

- ***Study 2 (TRIUMPH I trial)*****:** In 2007, a double-blind placebo-controlled clinical study was conducted to investigate the efficacy and tolerability of inhaled treprostinil in patients with severe PAH receiving therapy with either bosentan or sildenafil. The primary outcome was the change in 6-minute walk distance from baseline to week 12.

Two hundred thirty-five PAH patients treated with bosentan (70%) or sildenafil were randomized to inhaled treprostinil (up to 54µg) or inhaled placebo 4 times daily. The patients belonged to the New York Heart Association (NYHA) functional class III (98%) or IV with a 6-min walk distance (6MWD) of 200 to 450m.

[6] Tyvaso U.S. package insert
[7] Channick RN, Voswinckel R, Rubin LJ. Inhaled treprostinil: a therapeutic review. Drug Design, Development and Therapy. 2012;6:19-28.

Results indicated that inhaled treprostinil for 12 weeks among patients who remain symptomatic on oral monotherapy was safe and well-tolerated. The primary end point had an H-L between-treatment median difference of 20m. The change in 6MWD improved the exercise capacity as early as week 6. Inhaled treprostinil was beneficial for patients already on oral PAH therapy.



A: Patients on sildenafil (ruled bars),bosentan (dotted bars), all patients (solid bars)

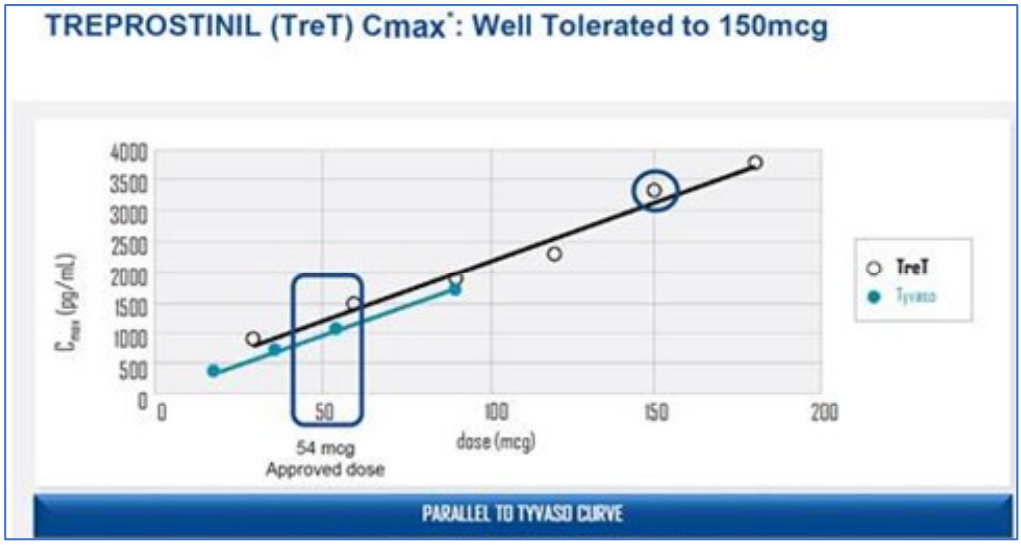
(Source: Journal of the American College of Cardiology, Volume 55(18),2010, P1915-1922)

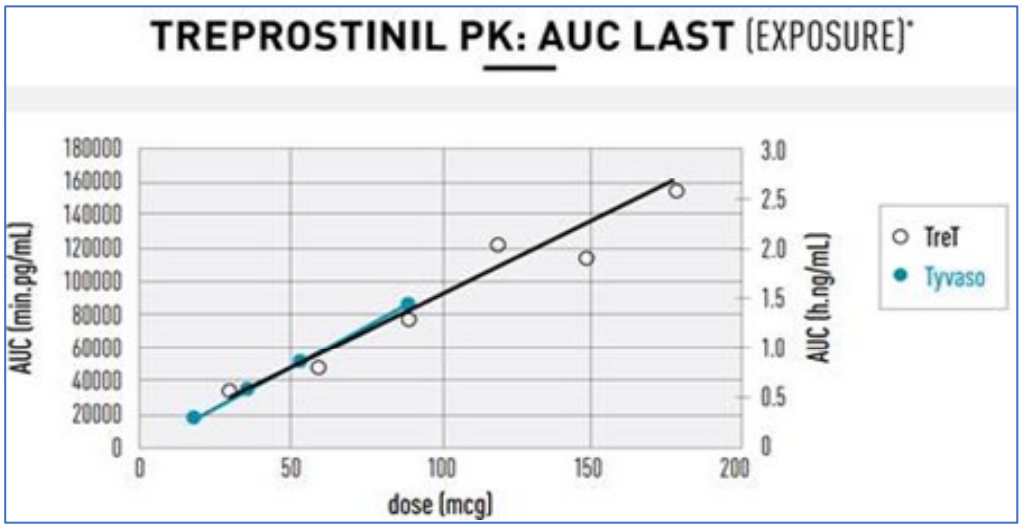
Inhaled treprostinil therapies under development…

MannKind's Technosphere Treprostinil (TreT): Based on the company's Technosphere platform, treprostinil is being developed as a dry powder formulation for PAH patients.

- ***Study 1:*** MannKind investigated the safety, tolerability, and bioavailability of TreT in a Phase 1 single ascending dose study with healthy volunteers. The study aimed to deliver TreT within 1-2 inhalations in less than ten seconds. In March 2018, the single site study enrolled 36 healthy, normal subjects. The volunteers were divided into 6 groups having 6 subjects each. The trial intended to establish the maximum tolerated dose, starting at 30µg and going up to 180µg. Each subject received one dose of TreT during the treatment period. Twelve blood samples were collected from each subject and analyzed for treprostinil.

  The study achieved its primary endpoint of acceptable safety and tolerability. Additionally, TreT closely mimicked the PK profile of Tyvaso. Peak plasma levels of TreT significantly exceeded the corresponding levels of Tyvaso inhalation solution.





Source: MannKind

Liquidia Technologies' LIQ861: LIQ861, a Phase 3 product candidate, is in development by Liquidia Technologies. While MNKD offers a special type of carrier-based formulation for TreT, Liquidia uses PRINT (Particle Replication In Non-wetting Templates) micromoulding technology to formulate its drug candidate. Liquidia has completed investigating the pharmacokinetic (PK) profile of LIQ861 in a single-dose study in rats and dogs and repeat-dose toxicity study in rats.

After consulting with the FDA, the company advanced the candidate directly to a single, pivotal Phase 3 trial (INSPIRE) which is an open-label, multicenter study. Liquidia anticipates reporting this two-week safety data in Q1'19. Liquidia has indicated that they intend to seek approval under the 505(b)(2) pathway and, if all goes to plan, they expect to file an NDA in late-2019.

How is TreT compared to currently available inhaled treprostinil therapies and those under development?

Drug	Ventavis	Tyvaso	LIQ861	TreT
Regulatory Status	2004	2009	Phase 3 - enrolling	Phase 3 - anticipated in 2019
Method of administration	proprietary nebulizer - I-neb AAD	proprietary nebulizer - Tyvaso Inhalation System	DPI	passive DPI - reusable DreamBoat or Single-use Cricket device
Frequency	6-9x	4x	4x	2x
Dose Range (µg)	2.5-5	18-72; recommended 54	25-150	90-180
Inhalations/dose	1-2	9	1-2	1-2
Supplies	inhalation system (10+ accessories)	inhalation system (10+ accessories)	inhaler + blister pack + cleaning brush	inhaler + blister pack
Device Replacement	no daily, weekly, or monthly scheduled part replacement	every 2 years	disposable	every year/disposable
Picture				

For PAH sufferers, reducing the frequency of inhalation and duration as well as eliminating the treatment-gap during night time could improve patient compliance and QoL. From the chart, TreT promises delivery of large dose with fewer inhalations in shorter time as compared to Ventavis, Tyvaso or LIQ861. We think this speaks to the benefits of the Technosphere technology – specifically the size and aerodynamic shape of Technosphere microparticles and MNKD's inhaler technology which allows for fast and efficient travel through the air and into the lungs. And with more than 90% of the microparticles in the respiratory range (i.e. >0.5 µm and <5.8 µm), Technosphere technology is optimized for deep inhalation into, and uniform dispersion throughout, the lungs. Additionally, Technosphere pH-activated powders are quickly dissolved in the interstitial fluid immediately after inhalation and coming into contact with the characteristically neutral pH conditions of the lung. This results in ultra-rapid absorption into the circulatory system, avoidance of peripheral circulatory degradation and high bioavailability.

The path forward for TreT

In January 2018, MannKind filed an IND with the FDA for TreT. MannKind planned to use the existing safety data of the component API to reduce Phase 3 requirements for a pivotal safety and efficacy trial and a pivotal bioequivalency trial. The regulatory submission in the U.S. was expected to utilize the 505(b)(2) pathway.

However, in September 2018, MNKD signed a worldwide exclusive licensing and collaboration agreement for TreT with United Therapeutics. Per terms of the agreement, United Therapeutics will be responsible for global development, regulatory and commercial activities while MannKind will manufacture clinical and initial commercial supplies of TreT at its manufacturing facility in Danbury, Connecticut. Long-term commercial supplies are expected to be manufactured by United Therapeutics.

MNKD received an upfront payment of $45 million from United Therapeutics in October 2018. An additional $50 million will be awarded contingent on MNKD achieving certain development milestones. Further, MannKind will also receive low double-digit royalties on net sales of the product. MNKD also entered into a research agreement with United Therapeutics to develop other candidates for which it received $10M upfront. MNKD is eligible to receive $30M upon achieving developmental milestones as well as double-digit royalties on net sales of the product.

Why collaborate with United Therapeutics?

Since its inception in 1996, United Therapeutics has been focused on developing prostacyclin analog therapy for PAH. The company's PAH universe comprises of prostacyclin analogs that can be administered orally, intravenously, subcutaneously or inhaled by patients categorized as WHO Group 1 to improve exercise capacity and quality of life. Further, with Tyvaso's patent expirations (two in November 2018 and one in 2028), resulting in subsequent decline in revenue, United Therapeutics will have an appropriate replacement in its pipeline with TreT.



Source: United Therapeutics

United Therapeutics and MannKind are hardly strangers to each other. United Therapeutics and Alfred Mann, former Chairman and CEO of MannKind Corp., have a long-standing relationship. It began when United Therapeutics introduced Remodulin therapy that administers treprostinil through an infusion pump called the MiniMed 407c, developed by Al Mann.

Next in line: Dronabinol

Chemotherapy-induced nausea and vomiting (CINV) is one of the adverse effects in 60%-80% of cancer patients undergoing therapy. Several market research studies estimate the size of the global CINV market to be more than $2 billion.

Receptor Life Sciences is developing an inhaled version of cannabinoid for chemo patients dealing with nausea and vomiting. As the table below summarizes, cannabinoids in their natural form promise to provide better relief and offer advantages that their synthetic analogs fail to accomplish. The dry powder formulation of inhalable dronabinol has a rapid onset of action (< 5 min), superior bioavailability and non-inferior safety profile as compared with marketed oral synthetics such as Marinol and Syndros. Marinol is a synthetic cannabinoid (dronabinol) which is associated with certain unpleasant and potentially serious side-effects such as tachycardia and dizziness.

Receptor Life Sciences Update:
THC (Dronabinol): Target Product Profile

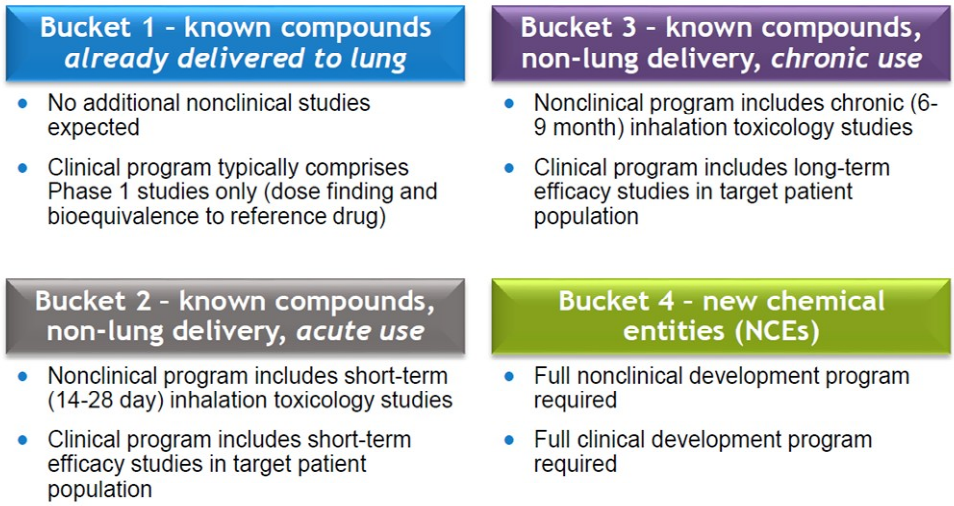
	Marinol	Syndros	RLS / MNKD Dronabinol powder
Indication	CINV and appetite stimulation in AIDS	CINV and appetite stimulation in AIDS	CINV and appetite stimulation in AIDS
Onset of action	0.5 – 1.0 hours (T_{max} fasted = 2.5 hrs)	Onset not reported (T_{max} fasted = 1.0 hrs)	Ultra-rapid (~5 mins)
Food effect	Considerable (T_{max} fed = 5.6 hrs)	Considerable (T_{max} fed = 7.7 hrs)	No food effect
Bioavailability	10 – 20 %	10 – 20 %	Superior to comparators
Safety	• Tachycardia • Dizziness • Euphoria	Non-inferior to Marinol	Non-inferior to Marinol
Storage	Refrigerated	Refrigerated until opened; discard after 28 days at room temperature	Refrigerated during transport; superior room temperature stability
Formulation	Gelatin Capsule	Liquid Solution	Inhaled Dry Powder
CSA Schedule	CIII	CII	?

Source: MannKind

In 2016 MannKind signed a clinical collaboration with Receptor Life Sciences to develop inhaled therapeutic products to treat chronic pain, neurologic diseases and inflammatory disorders. As per the agreement, MannKind

is eligible to receive development and commercialization milestones of up to $102 million[8] as well as mid-single to low double-digit royalties on net sales of the product. RLS's website includes a picture and description of MannKind's inhaler device and cartridges as the inhalation system for their cannabinoid candidates. In late-October 2018, Receptor raised $29 million in its first round of financing to initiate IND-enabling studies related to dry powdered formulation of cannabinoids in the U.S.

Other potential pipeline programs...



Source: MannKind

MannKind compiled a broad list of compounds that the company might pursue as potential drug candidates. Management is open to partnering opportunities to further the development of drug candidates towards the clinic. The development programs are categorized into different buckets as shown in the above graphic;

1. Known compounds already delivered to the lung,
2. Non-pulmonary delivery acute use,
3. Non-pulmonary delivery chronic use and
4. New chemical entities (NCEs).

Of this list, MannKind has a patent on Technosphere sumatriptan, an inhalable version of a triptan, a drug that is commonly used in patients suffering from migraine headaches. Preclinical studies have demonstrated Technosphere sumatriptan's rapid acting profile. Currently, triptans are the first line of defense against acute migraine. However, a study[9] conducted on approximately 15,000 migraine sufferers revealed high rates of discontinuity of oral, injectable, and nasal forms of triptan due to adverse side effects including nausea, vomiting and dizziness. This indicates a significant unmet medical need in the treatment and management of acute migraine. This drug candidate could be next in line in MannKind's pipeline.

Manufacturing

The Technosphere technology is unique and warranted a novel process for manufacturing which could only be realized in a new facility. The company spent approximately $160M to design and build a ~300ksf facility in Danbury, CT in 2008.

The engineering team that worked with MannKind developed a novel way to modify the cryopelletizer to flash freeze the Technosphere insulin suspension in order to make uniform dry pellets. This technology promises better quality of drugs produced by bulk lypholization. Several innovations emerged from the expert team that helped reduce process time and cost as well as improve consistency in manufacturing. For its innovation in pharmaceutical engineering, MannKind's facility received International Society for Pharmaceutical Engineering's

[8] http://investors.mannkindcorp.com/news-releases/news-release-details/mannkind-enters-collaboration-and-license-agreement

[9] Triptan Use and Discontinuation in a Representative Sample of Persons With Migraine: Results From Migraine in America Symptoms and Treatment (MAST) Study

(ISPE) 2010 Facility of the Year awards in two categories - Equipment Innovation and Process Innovation Categories.

We had the opportunity to visit the state-of-the-art manufacturing facility at Danbury and received a comprehensive tour. We also met with MannKind's leadership team and their employees who were involved in preparing the products.

The facility has two separate sections:

- One section is dedicated for manufacturing Technosphere particles, then making TI and packaging it for bulk storage
- The other section is where cartridges are filled with predefined doses combined with fillers, packaged into blister packs and assembled as kits for sale

OUTLOOK and VALUATION

We think the general investor sentiment implied by MNKD's current market capitalization is underestimating the long-term potential of Afrezza and is mistakenly categorizing it as a perennial niche product. Our case for why we believe Afrezza will likely grow to significant double-digit market share and represent formidable competition to traditional exogenous insulin therapy hinges on several catalysts…

- **Afrezza's label** recently updated to include language of its rapid onset of action, specifically that it gets into the blood within ~1 minute and reaches measurable effect in 12 minutes. Update also includes new table describing optimal titration. As determining 'correct' injected insulin-to-Afrezza conversion and lack of physician awareness of Afrezza's superior time-action-profile have been cited as impediments to uptake, this label update has the potential to facilitate steepening sales growth

- **New published data** such as from the STAT study should bolster MNKD's direct-to-physician awareness efforts. Management has commented that physicians largely lack understanding of the significant clinical and quality-of-life benefits of Afrezza's time-action-profile. That has undoubtedly stunted adoption and utilization. Expect additional manuscripts to be published in the near term as MNKD looks to further leverage clinical evidence to support the case of Afrezza's superiority to injected insulin

- **DTC campaigns**. MNKD has recently tested new DTC programs in certain markets. If conducted effectively we think this marketing channel can drive patient demand - key will be to prompt insulin users to ask their doctors about Afrezza as physician inertia to move away from injected insulin can be significant

- **Patient stickiness** will also be key and with the updated labeling providing more hand-holding as to adjusting dosing, along with the outcomes of STAT, demonstrating benefits of doing so, we think stickiness will benefit. DTC campaigns could be an important tool in that regard. Repeat Rx increased an average of 75% through the first nine months of 2018, which also indicates patients who try Afrezza, remain on it

- **Cash and debt position have greatly improved.** Total debt has been cut by nearly $40M over the last 12 months. Liquidity benefitted from recent $45M upfront payment from UTHR related to TreT and another $10M for research unrelated to the agreement. MNKD expects to receive $25M of milestones in 2019 and another $25M in 2020 from the United agreement. The improved debt and liquidity position should provide MNKD with added flexibility to put resources behind Afrezza marketing – such as expanding the direct sales force and advertising, including TV and digital

- **Payers loosening their grip.** Requisite prior authorization has undoubtedly been a headwind. Based on our due diligence and conversations, we believe the reimbursement picture is evolving to MNKD's benefit. Lawsuits against Eli Lily, Novo Nordisk and Sanofi claiming unfair trade practices as a result of collusive insulin price hikes appears to have made payers and pharmacy benefit managers somewhat skittish in continuing to protect (our words and our conclusions) the big three injected insulin makers. If that is indeed the case, MNKD could be a major benefactor as eliminating prior authorizations would essentially put Afrezza pari passu with the likes of Humalog, Novolog and Apidra. In addition, management mentioned on the Q3 call in early November that managed-care contract resets for 2019 should reduce the amount of rebates they pay – which should increase the gross-to-net Afrezza sales ratio (and also benefit margins)

- **Patient testimonials.** While we typically would not cite patient feedback as a catalyst towards increasing adoption, we think for Afrezza it is warranted. Users have documented the ability to change their lifestyle and overall QoL with Afrezza in ways that were not possible with injected insulin. Such as dosing as they take their first bite of a meal or even afterwards. The relative lack of hypoglycemia appears to have significantly changed the way diabetics can live. This may be the most compelling illustration of the difference between injected insulin and inhaled insulin. While there is little to no difference between when, how and how much Novolog vs Humalog an insulin user will take and little to no difference in how they feel afterwards, there is a difference between injected insulin and Afrezza on these same parameters. Patients' desire to have access to Afrezza may eventually prove to be one of the most potent catalysst to driving payer access and by extension, adoption of MNKD's product

- **Pediatric indication.** MKND is pursuing a pediatric indication for Afrezza that, if successful, would expand its total market opportunity

- **International commercialization.** MKND has regulatory filings for Afrezza in-progress in Mexico and Canada. They are also pursuing commercialization in Brazil and India. While we do not anticipate international

commercialization to generate anywhere near the profit potential as the U.S., they can be important from a manufacturing capacity utilization standpoint (i.e. margins) as well as for pass-through demand to help meet MNKD's insulin purchase agreement

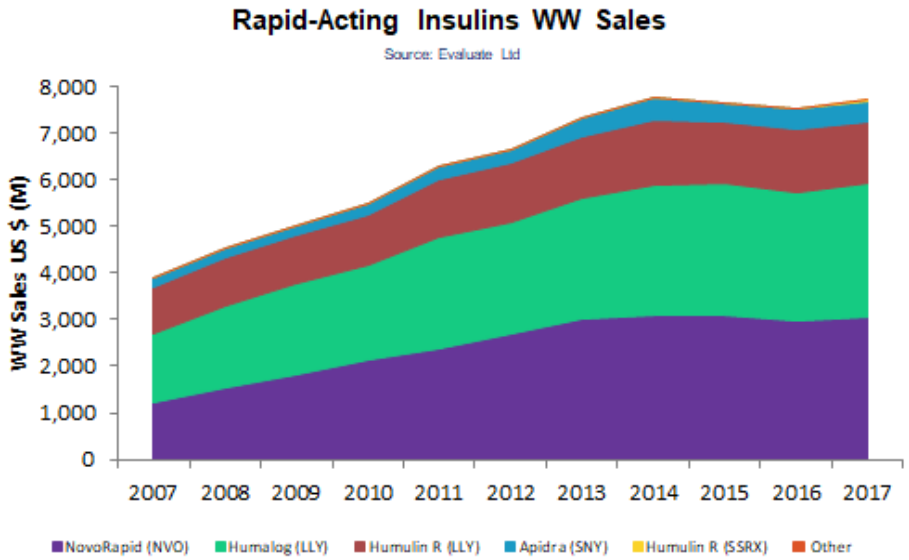
- **Collaborations increase shots on goal, add credibility to Technosphere.** R&D collaborations have been a significant source of capital for MNKD but they also add pipeline shots-on-goal. Such an approach could help mitigate the risk of significant idle capacity of the facility. Tyvaso was the most prescribed medication for PAH and generated more than $370 million in net sales in 2017 for United Therapeutics. Along with TreT, RLS' cannabinoid program for inhalable Dronabinol could be a fast-moving development program. Management is actively evaluating additional opportunities. These partnerships also further bolster the credibility of the Technosphere platform technology and, by extension, the differences between injected insulin and Afrezza

Outlook - Afrezza

An aggressive attempt to create maximum awareness of Afrezza and drive physician and patient adoption is underway. Based on the aforementioned catalysts, we anticipate a steeper rate of sales growth during 2019. Effectiveness will be measured by patient wins, new and repeat prescription growth, and declining gross-to-net revenue percentage. But it will also be measured by efficiency - that is revenue growing at a faster rate than that of SG&A. The company is closely monitoring market uptake, making necessary adjustments and fine tuning their sales, marketing and reimbursement strategies – which we think results in improvement in operating leverage. We model gross margin to widen and suspect that this may expand further with favorable evolvement of the reimbursement picture.

In an effort to increase their reach, over the last year Mankind has beefed up its online presence through social media, optimized the size of their sales force, launched targeted TV commercials and attended conferences. Efficient sales and marketing will require an ability to pick-their-spots and grab low hanging fruit. MannKind has effectively utilized targeted DTC campaigns in the past, although widespread use is not something that we anticipate. Management has also indicated that productivity gains from the existing sales force, as opposed to significant expansion of the sales team, is a priority – which we think also supports anticipated efficient revenue growth going into 2019. The marketing strategy also includes focusing on areas of the country which offer the most profitable return.

Growth in Afrezza production volume and collaborative activities, including those related to the United Therapeutics and RLS agreements should reduce current overcapacity of the company's Danbury, CT manufacturing facility and 'soften' the impact of fixed expenses flowing through the income statement. We also anticipate that the company will continue to develop other potential candidates in its pipeline.

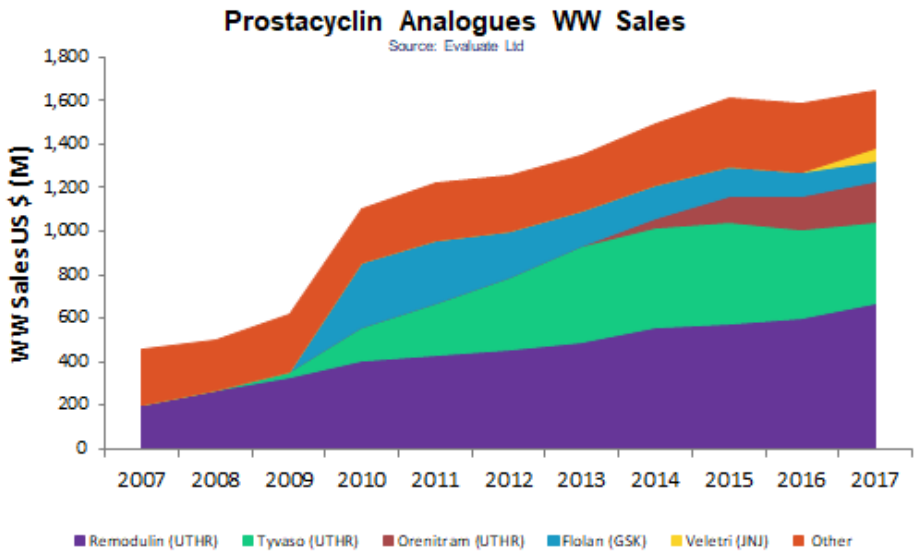


Outlook – TreT

Prostacyclin analogs account for ~45% of the U.S. PAH market, which is valued at approximately $3.5 billion. Inhaled prostacyclin analogs account for about 11% of the total. United's Tyvaso, approved in 2009, currently

generates about $370M in annual sales. Liquidia's experience, including regulatory pathway, with their LIQ861 candidate presents UTHR with a potential template to follow as they finalize next-steps for late-stage development of TreT. Following a 505(b)(2) FDA pathway, LIQ861 advanced directly from a Phase 1 to a single, pivotal Phase 3 trial. Enrollment of LIQ861's pivotal trial commenced in March 2018 and, per the most recent investor presentation (Nov 2018), Liquidia anticipates making an NDA filing in late-2019.

Assuming UTHR can follow a similar pathway and timeline, it is conceivable that TreT could enter Phase 3 testing sometime next year and, if all goes to plan, be the subject of an NDA 505(b)(2) filing in late-2020 and launch shortly thereafter. Our DCF, which incorporates a 60% chance of development and regulatory success, assumes MNKD receives $25M in 2019, $25M in 2020 and, upon launch of the product, 12% royalties on net sales. All assumed milestones and royalties are currently risk-adjusted by 60% - which would likely increase (i.e. risk of failure would be assumed to decrease) with further substantive development progress.

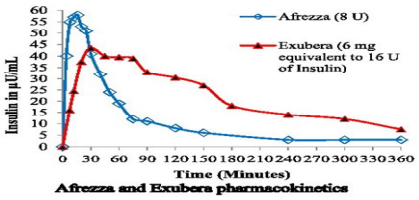
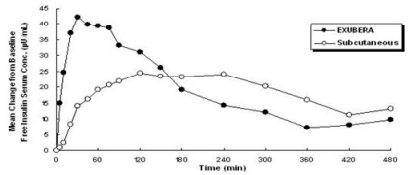
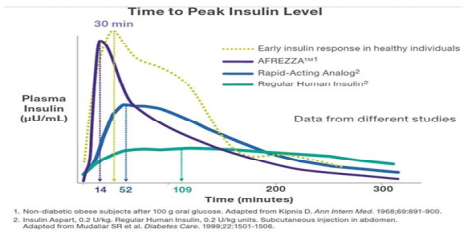
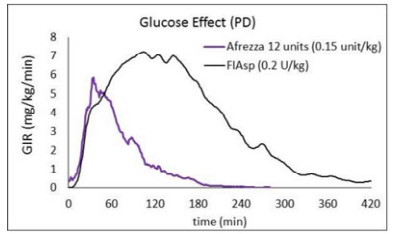
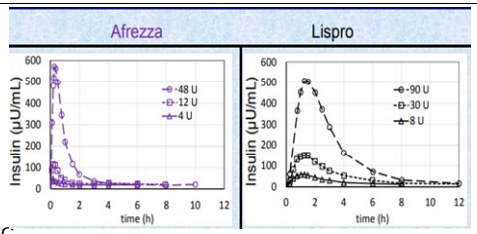
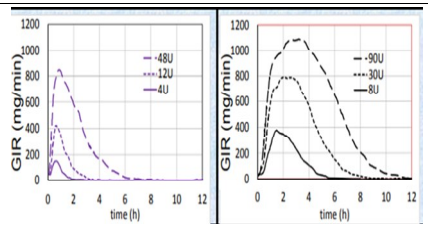
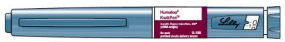


We use a sum-of-the-parts methodology to value MNKD, applying a P/S multiple to the Afrezza portion of the business while using DCF to value the UTHR collaboration related to TreT. Our model and valuation are subject to updating, including incorporating other collaboration candidates, if and when we feel there is enough information with which to base reasonably-confident assumptions (including related to RLS) – which could provide upside to our current target price. We note that, given current lack of clarity on how and when upfront and milestone payments will be recognized on the income statement, that as a placeholder and for DCF-valuation purposes, we assume for now that there are no income statement implications. So, while this assumption implies any cash payments remain on the balance sheet, they are included in our DCF model.

LLY and NVO trade at an average of approximately 5.5x forward sales. Given MNKD's much more rapid estimated percentage revenue growth, we apply that same multiple to our forecasted 2021 Afrezza sales of $106M, which values the Afrezza portion at approximately $3.65/share. Our 10-year DCF uses a 15% discount and values the TreT collaboration at approximately $98M, or ~$0.60/share (which is subject to our 40% risk-of-failure discount). **Our sum-of-the-parts calculation puts total value of the company at ~$4.25/share.**

APPENDIX

Comparison of Rapid-Acting Mealtime Insulins

Company	Drug (Brand Name)	Active Substnce	FDA approval date	Route of admin.	Onset of Action (mins)	Time to Peak (mins)	Duration (hrs)	Comparative PK profile	GIR profile	Picture
Mannkind	Afrezzaa	Human Insulin	2015	Inhaled	12 to 15	53	2.5 to 3			
Pfizer	Exubera	Human Insulin	2006	Inhaled	10 to 20	30 to 90	6	 A	 a	
Novo Nordisk	Fiasp	Insulin Aspart, B3 (niacinamide)	2017	Subq (sc)	20	63	5	 B	 b	
Eli Lilly	Humalog	Insulin Lispro	1996	Subq (sc)	15 to 30	30 to 150	3 to 6.5	 C	 c	
Sanofi-Aventis	Apidra	Insulin Glulisine	2004	Subq (sc)	10 to 15	60 to 90	3 to 5			
Novo Nordisk	Novolog	Insulin Aspart	2000	Subq (sc)	10 to 20	40 to 50	3 to 5			

A. JControl Release. 2015 Oct 10;215:25-38
B. http://ocdiabetesconference.org/presentations/bhangoo-research-t1dm-and-t2dm/
C. http://www.mannkindcorp.com/assets/Baughman-2016-TI-displays-earlier-onset-and-shorter-duration-than-insulin-lispro-ADA-100-LB.pdf
a. https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=4e25a881-dfc3-44a2-9ede-49f7443776d8&type=display
b. http://files.shareholder.com/downloads/AMDA-22AIJ9/5936705050x0x969834/34160268-2B2F-4FBA-ADBA-98310CF45943/MannKind_NobleCon_2018_FINAL.pdf
c. http://www.mannkindcorp.com/assets/Baughman-2016-TI-displays-earlier-onset-and-shorter-duration-than-insulin-lispro-ADA-100-LB.pdf

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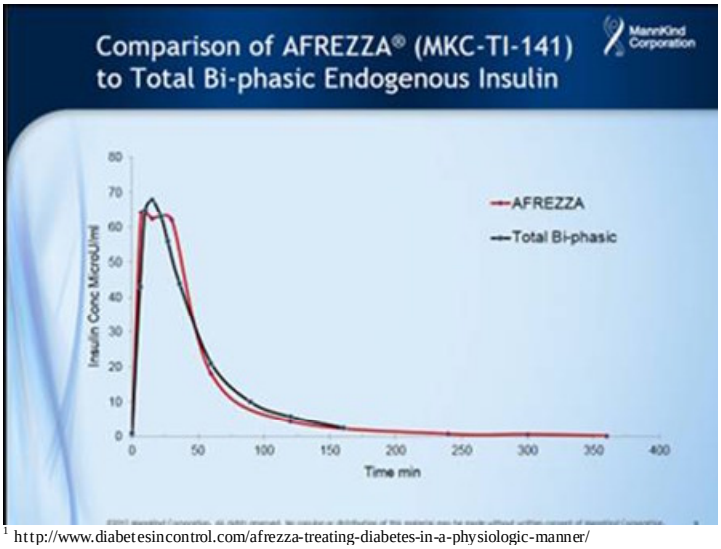
Afrezza vs Exubera

For those who remember Exubera (rapid-acting insulin), the name is synonymous with inhaled insulin. Exubera, much like RAIAs, was approved for the treatment of adults with T1D and T2D for controlling postprandial hyperglycemia. Inhaled insulin therapy is still overshadowed by the dark clouds that Exubera left behind when Pfizer withdrew the drug in 2007 due to under-performance in sales. In the following paragraphs, we elaborate on how Afrezza differs from other RAIAs as well as Exubera in its clinical performance, outcomes and cost.

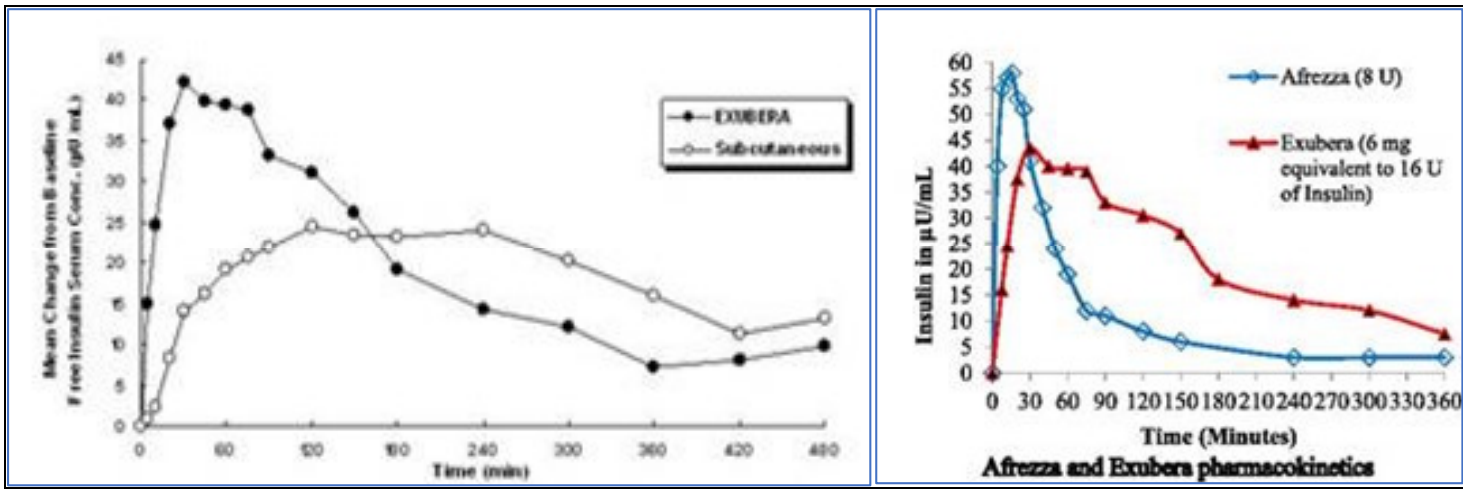
Pharmacokinetic profile

Afrezza exhibits a linear, dose-related PK profile analogous to that of endogenous insulin. It dissolves very quickly upon inhalation and consequently has an ultra-rapid-acting profile. It passes into the bloodstream in less than one minute, affording it a relatively rapid onset of action (12 to15 minutes), and reaches peak plasma concentration in ~53 minutes. Moreover, its short duration, at approximately two hours, means that there is much less risk of hypoglycemia as compared to subcutaneous insulin.



[1] http://www.diabetesincontrol.com/afrezza-treating-diabetes-in-a-physiologic-manner/

In comparison, Exubera had a relatively slow onset of action (10 to 20 minutes), took 30 to 90 minutes to reach peak concentration and remained at elevated serum levels for two hours or longer. An insulin therapy delivered through the pulmonary route taken at meal time should offer quick onset of action to enable tighter glycemic control. Afrezza appears to perform better than Exubera in this respect.



In healthy individuals, endogenous insulin tightly controls the concentration of glucose circulating in the blood. Insulin is secreted in the blood only if glucose concentrations reach beyond a specific threshold. The metabolic response following a meal shows that insulin is secreted bi-phasically; initially there is a spike in insulin which is followed by insulin secretion in response to circulating glucose levels.

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A randomized, open label, 3-way cross over study in T2D patients[10] was conducted by MannKind to assess the effect of TI on endogenous glucose production. Specifically, researchers wanted to know if TI was able to suppress glucose much more swiftly than sc insulin or Exubera. Figure A shows blood glucose levels over time for the three treatments. The chart shows that TI controlled blood glucose much earlier (up to two hours post dosing) than Exubera or sc insulin. Beyond four hours of dosing, more than ten subjects in the Exubera and sc groups and five in the TI group required supplemental dose of insulin to maintain optimal blood glucose levels. The graph in Figure B reveals that endogenous glucose production was suppressed to a greater proportion by TI within an hour of dosing as compared to Exubera or sc. Treatment with TI is also associated with less weight gain and lower incidence of hypoglycemia as compared to sc insulin.

Fig A.

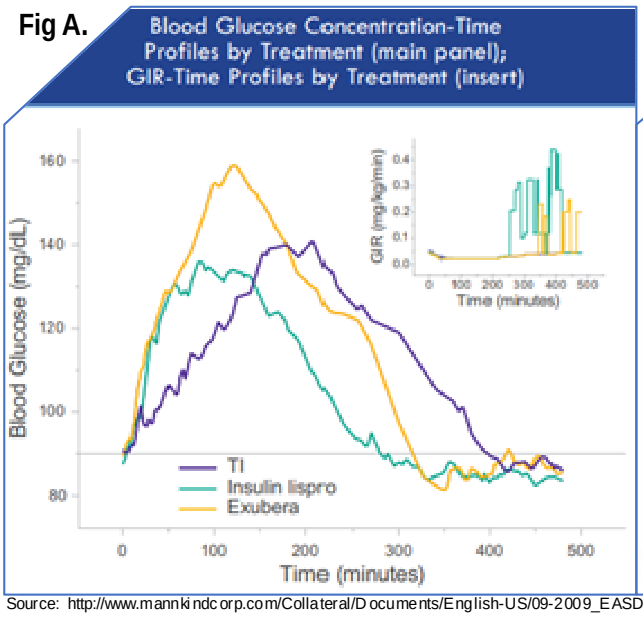
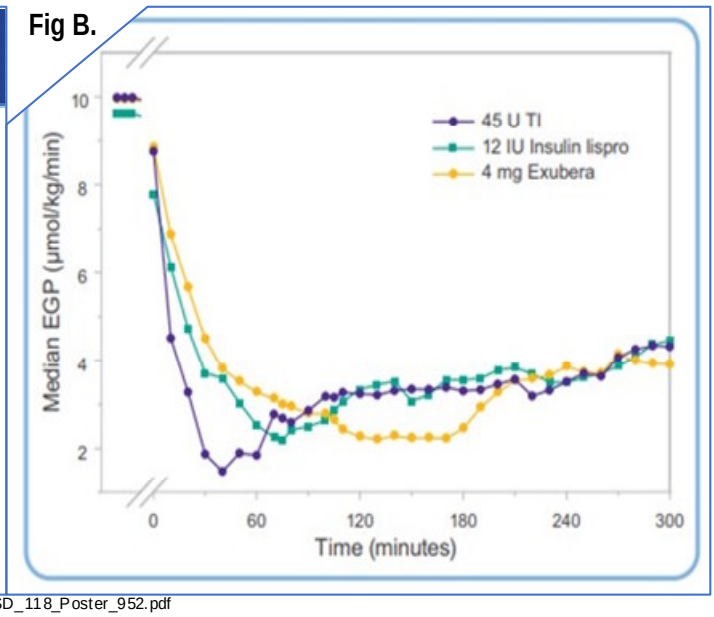


Fig B.



Source: http://www.mannkindcorp.com/Collateral/Documents/English-US/09-2009_EASD_118_Poster_952.pdf

Pharmacodynamics

In a 12-week study conducted involving T1D and T2D patients, results revealed that the change in HbA1c levels in patients treated with Exubera is comparable to those administered sc insulin[11]. A subset of the AFFINITY 1 trial evaluated the overall and severe hypoglycemic event rates in patients treated with TI relative to sc insulin. The results revealed that TI allows for greater HbA1c reduction and the hypoglycemic event rates with TI were 26% lower across all levels of HbA1c. For some patients, HbA1c levels could be reduced by 1.2% from 8% at baseline with no increase in hypoglycemic rates while for others, who were already at or below 7% HbA1c levels, would expect to experience four fewer hypoglycemia events per month.

Label

Exubera ran into safety concerns when six out of 4,740 and one out of 4,292 patients developed lung cancer in a clinical trial conducted in 2008[12]. However, the cases that developed lung cancer had a prior history of smoking. Consequently, it was difficult to determine whether the development of lung cancer was related to the use of Exubera. It warranted a larger clinical trial to demonstrate statistically conclusive results. Pfizer did not conduct any further studies and the drug was soon removed from the market. The safety issue concerning Exubera affected the risk-benefit profile of any and all inhaled insulins.

Interestingly, FDA acknowledged that they had no substantive evidence that Exubera had any association with or increased the risk of lung cancer. This is evident in Exubera's FDA review document. In fact, not only does FDA note that they had found no evidence of lung cancer risk but that they also had seen no evidence that the inhaled insulin increases risk of any long-term lung disease. It is clear that FDA was erring on the side of caution when they required contraindications for lung disease and warnings of possible cancer and other lung conditions. This overzealous caution is notable in this sentence from the document, "As a pulmonologist, I have been quite skeptical of the safety of this product from early in its development. However, despite the extensive work done by Pfizer [on Exubera], including long-term follow-up with PFTs and HRCTs in patients without underlying lung

[10] Source: http://www.mannkindcorp.com/Collateral/Documents/English-US/09-2009_EASD_118_Poster_952.pdf
[11] Patient satisfaction and glycemic control after 1 year with inhaled insulin (Exubera) in patients with type 1 or type 2 diabetes. Diabetes Care. 2004;27:1318-1323.
[12] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/022472Orig1s000MedR.pdf

disease, little evidence of a significant, progressive lung effect has resulted. Further, the animal data are quite reassuring." In other words, since this reviewer (a pulmonologist) had a preconceived idea that inhaled insulin would cause long-term lung disease (including, potentially cancer) he advocated for the contraindications and black box warning – despite zero evidence of any association. Unfortunately for MannKind, Afrezza has been considered guilty by association – as there is, similarly, no evidence that Afrezza increases the risk of lung cancer or long-term lung dysfunction.

Afrezza's package insert has a boxed warning that it is contraindicated in patients with chronic lung disease (asthma or chronic obstructive pulmonary disease (COPD)). Clinical studies involving Afrezza had four people develop lung cancer of which two smoked cigarettes. This is actually lower than the rate of lung cancer among the general public. A study[13][14] conducted with MannKind's MedTone inhaler uniformly distributed TI throughout the lungs. More than 70% of insulin and 55% of its carrying molecule were cleared from the lungs within four hours of administration. The total amount of these two components in the lungs after 12 hours of dosing was found to be less than 0.1%. TI's rapid elimination may be responsible for its relatively strong safety profile.

Both Afrezza's and Exubera's labels state a requirement for pulmonary function testing before starting therapy in patients and then at intervals afterwards. In 2017, Afrezza's label was updated for language related to its time-action profile and recommendations on dose titrations, providing additional information around flexibility in dosing regimen.

[13] http://www.mannkindcorp.com/Collateral/Documents/English-US/11-2009_EASD_007-122_Poster_955.pdf
[14] Pharm Res. 2011 Sep;28(9):2157-64.

MannKind Financial Model

	2017 A	Q1A	Q2A	Q3A	Q4E	2018 E	2019 E	2020 E
Product sales	$9.2	$3.4	$3.8	$4.4	$4.6	$16.2	$35.0	$70.4
YOY Growth	385.1%	184.4%	142.4%	121.5%	3.6%	75.9%	116.6%	101.1%
Collaboration revenue	$0.3	$0.1	$0.1	$0.1	$0.1	$0.3	$0.3	$0.3
YOY Growth	-99.9%	0.0%	38.1%	32.3%	61.3%	32.8%	-9.6%	0.0%
Other revenue	$2.3	$0.0	$0.1	$0.0	$0.0	$0.1	$0.1	$0.1
YOY Growth	156.5%	-100.0%	-90.4%	-	-100.0%	-97.7%	88.7%	0.0%
Revenue	$11.7	$3.5	$3.9	$4.5	$4.7	$16.6	$35.4	$70.8
YOY Growth	-93.3%	15.2%	80.0%	118.7%	4.4%	41.0%	114.0%	99.9%
Cost of Goods Sold	$17.2	$4.0	$5.1	$5.3	$5.4	$19.8	$31.2	$58.1
Cost of collaboration rev	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Income	($5.5)	($0.5)	($1.2)	($0.8)	($0.7)	($3.3)	$4.3	$12.7
Gross Margin	-46.7%	-15.7%	-30.9%	-18.7%	-15.0%	-19.9%	12.0%	18.0%
R&D	$14.1	$2.6	$3.0	$2.0	$2.7	$10.4	$18.4	$22.2
R&D % sales	120.2%	76.3%	76.2%	45.7%	57.1%	62.5%	51.9%	31.3%
SG&A	$75.0	$20.6	$21.7	$19.4	$24.2	$86.0	$103.5	$140.2
SG&A % Sales	638.2%	595.0%	558.2%	434.0%	512.0%	519.2%	292.2%	198.0%
Operating Income	($94.6)	($23.8)	($25.9)	($22.3)	($27.6)	($99.6)	($117.7)	($149.7)
Operating Margin	-	-	-	-	-	-	-	-
Total Other Income, net	$1.6	($6.6)	$3.5	$0.7	($0.5)	($2.9)	$5.7	$0.2
Pre-Tax Income	($117.3)	($30.4)	($22.4)	($24.2)	($27.1)	($102.2)	($123.4)	($149.9)
Taxes (benefit)	$0.1	$0.0	$0.2	$0.0	$0.0	$0.2	$0.0	$0.0
Tax Rate	0.0%	0.0%	-1.1%	0.0%	0.0%	-0.2%	0.0%	0.0%
Net Income	($117.3)	($30.4)	($22.7)	($24.2)	($27.1)	($102.4)	($123.4)	($149.9)
Net Margin	-999.0%	-876.9%	-582.5%	-540.8%	-573.5%	-618.8%	-348.2%	-211.6%
EPS	($1.13)	($0.25)	($0.16)	($0.16)	($0.17)	($0.71)	($0.63)	($0.68)
YOY Growth		-	-	-	-			
Diluted Shares O/S	104.2	120.9	140.1	153.6	160.0	143.6	195.0	220.0

Brian Marckx, CFA / Anita Dushyanth, PhD

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LEADERSHIP

Management -

Michael Castagna
CEO and Director
Michael Castagna is Chief Executive Officer and serves on the Board of Directors for MannKind Corporation. Dr. Castagna has over 20 years of experience in healthcare, pharmaceutical, biotech and specialty pharmacy industries. He joined MannKind from Amgen, Inc., where he spent over three years as Vice President, Global Commercial Lead for a portfolio of nine biosimilar drugs, and Vice President, Global Lifecycle Management. Prior to Amgen, Dr. Castagna, was Executive Director of Bristol-Myers Squibb's Immunology franchise, where he served as co-lead to relaunch Orencia IV and launch Orencia SC, both rheumatoid arthritis drugs. Before BMS, Dr. Castagna was with Sandoz (Novartis) as Vice President and Division Head for Biopharmaceuticals, North America, where he established the US Biologics Business Unit and relaunched its lead product, Omnitrope, a human growth hormone. Prior to Sandoz, Dr. Castagna held a variety of positions with EMD (Merck), Serono, Pharmasset and DuPont Pharmaceuticals. Dr. Castagna serves on the board of directors of Pet Partners headquartered in Bellevue, Washington. Dr. Castagna received his Bachelors of Science – Pharmacy degree from Philadelphia College of Pharmacy, his Doctor of Pharmacy from Massachusetts College of Pharmacy, and his MBA from the Wharton School of Business at the University of Pennsylvania.

Patrick McCauley
Commercial Officer
Patrick McCauley is the Chief Commercial Officer for MannKind Corporation. Mr. McCauley has over 25 years of experience in the biopharmaceutical industry. He has spent the last twelve years at Astellas Pharma in a series of senior sales and compliance leadership roles of increasing responsibility. Prior to Astellas, Mr. McCauley was a member of the U.S. commercialization team and held a sales leadership role with Yamanouchi Pharma before the merger of Yamanouchi and Fujisawa Pharma to create Astellas in 2005. Before Astellas/Yamanouchi, Mr. McCauley spent thirteen years with DuPont Pharmaceuticals and one year with Bristol-Myers Squibb which acquired DuPont Pharmaceuticals in 2001. At DuPont and Bristol-Myers Squibb, Mr. McCauley held a series of leadership roles across the sales, contracting and pricing, and clinical areas. Throughout his various career moves, Mr. McCauley has developed deep commercial expertise serving both specialty and primary care healthcare providers. He received a MBA degree from the Kellogg School of Management at Northwestern University, a JD from the South Texas College of Law, and a BA in Economics from the University of Notre Dame.

David Kendall
Chief Medical Officer
David M. Kendall, MD, is the Chief Medical Officer for MannKind Corporation. In this role, he is responsible for leading MannKind's scientific research, clinical development, regulatory, and medical affairs activity. Dr. Kendall's career includes over 30 years of experience in diabetes and metabolism research, clinical management, research, and policy advocacy. Most recently, he served as Research Physician and Vice President of Global Medical Affairs for Lilly Diabetes, and led all medical affairs activities and guided research and development strategy across multiple geographies. During this time, Dr. Kendall worked to re-establish Lilly Diabetes as a world class medical organization — and added to his extensive experience with both injected and mealtime insulins, as well as devices and continuous glucose monitors. Prior to Eli Lilly, Dr. Kendall served as Chief Scientific and Medical Officer at the American Diabetes Association, where he was responsible for all medical affairs, medical education, research, outcomes, and medical policy activities. Earlier in his career, Dr. Kendall served as Medical Director at the International Diabetes Center, and the Park Nicollet Clinic, as well as at Amylin Pharmaceuticals. Dr. Kendall received his M.D. and completed his Post Graduate Medical Training at the University of Minnesota, and earned a B.A. in Biology from St. Olaf College.

Joespeh Kocinsky
Chief Technology Officer
Joseph Kocinsky is Corporate Vice President of Technical Operations and Chief Technology Officer. Mr. Kocinsky has over 28 years experience in the pharmaceutical industry in technical operations and product development. Prior to joining MannKind in 2003, he held a variety of technical and management positions with increased responsibility at Schering-Plough. Mr. Kocinsky holds a bachelor's degree in Chemical Engineering and a master's degree in Biomedical Engineering from New Jersey Institute of Technology and a master's degree in Business Administration from Seton Hall University.

Garrett Ingram
Chief Marketing Officer
Garrett Ingram is the Chief Marketing Officer for MannKind Corporation. Garrett comes to MannKind with a significant depth of experience in the biopharmaceutical industry and in diabetes marketing and market access. Most recently, Garrett served as Senior Vice President, Managed Markets for Dexcom, where she was responsible for developing long-term health outcomes and market access strategy for their portfolio of products. Before joining Dexcom, Garrett served as U.S. Country Head of Market Access at Sanofi, where she was responsible for all market access activities across four U.S. Business Units: Diabetes & Cardiovascular, General Medicines, Sanofi Genzyme Specialty Care, and Sanofi Pasteur. Prior to this, she held the position of Vice President, Market Access Strategy at Bristol Myers Squibb (BMS), where she led the access, reimbursement, patient affordability and emerging customer strategy teams across the portfolio of diabetes, rheumatoid arthritis, cardiovascular, oncology, immunology, neuroscience, and pipeline assets. Prior to BMS, she held various leadership roles for the commercial and medical organizations at Novo Nordisk, including Senior/Executive Director and Assistant Vice President, where she oversaw managed markets strategy, pricing and contracting, and health economics and outcomes research. Garrett received a Bachelor of Science degree from East Carolina University and a Master of Education in Community and Occupational Programs from the University of South Carolina.

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Steven Binder
Chief Financial Officer
Steven Binder is the Chief Financial Officer for MannKind Corporation. Mr. Binder has over 25 years of experience in the healthcare industry. He most recently spent four years at Stryker Corporation, a leading global medical technology company, where he served as Vice President and Chief Financial Officer for Stryker's International Group, based in Singapore. Prior to Stryker, Mr. Binder served in a series of senior leadership roles at Bristol-Myers Squibb Company, an innovative global biopharmaceutical company. His last four positions at BMS were Vice President, Finance roles over different geographic operating units: United States (2012-2013), Europe (2008-2011), AsiaPacific (2005-2007), and Japan (2003-2005). Prior to his international experience, Mr. Binder served in three senior leadership roles for Oncology Therapeutics Network, a U.S. based independent subsidiary of BMS: Vice President, Strategic Development (2001-2003), Vice President, Customer Operations (2000-2001), and Chief Financial Officer (1997-2000). Before OTN, Mr. Binder progressed through three finance and accounting roles for BMS Worldwide Medicines Group after joining the company in 1992. Before BMS, he worked for Deloitte & Touche in a series of auditing roles with increasing responsibility over an eight year period beginning in 1984. Mr. Binder received a B.S. degree in Accounting and Business Administration from Muhlenberg College and is a Certified Public Accountant.

Rose Alinaya
Senior Vice President
Rose Alinaya is the Senior Vice President for MannKind Corporation. Ms. Alinaya has been our Vice President, Finance since March 2011 after serving as our Corporate Controller since June 2003 with responsibility for finance, accounting, tax, treasury, investor relations and risk management. Ms. Alinaya began her career at Deloitte & Touche LLP, graduating from California State University, Northridge. She is also a member of the American Institute of Certified Public Accountants and a member of the California Society of Certified Public Accountants.

David B. Thompson
General Counsel
David B. Thomson, PhD, JD, has been General Counsel and Corporate Secretary of MannKind since January 2002. Prior to joining MannKind, he practiced corporate/commercial and securities law at the Toronto law firm of Davies Ward Phillips & Vineberg LLP. Earlier in his career, Dr. Thomson was a post-doctoral fellow at the Rockefeller University in New York. Dr. Thomson obtained his bachelor's degree, master's degree and Ph.D. degree from Queens University and obtained his J.D. degree from the University of Toronto.

Courtney Barton
Chief Compliance Officer
Courtney Barton, CCEP, CIPP (US/E) is our Chief Compliance and Privacy Officer. Ms. Barton joined MannKind Corporation in March 2017 and is responsible for leading all aspects of our corporate and healthcare compliance programs. Ms. Barton brings broad, global compliance and ethics expertise to the role, having begun her compliance and ethics career at Winn-Dixie Stores, Incorporated before transitioning to roles in the pharmaceutical and medical device sector with Bausch + Lomb, Allergan, KYTHERA (Allergan) and Anacor (Pfizer). She has also held positions with Merrill Lynch and Janus, including an international appointment. A graduate of Syracuse University, Ms. Barton holds Bachelor's degrees in Political Science and International Relations and is a Certified Compliance and Ethics Professional (CCEP) and Certified Information Privacy Professional (CIPP US/E).

Stuart A. Tross
Chief People and Workplace Officer
Stuart A. Tross, PhD, is MannKind's Chief People and Workplace Officer, with responsibilities for Human Resources, Information Technology, Corporate Communications and Office Facilities. Dr. Tross joined MannKind in 2016 with extensive experience in the life sciences industry. From 2006 to 2016 he served in roles of increasing responsibility at Amgen, the last three years as Senior Vice President and Chief Human Resources Officer responsible for Human Resources and Security on a global basis. From 1998 to 2006 he served in a series of leadership roles at Bristol-Myers Squibb, the last three years as Vice President and Global Head of Human Resources for Mead Johnson Company. Stuart received a B.S. degree from Cornell University and M.S. and Ph.D. degrees in Industrial-Organizational Psychology from the Georgia Institute of Technology.

Board of Directors –

Kent Kresa
Chairman
Kent Kresa is Chairman of the Board. Mr. Kresa has been a director of MannKind since June 2004 and was named Lead Director in November 2011 until he was named Chairman of the Board in February 2016. Mr. Kresa is Chairman Emeritus of Northrop Grumman Corporation, having previously served as its Chairman and Chief Executive Officer. Mr. Kresa also served on the boards of General Motors Company, Avery Dennison Corporation (including as Chairman), and Fluor Corporation. Mr. Kresa has been a member of the Caltech board of Trustees since 1994, and he also serves on the boards of several non-profit organizations and universities. As a graduate of Massachusetts Institute of Technology, he received a B.S. in 1959, an M.S. in 1961, and an E.A.A. in 1966, all in aeronautics and astronautics.

Michael Castagna
(bio above)

Ronald J. Consiglio

Ronald J. Consiglio has been one of MannKind's directors since October 2003. Since 1999, Mr. Consiglio has been the managing director of Synergy Trading, a securities-trading partnership. From 1999 to 2001, Mr. Consiglio was Executive Vice President and Chief Financial Officer of Trading Edge, Inc., a national automated bond-trading firm. From January 1993 to 1998 Mr. Consiglio served as Chief Executive Officer of Angeles Mortgage Investment Trust, a publicly traded Real Estate Investment Trust. His prior experience includes serving as Senior Vice President and Chief Financial Officer of Cantor Fitzgerald & Co. and as a member of its board of directors. Mr. Consiglio has served as a member of the board of trustees for the Metropolitan West Funds since 2003. Mr. Consiglio is a certified public accountant and holds a bachelor's degree in accounting from California State University at Northridge.

Michael A. Friedman
Michael A. Friedman, M.D. has been one of our MannKind's directors since December 2003. In 2014, Dr. Friedman completed a decade of service as the President and Chief Executive Officer of the City of Hope National Medical Center. Previously, from September 2001 until April 2003, Dr. Friedman held the position of Senior Vice President of Research and Development, Medical and Public Policy, for Pharmacia Corporation and, from July 1999 until September 2001, was a senior vice president of Searle, a subsidiary of Monsanto Company. From 1995 until June 1999, Dr. Friedman served as Deputy Commissioner for Operations for the Food and Drug Administration, and was Acting Commissioner and Lead Deputy Commissioner from 1997 to 1998. He joined the board of Celgene Corporation in February 2011 and the board of Smith & Nephew plc in April 2013. Dr. Friedman received a Bachelor of Arts degree, magna cum laude, from Tulane University, New Orleans, Louisiana, and a doctorate in medicine from the University of Texas, Southwestern Medical School.

David H. MacCallum
David H. MacCallum has been one of MannKind's directors since June 2004. Since 2002, Mr. MacCallum has served as the Managing Partner of Outer Islands Capital, a hedge fund specializing in health care investments. From June 1999 until November 2001, he was Global Head of Health Care investment banking for Salomon Smith Barney, part of Citigroup, a financial institution. Prior to joining Salomon Smith Barney, he was Executive Vice President and Head of the Health Care group at ING Barings Furman Selz LLC, an investment banking firm and subsidiary of ING Group, a Dutch financial institution, from April 1998 to June 1999. Prior to that, Mr. MacCallum formed the Life Sciences group at UBS Securities, an investment banking firm, where he was Managing Director and Global Head of Life Sciences from May 1994 to April 1998. Before joining UBS Securities, he built the health care practice at Hambrecht & Quist, an investment banking firm, where he was Head of Health Care and Co-Head of Investment Banking. From 2005 to October 2010, Mr. MacCallum served as a director of Zymogenetics, Inc. From 2002 to 2008, he served as a director of Vital Signs, Inc. Mr. MacCallum received an A. B. degree from Brown University and an M.B.A. degree from New York University. He is a Chartered Financial Analyst.

Christine Mundkur
Christine Mundkur has been one of MannKind's directors since November 2018. Ms. Mundkur most recently served as chief executive officer and the non-voting chairman of the board of directors for Impopharma Inc., a developer of complex formulations focused on inhalation pharmaceutical products. While at Impopharma, Ms. Mundkur led the transition of the company from a successful clinical research organization into a generic pharmaceutical inhalation development company. Her work included the internal development and filing of Abbreviated New Drug Applications of spray and inhalation products. Ms. Mundkur also held leadership positions as president and chief executive office of the US Division and head of commercial operations for North America for Sandoz, Inc. Earlier, she served as chief executive officer of Barr Laboratories, Inc., where she started her career as quality and regulatory counsel. In addition, Ms. Mundkur served as a strategic consultant advising several clients on global pharmaceutical business strategies. Ms. Mundkur holds a J.D. from the St. Louis University School of Law and received her B.S. degree in chemistry from St. Louis University.

Henry L. Nordhoff
Henry L. Nordhoff has been one of MannKind's directors since March 2005. He has served as a director of BioTime, Inc. since June 2013 and as a director of Asterias Biotherapeutics, Inc. since October 2013. Mr. Nordhoff retired as Chairman of the Board of Gen-Probe Incorporated, a clinical diagnostic and blood screening company, at the end of 2011, after serving as its Chairman since September 2002. He also served as Chief Executive Officer and President of Gen-Probe from July 1994 until May 2009. Prior to joining Gen-Probe, he was President and Chief Executive Officer of TargeTech, Inc., a gene therapy company that was merged into Immune Response Corporation. Prior to that, Mr. Nordhoff was at Pfizer, Inc. in senior positions in Brussels, Seoul, Tokyo and New York. He received a B.A. in international relations and political economy from Johns Hopkins University and an M.B.A. from Columbia University.

James S. Shannon
James S. Shannon, M.D., MRCP (UK) rejoined MannKind's board in May 2015 after previously serving as a director from February 2010 until April 2012. From May 2012 until his retirement in April 2015, Dr. Shannon was the Chief Medical Officer of GlaxoSmithKline. He formerly held the position of Global Head of Pharma Development at Novartis AG, based in Basel, Switzerland from 2005 until 2008. After joining Sandoz in 1994 as Head of Drug Regulatory Affairs, Dr. Shannon led of the Integration Office for R&D overseeing the creation of the Novartis R&D groups from those of Ciba-Geigy Ltd and Sandoz. Following the merger he was appointed Head of the Cardiovascular Strategic Team and subsequently became Global Head of Project Management before being appointed Global Head of Clinical Development and Medical Affairs in 1999, a position that he held until 2005 when he was appointed to Head Pharma Development. Between 2008 and joining GSK, Dr. Shannon served on the boards of a number of companies, including Biotie, Circassia, Crucell, Endocyte and MannKind. He also sat on the board of Cerimon Pharmaceuticals where he held the position of interim Chief Executive Officer and President from January 2009 until April 2010. He first entered the pharmaceutical industry in 1987 joining Sterling Winthrop Inc., working initially in Europe and subsequently in the USA, where he held positions of increasing responsibility in the management of research and development ultimately serving as Senior Vice-President, Clinical Development. Dr. Shannon is trained in Medicine and Cardiology. He received his undergraduate and postgraduate degrees at Queen's University of Belfast and is a Member of the Royal College of Physicians (UK).

HISTORICAL STOCK PRICE



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