



White Paper on Afrezza Insulin

A 12-month Study

The product analysis that has led to the proposal
of a new treatment paradigm for Type 1 and Type 2 diabetes.

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Introduction

The purpose of this White Paper is to report Vdex' findings in its study of Afrezza, an FDA-approved, inhaled, prandial insulin product manufactured by MannKind Corporation. Specifically, Vdex conducted numerous studies over a 12-month period to understand various attributes of Afrezza, to help define the best use of the product, and to understand the best practices to be followed in prescribing or recommending the product. As a result of what we have learned, Vdex is recommending a new treatment paradigm for what is the world's most prevalent disease, and also one of the most expensive to treat. We encourage others to perform their own follow-on testing to add to the knowledge base about Afrezza.

These studies were designed for internal use only and DO NOT purport to meet the standards of FDA clinical trials. Nevertheless, Vdex finds the results highly probative.

Vdex has chosen to release this White Paper publicly due to the need for better therapies to control the exploding disease of diabetes. The level of care for people with diabetes in the US is in need of significant improvement. While over the past decade or so there has developed a profusion of medications to treat the disease, the level of care seems to be relatively unchanged, if not declining.

Disclaimer

All readers should be aware that some of the people associated with Vdex, who also participated in some of the studies, are shareholders of MannKind Corporation. None works at, or is compensated by, MannKind Corporation, however. **We present this disclaimer so readers will be aware of the potential for bias in the results presented.** Vdex receives no compensation for prescribing Afrezza from any source, and no compensation from MannKind Corporation for its research or conclusions, nor has anyone associated with Vdex ever received any compensation from MannKind. We were neither guided, nor advised by MannKind Corporation in our studies, and the company was completely unaware that we had even conducted such studies. As stated above, these studies were performed SOLELY for Vdex' internal use.

This report will lack some of the rigors of peer-reviewed articles published in medical journals, but that is not its purpose. Due to reports that the FDA-required label of Afrezza is highly misleading of its actual risks and benefits, and owing to Vdex' interest in offering state-of-the-art diabetes care, it was our desire to "learn for ourselves" the truth about the product. If we were going to prescribe it, we were going to understand it.

Some of our studies were purely observational. We prescribed the drug and monitored the results that patients achieved. From those initial observations, we designed tests to further understand various aspects of the product. We DO NOT attempt here to fully explain how this drug works. It is for others to detail the precise mechanism of action. We sought to understand WHAT the drug does, not necessarily HOW it does it. We will hypothesize about the HOW to the extent we feel comfortable, but we encourage further study by others to completely explain our observations.

Elements of Evaluation

In our evaluation of Afrezza, we focused on the following key points: safety, efficacy, relative utility, and usage guidelines. Safety was our first point of concern given that diabetes is a self-managed disease. Further, insulin has a deserved reputation in the medical community as being potentially dangerous, sometimes deadly. It is the reason that the diabetes treatment protocols call for use of insulin only late in the disease process after patients have sometimes suffered severe, even permanent, dysfunction.

Afrezza is insulin, and upon learning this, many providers pigeon-hole the product on that basis. Yet, most professional organizations recommend earlier use of insulin to control the disease. MannKind Corporation and many other advocates contend, though the FDA clinical data does not support, a claim of greater safety with Afrezza. Our purpose was to investigate this for ourselves.

Efficacy is, of course, an obvious issue to examine. We wanted to evaluate efficacy both in the absolute sense of reducing circulating blood glucose levels, and in the relative sense as compared to other glucose lowering therapies currently in use.

We also wanted to study the use of Afrezza to understand the practical realities impacting patients' use of the product and physician prescribing thereof.

Finally, our goal was to understand where, based upon the factors above, Afrezza fits within the physician's diabetes treatment armamentarium. ADA protocols currently call for the use of insulin after patients reach a persistent A1c of 9 or above. Such patients are severely uncontrolled and may have already suffered permanent damage. We wondered if it were possible to make greater use of Afrezza to better treat patients earlier in their disease. We also sought to provide guidance to Vdex physicians who would be using the product. With the public release of this paper, we now share that guidance with other physicians desiring to add Afrezza to their practices.

As a result of our investigation, we are compelled to recommend a new treatment paradigm for diabetes. Old ideas die hard, especially in medicine. But, there is a point when the body of knowledge becomes so substantial that it can no longer be ignored. Nor can it ethically or morally be ignored when lives are at stake. As measured by HbA1c, diabetes is less effectively managed today than in years past. This is not acceptable, and treatment necessarily needs to change.

Clearly, a different approach to the treatment of diabetes is called for. The tried and true, the conventional, hasn't worked. It is time for blunt, honest, clear-headed, and creative thinking about this problem. We hope this report stimulates discussion and contributes to a better solution.

Hypoglycemia

With all diabetes treatments, safety assumes greater importance than with most other diseases. Diabetes is self-managed, and mostly a permanent disease. Patients take medication often multiple times per day under all sorts of conditions, yet rarely under direct medical supervision. They are bound to make mistakes in their use of any medication. Therefore, it is essential that any medication used has as broad a safety margin as possible.

There are different elements affecting the issue of safety. For example, how easy is it to make a mistake with a particular medication, what is the degree of damage or impairment resulting from that mistake, and how is easy is it to correct that mistake after it is made. Ideally, a medication would be difficult to misuse, and if misused, would produce little impairment, and any impairment would be easily corrected.

Our main concern was overdosing of Afrezza and producing hypoglycemia, by far the greatest concern with any use of insulin. Since Afrezza is bio-identical and not an insulin analog, and because its pharmacokinetic/pharmacodynamic (PK/PD) profile nearly perfectly replicates normal pancreatic function, our belief was that it would be difficult to produce hypoglycemia. We reasoned further that due to the PK/PD profile, communication between the pancreas and liver would be improved such that the liver would work to counteract low blood glucose levels with the release of hepatic glucose when needed. In effect, the liver would regain its normal function of working harmoniously with the pancreas to balance and stabilize blood glucose levels.

With injected insulin, the breakdown in communication between pancreas and liver is the source of the fears of hypoglycemia. It appears that the liver needs an early spike of insulin, the so-called First Phase insulin response, to be in proper communication with the liver. That spike of insulin signals the liver. We know that injected insulin DOES NOT produce an early spike.

Study #1 – General Patient Observation

In the course of Vdex' treatment we have followed 30 randomly selected patients of different ethnicities, genders, ages (including juveniles) and different types (both 1 & 2), as well as different stages of disease (early and late), mildly controlled to severely uncontrolled. We have yet to see a single case of severe hypoglycemia. In fact, we saw less hypoglycemia overall as patients' blood glucose levels flattened and stabilized. We have treated both insulin naïve and insulin dependent patients, patients with reasonable control (A1c of 6.8) and severely uncontrolled (A1c of 14). We have treated patients at low doses (4 units at dinner only) and high doses (30 units at three meals for 100 units in a day).

We strongly recommended the use of continuous glucose monitors (CGM) initially in all patients, but not all opted to use the devices. From their CGM readings we saw a very consistent pattern. Patients' blood glucose levels flattened, the highs weren't as high and the lows weren't as low. In other words, **we saw lowered HbA1c readings AND less hypoglycemia AT THE SAME TIME.**

Figures 1. – 3. below serve to make the point well. The first illustrates typical, non-diabetic glucose levels as measured on a CGM. The second shows CGM tracings for typical insulin-dependent diabetic blood sugar levels, and the third shows what can be achieved on Afrezza. While not all patients can achieve the level of control reflected in the third graph, **ALL AFREZZA USERS THAT WE STUDIED SHOWED FLATTENED CURVES** such as is illustrated here.

NON-DIABETIC BLOOD SUGAR LEVELS

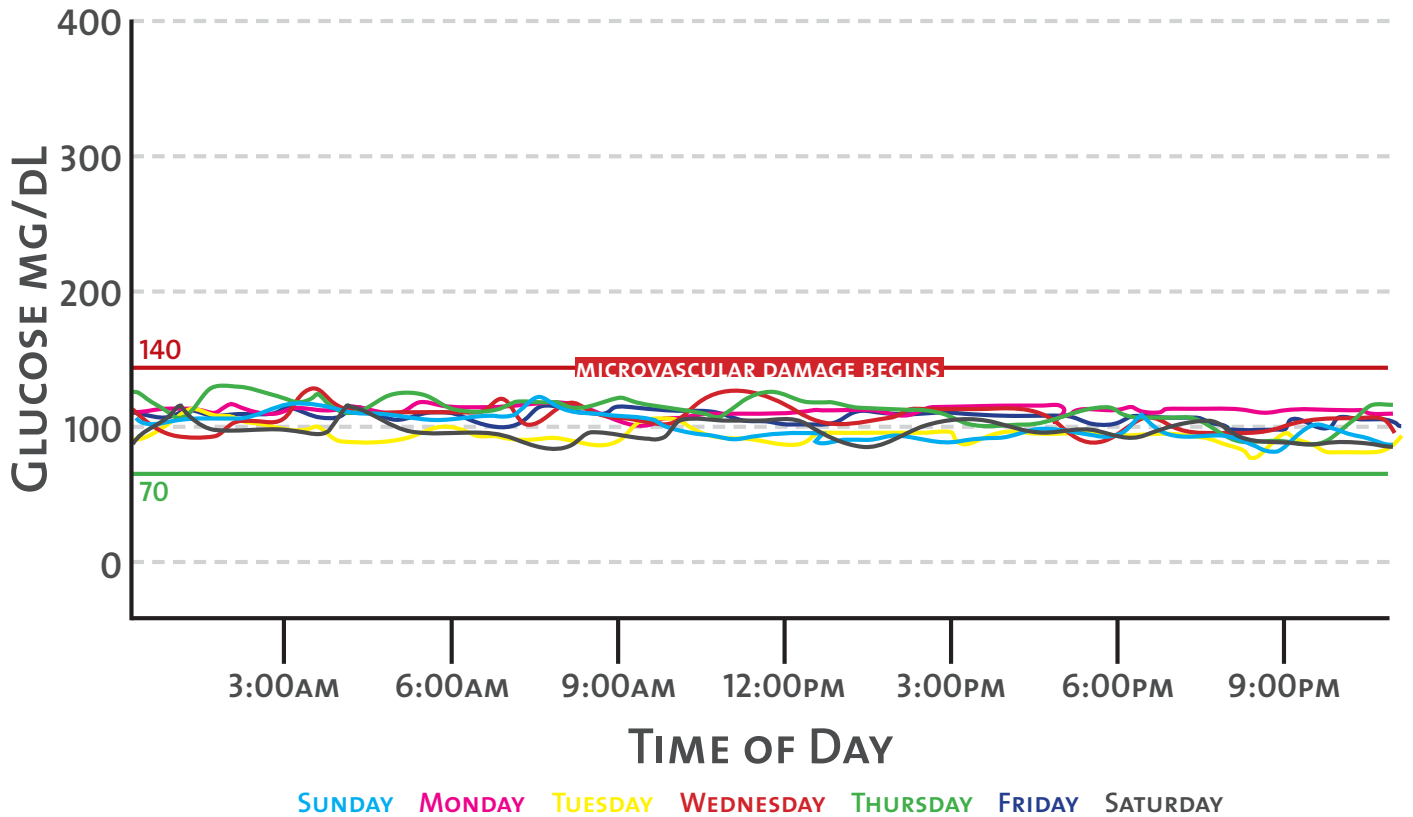


Figure 1. – Non-Diabetic Blood Glucose Levels

DIABETIC BLOOD SUGAR LEVELS

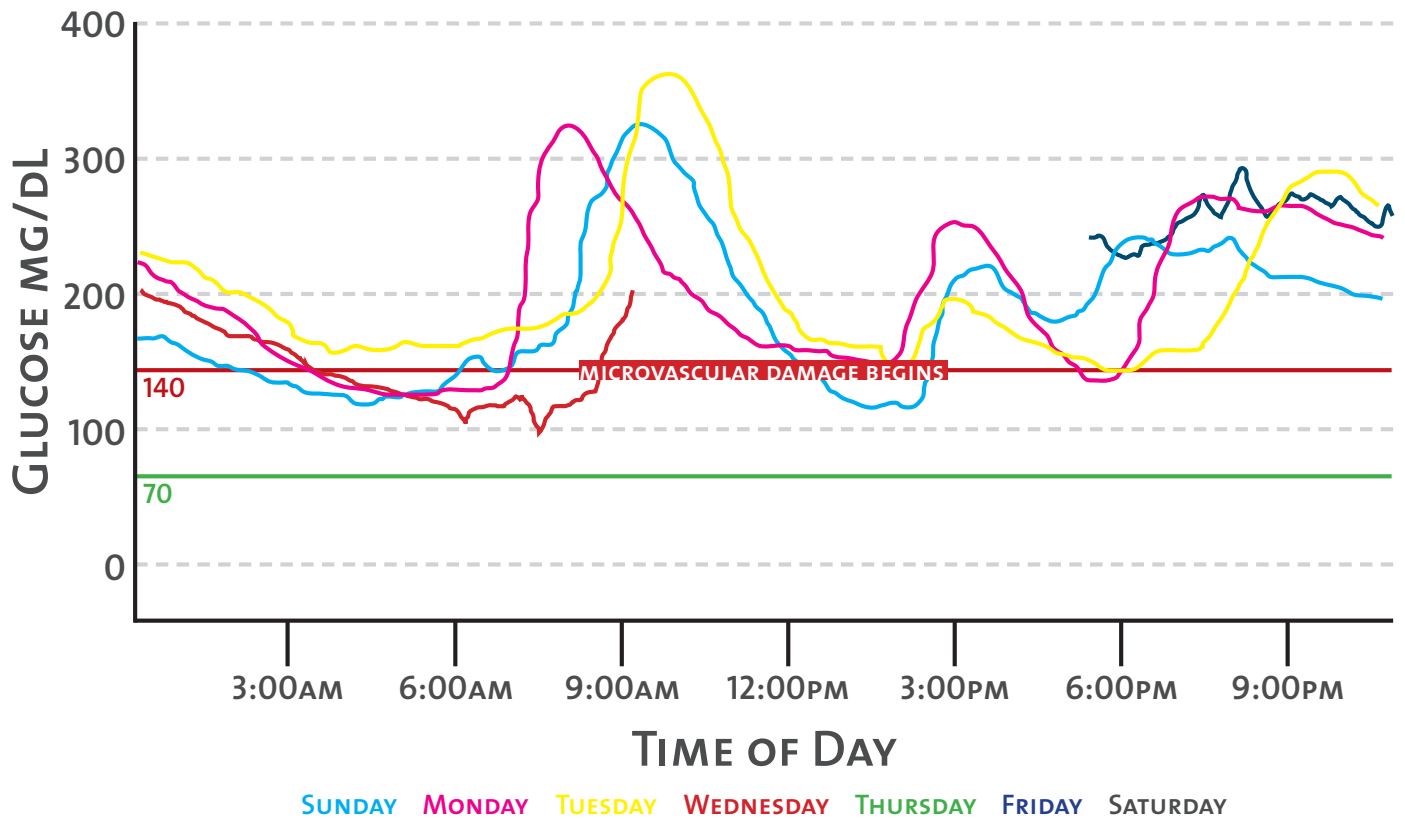


Figure 2. – Diabetic Blood Glucose Levels

BLOOD SUGAR LEVELS WHILE ON AFREZZA

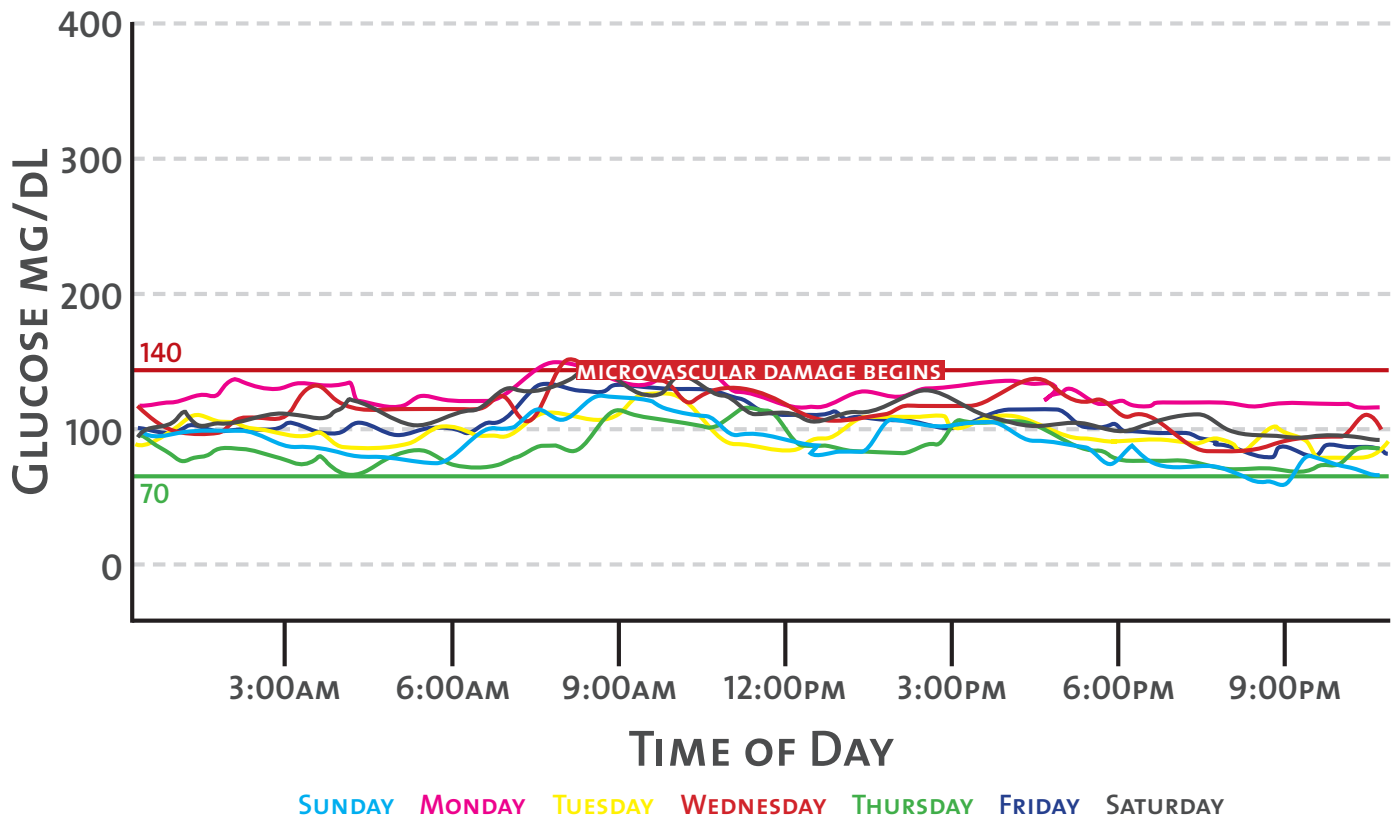


Figure 3. – Afrezza Blood Glucose Levels

Study #2 – Severely Insulin Resistant Patient – C. M.

We treated one Type 2 patient who presented with fasting glucose levels well above 200 and post prandial spikes well above 400. The patient was using prandial plus injected insulin and exhibited severe insulin resistance (SIR). We began treatment by substituting Afrezza for the prandial insulin, and steadily increased dosages of Afrezza until the patient was administering 96 units of insulin each meal or almost 300 units of insulin daily. We DID NOT adjust the basal dosing.

Within two weeks, the patient’s fasting glucose dropped into a range of 130 – 180, levels that she “couldn’t remember when [she] was ever that low.” She had no hypoglycemia. Her post prandial spikes were greatly reduced. Despite this dramatic improvement, we were not able to continue care for this patient due to a lack of insurance coverage for the medication.

Conclusion: even massive doses of Afrezza in some patients seem not to produce hypoglycemia.

Study 3A – G, How Afrezza Works in a Non-Diabetic

In this series of studies, we evaluated the action of Afrezza in a non-diabetic, i.e. normal, person. Our rationale was that with a normally functioning liver and pancreas, we could use Afrezza with little risk, despite the fact that the subject had normal insulin sensitivity. These were not brittle subjects. The symphony maintaining blood glucose homeostasis should be able to absorb the effects of Afrezza with little risk. We, of course, proceeded gradually to greater levels of challenge.

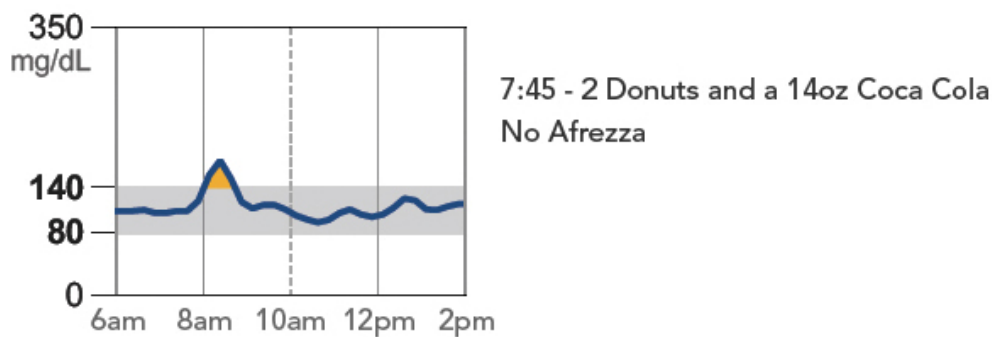
We also felt we could view Afrezza in a somewhat “clean” setting since these individuals had no obvious blood sugar control problems. They were normal.

We were able to replicate the findings below in other patients and present what we believe to be representative results.

Study 3A – Glucose monitoring of simple carbohydrate meal - baseline

Design. The volunteer subject, a male, non-diabetic, not obese, 56 years of age, wearing a FreeStyle Libre Pro Continuous Glucose Monitor (CGM) by Abbott, was instructed to fast from 10:00pm until 7:45am and then eat an extremely high, simple-carbohydrate meal consisting of two donuts plus 14 ounces of regular Coca Cola first thing in the morning and nothing else. In total, this meal involved approximately 800 calories of food, comprised of 27 grams of fat, 132 grams of carbohydrate, and 9 grams of protein. The carbohydrate content included 41 grams of simple sugar. The subject consumed both donuts and drank the Coke within 10 minutes and did not eat again for at least two hours.

Results. The CGM was set to display a “normal” range of blood glucose as between 80 mg/dl and 140 mg/dl. Below is the CGM graph of the subject’s blood sugar showing the expected spike in blood sugar appearing almost immediately upon completion of the meal. The subject’s blood sugar reaches a peak (outside the normal range) approximately 20-25 minutes after the meal at which point, presumably, the normal pancreatic response occurs with insulin being released driving the blood sugar back down to the normal range within about 20-30 minutes. In the 60 – 90 minutes following the meal, the subject’s blood glucose level drifts slightly lower.

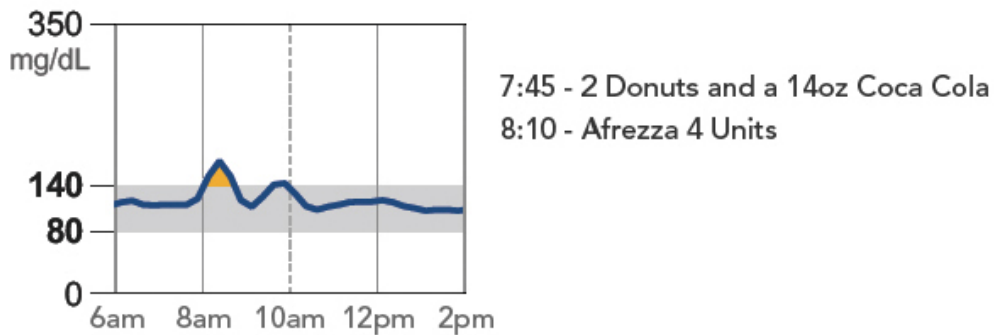


Areas of Possible Further Study. Does the “normal, healthy” pancreas overreact to a high, simple-carbohydrate meal as has been suggested in some of the literature? We did see evidence of this in other studies when the simple carbohydrate meal was extended over several hours and then abruptly terminated.

Study 3B – Afrezza Administered 15 min after meal

Design. This study involved the same subject, eating exactly the same meal, at the same time, as in Study 3A. In this study, the subject administered a 4 unit dose of Afrezza, approximately 15 minutes following the end of the meal, which itself took slightly less than 10 minutes to complete.

Results. In the CGM readout below, you see a nearly identical peak in blood sugar as seen in Study 3A. Presumably, the Afrezza did not go into effect in time to avert the rise in blood glucose level from the meal. The similarity of the post-prandial spike to that in Study 3A suggests that the normal pancreatic response occurred before the effect of Afrezza. Curiously, while the previous study saw the subject’s blood glucose level go lower in the 60-90 minutes following the meal, in this study the subject’s blood sugar spiked up slightly in the 60 – 90 minutes following the meal, though he did not eat any additional food.

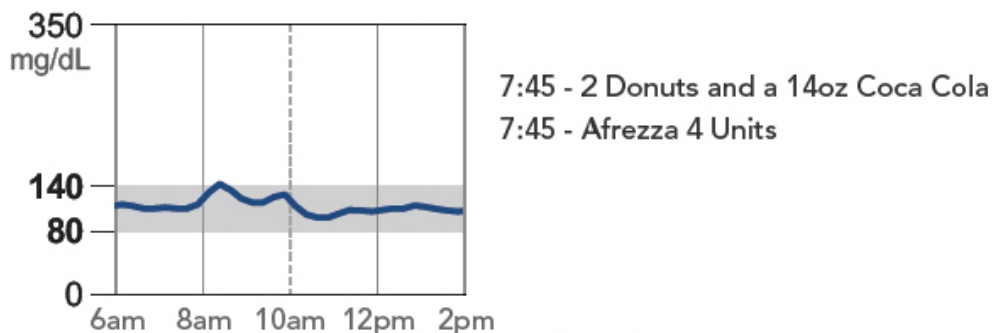


Areas of Possible Further Study. Does use of Afrezza cause the liver to be “extra-vigilant” thereby initiating gluconeogenesis in response to an insulin challenge, and thus producing the second spike seen in this study?

Study 3C – Afrezza Administered at start of meal

Design. This study involved the same subject, eating exactly the same high carbohydrate meal at the same time as in Study 3B. In this study, the subject administered a 4 unit dose of Afrezza, immediately before beginning to eat the meal, which itself took less than 10 minutes to complete.

Results. The CGM results show that Afrezza went to work in time to eliminate the spike of blood sugar outside the normal range, though there was still an increase in blood sugar. Further, there was a second spike much like we observed in Study 3B, although muted in its intensity.

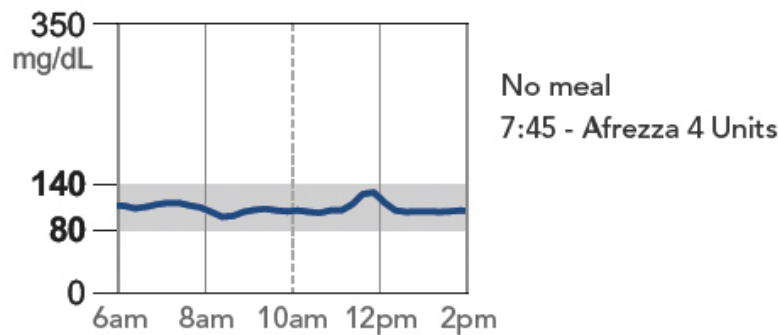


Areas of Possible Further Study. If Afrezza had been taken 10 minutes earlier, would the spike be entirely eliminated? Would there then be a second spike? What if an 8 unit dose were used for such a meal instead of 4? How much carbohydrate can 4 units handle with a healthy subject like this one?

Study 3D – Afrezza Administered with NO MEAL

Design. This study involved the same subject, eating NO MEAL since approximately 10:00pm the previous evening. In this study, the subject administered a 4 unit dose of Afrezza, at the same time as in Study 3C with NO MEAL for 2 hours following administration of Afrezza.

Results. The CGM results show a slight dip in blood glucose in the 60 minutes after administration. This dip, which looks to be approximately 20 points, never goes out of range. The subject’s blood glucose level returns to normal in about 60 – 90 minutes.

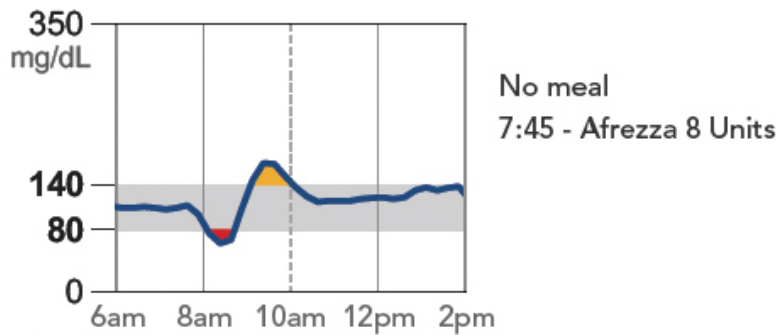


Study 3E – Large dose of Afrezza, NO MEAL

Design. This study involved the same subject, eating NO MEAL since approximately 10:00pm the previous evening. In this study, the subject administered an 8 unit dose of Afrezza, at same time as in Study 3D with NO MEAL immediately following administration of Afrezza.

Results. The CGM results show a sharp dip in blood glucose in the 45 minutes after administration. This drop reached its low point approximately 45 minutes after administration of Afrezza at which time the subject was exhibiting clear signs of hypoglycemia: sweating and dizziness. The decision was made to terminate the test, though the subject felt he could “work through it” and the subject drank 20 ounces of regular Coca Cola. His symptoms resolved completely in 10 minutes or less as the CGM reading shows with the sharp rise in blood glucose.

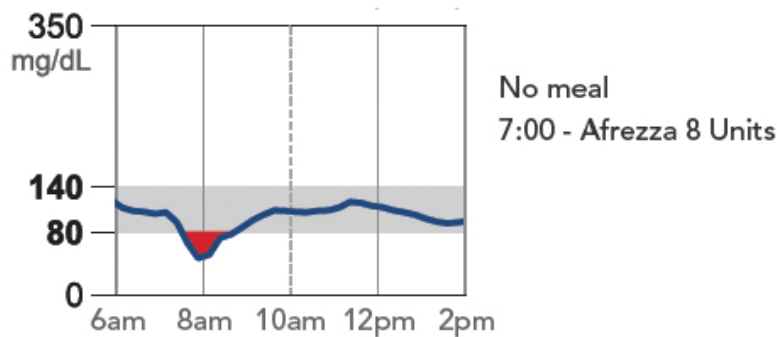
Because of the graphical nature of the results from the FreeStyle Libre CGM, precise blood glucose readings aren’t possible in this study, but clearly the subject’s blood sugar dropped into the hypoglycemic range. However, the blood sugar level never reached the point of severe hypoglycemia. This drop took 45 minutes to get to a point where symptoms of hypoglycemia were present. According to the previous experimentation at Vdex, the subject was likely at his lowest point and could have seen a rapid recovery without the “rescue” drink of Coke.



Study 4E – Large dose of Afrezza NO MEAL

Design. This study was the same as Study 3E above but with a different subject. The subject was of similar age and fitness level.

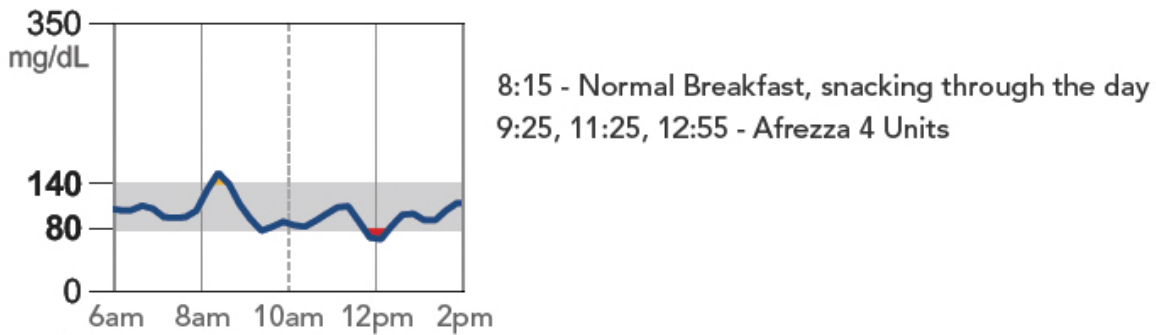
Results. At the 45 minute mark after administration of Afrezza, the subject had symptoms of hypoglycemia, just as with the previous subject. This subject DID NOT take a rescue drink, however. Notably, his chart appears to be very similar to the subject in 3E who did take a rescue drink. The only conclusion we could reach here is that subject’s liver must have supplied the glucose to produce the rapid recovery in blood sugar level and kept the patient safe.



Study 3F – Multiple Small Afrezza Doses with Normal Meals

Design. This study involved the same normal subject as in Study 3E, eating normally throughout the day. In this study, the subject administered 4 unit random doses of Afrezza at 9:45am, 11:25am, and 12:55pm. The subject followed no specific meal plan or timing of administration of Afrezza.

Results. The CGM results show that the subject had two episodes of blood sugar outside the normal range. The first was a rise slightly above the normal range following breakfast and before administration of the first dose of Afrezza. The breakfast involved a large omelette with wheat toast, jam, and a fruit bowl. Approximately 90 minutes after this breakfast the subject took his first dose of Afrezza. Then the subject had a protein bar followed by a second dose of Afrezza about 70 minutes after the first. Approximately 30 minutes following this second dose, the CGM recorded a slight hypoglycemic episode, but the subject was asymptomatic and recovered on his own.



Study 3G – Multiple Small Afrezza Doses with NO MEAL

Design. This study involved the administration of Afrezza to the same subject as in Study 3F who had been fasting since approximately 10p the prior evening. The subject administered a 4 unit dose of Afrezza at 7:30am, followed by additional 4 unit doses at 9:00am, 10:30am, and 12:00pm, all while eating nothing throughout the entire period of the test. The issue being investigated was the speed with which the Afrezza leaves the system, or stated differently, whether there is a tendency for Afrezza insulin to “stack” one dose on top of another, a common problem with injected insulin.

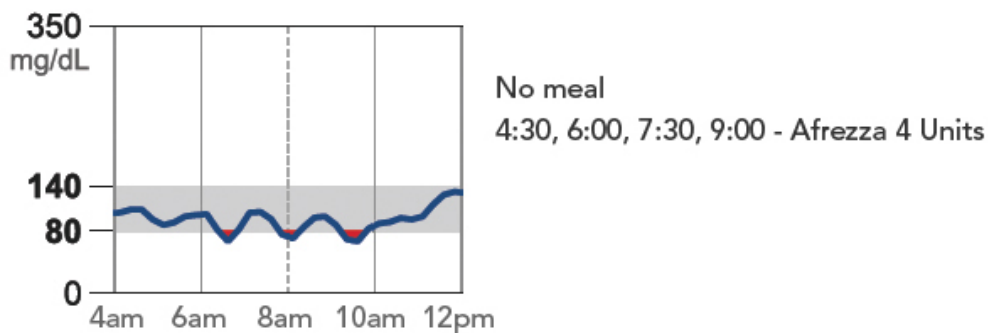
Results. The CGM reading shows that the subject had dips in blood sugar immediately following the administration of the first and second doses of Afrezza but neither dropped out of the normal range. Following the third dose, the subject’s blood sugar did drop out of the normal range. The hypoglycemic episode was short-lived and not severe. The estimated glucose level at its low point was approximately 60-70 mg/dl, did not require rescue, and the patient was mildly symptomatic, a slight tremor with no incapacitation. The blood sugar then quickly recovered and the patient took the fourth dose on schedule without another hypoglycemic episode, although the CGM device had reached the end of its recording life and does not display the full effects (2 hours post administration).



Study 4G – Multiple Small Afrezza Doses with NO MEAL

Design. The study involved a different, but normal, subject as in Study 3G, but the same basic design. The four, 4 unit Afrezza doses were administered 90 minutes apart beginning at 4:30am, with the subject TAKING NO MEAL.

Results. The CGM reading shows the results. The patient's blood glucose clearly reacts to the Afrezza doses, and while it drops slightly out of the normal range, it never gets to a point of severe hypoglycemia. This subject also had mild symptoms of hypoglycemia, but recovered without rescue.



Comments on Studies in Normal, Non-Diabetic Individuals

We clearly observed the action of Afrezza in lowering blood glucose levels, but more importantly, we observed the natural response of the body to an Afrezza insulin challenge. As blood glucose levels plummeted the liver activated to keep the subjects' levels from getting dangerously low. **We observed remarkably little hypoglycemia EVEN IN PEOPLE TAKING AFREZZA WITH NO MEAL.** These results were replicated numerous times, in different subjects.

We have not investigated this phenomenon in non-diabetic people using injected insulin, and we DO NOT recommend such a test. Experience with injected insulin suggests that giving it to non-diabetics in anything close to the levels we did with Afrezza, and with no food, could be deadly.

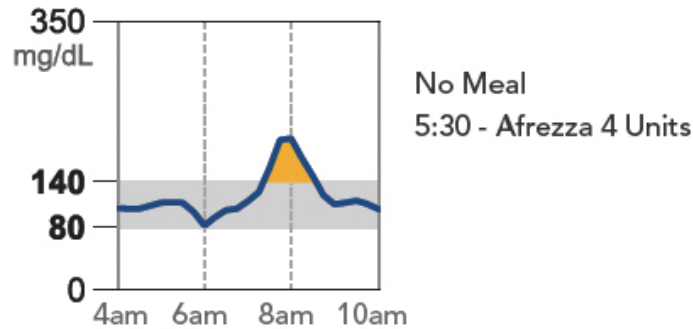
Study 5A-C, Safety of Afrezza in Type 2 Patient

The subject of this series of studies was a recently-diagnosed Type 2 with an HbA1c of 7.5 at the time of diagnosis. Because of the robust safety profile of Afrezza that we observed in use with non-diabetic subjects, we performed similar studies in Type 2 patients with similar results. Below, are results we believe are representative.

Study 5A – Small Dose, NO MEAL

Design. This subject, after fasting from approximately 10:00pm the previous evening, administered 4 units of Afrezza at 5:30am while having no food for two hours after dosing. The subject then administered another 4 unit dose at 8:15am.

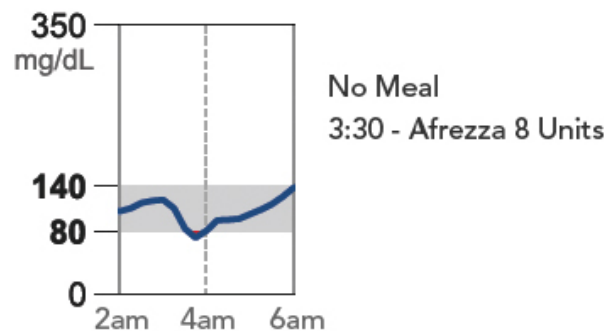
Results. The subject's blood sugar dips slightly but does not go out of range. The rapid rise is due to the subject's breakfast at 7:30am. The second Afrezza dose quickly brought it down.



Study 5B – Large Dose, NO MEAL

Design. This study involved a single dose of 8 units of Afrezza after 8 hours of fasting. The subject did not eat for two hours after dosing.

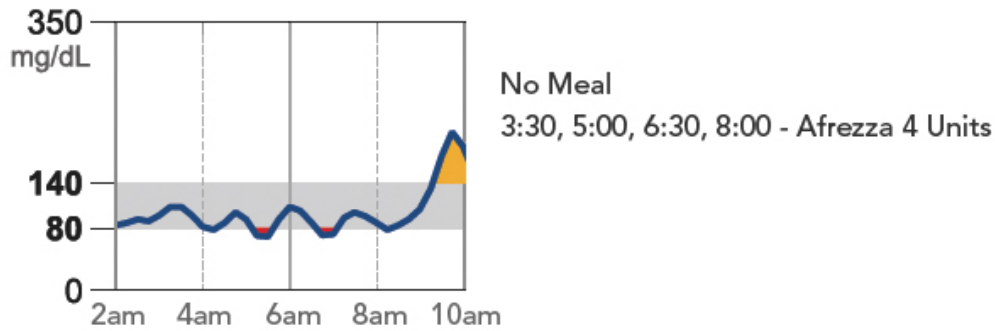
Results. The subject's blood sugar does drop to slightly hypoglycemic but doesn't go below 70. It then recovers steadily despite not taking any food.



Study 5C – Multiple Small Doses, NO MEAL

Design. In this study we had the Type 2 diabetic subject administer 4 doses of 4 units of Afrezza approximately 90 minutes apart, all while eating NOTHING. The doses were administered at 3:30am, 5:00am, 6:30am, and 8:00am. We were interested to see if Afrezza insulin “stacks” in diabetic subjects the way injected insulin does.

Results. It is clear what time the subject took the Afrezza as there are dips in the blood sugar reading immediately following. However, following each, the subject's blood sugar recovers on its own. Further, while the subject was slightly hypoglycemic, she was asymptomatic. Each subsequent dose seemed independent of the previous as we observed no progressive lows, as was the case with normal, nondiabetic individuals. The spike that occurs at the end of the tracing is a result of the patient taking a meal at approximately 9:00am with NO AFREZZA.



Comments on Studies in Diabetic Patients

We saw similar results, with similar challenges, in both diabetic and non-diabetic patients. The salient result from all these studies is the very broad safety margin with the use of Afrezza. Simply put, it is very difficult for patients to have adverse events. In terms of both timing of administration, and dosage strength, Afrezza stands alone among all insulin products. Patients and health care providers can use this insulin with little concern over safety.

Other General Medical Risks

Lungs

Vdex is not a research facility and therefore, is not in the position to perform detailed analysis of the effects of Afrezza on pulmonary tissues. Rather, our analysis amounted to gross observations of pulmonary function and tolerance over several months.

Cough. In many patients, we observed a brief cough following inhalation of the powder. This amounted to, in most cases, a single, brief, throat-clearing cough. In no cases did we observe a sustained “hacking” cough. Most patients could mitigate the cough with a sip of water immediately prior to inhalation, but in general, with or without mitigation, the cough lessened in intensity after a week or two of use. We had no patients discontinue treatment due to the cough. It was not a significant complaint.

Pulmonary function/capacity. We performed spirometry testing as required prior to prescribing the medication and found that test to be very difficult for many patients. In fact, many failed the test and became quite frustrated. Over the relatively brief period of our analysis of spirometry (approximately 6 months), we did not observe any change in patients’ pulmonary function or capacity. We do, however, see spirometry as a significant obstacle to adoption of this therapy.

The recent change to the use of FEV1 testing (one second forced expiratory volume) in place of spirometry is a clear improvement. As with spirometry, we have not had a long enough period to evaluate, using FEV1, the issue of pulmonary function or capacity in patients. While there have been reports of changes in pulmonary function with the use of Afrezza, such changes were de minimus. The vast majority of diabetes sufferers are older and sedentary. The minimal change in lung function or capacity is highly unlikely to be something these patients ever notice.

Smokers. We prescribed the product in smokers despite the contraindication, and we saw no difference in the tolerance of the product among these patients as compared to non-smokers. In fact, smokers tended to have less difficulty using the inhaler, probably as a result of their familiarity with inhaling on a cigarette.

Cancer. Here again, given the short duration of our evaluation, it unlikely that we would see any conclusive evidence on this issue. In reviewing the carcinogenicity studies from the manufacturer, MannKind Corporation, we are comforted that this is not a significant concern. It appears the company studied this issue in depth, even performing histological examinations on transgenic mice exposed to high concentrations of the product. They observed no unusual conditions and no neoplasms. The product is in the lungs for a very brief time. It passes rapidly into the blood stream. It does not seem to irritate the lungs to any significant extent, a conclusion that we reach based only upon our brief observation with use of the product.

Other

Afrezza is regular human insulin bound to a carrier molecule, Technosphere. Circulating insulin is obviously not a troubling condition as this happens normally and further, Afrezza insulin is bio-identical to the insulin released by the pancreas. It is not a foreign molecule to the body as are insulin analogs. The Technosphere carrier molecule, while foreign to the body, has been judged by the FDA to be inert. It neither remains in the lungs, nor in the body at all, but is excreted unmetabolized in urine. We did not independently verify this.

In comparison, many of the therapies used to treat diabetes today are foreign molecules with uncertain long term risks. For example, metformin, a relatively benign drug and the most prevalent medication prescribed for blood sugar control, has recently been implicated in some serious medical conditions, including Alzheimer's disease. Invokana has recently received a Black Box warning for increased risk of lower extremity amputations.

Summary of Safety Findings

Hypoglycemia. Our experience has been that Afrezza is extremely safe for all patients. It appears difficult to induce hypoglycemia even if one tries. We gave large doses to insulin sensitive subjects, who ate nothing and did not produce severe hypoglycemia. This would be unheard of with injected insulin. Consider that a unit of injected insulin is estimated to drop glucose levels 50-100 points. A unit of Afrezza has a little less glucose-lowering effect. We administered 8 units of Afrezza to a non-diabetic who had not eaten and whose blood glucose level at the start of the test was between 90 – 100. Theoretically, that should have dropped the subject's glucose level to an extremely low level exposing that individual to severe central nervous system damage. Even taking into account the fact that a unit of Afrezza is less potent than a unit of injected insulin, the subject's blood sugar should still have dropped down to a very dangerous level if Afrezza acted like injected insulin. To put it bluntly, in other words, it could have killed him. This did not happen, not even close.

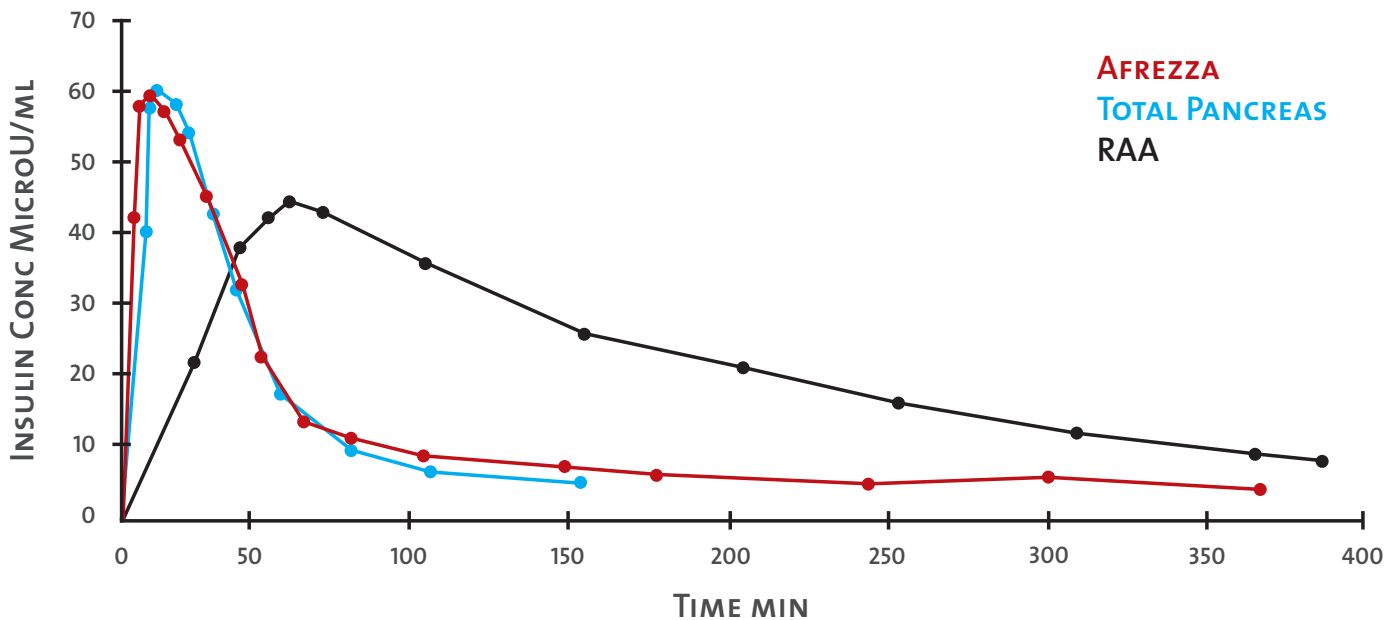
Even at very low A1c levels, such as 6.0 and less, we do not see an issue with hypoglycemia. This confirms what the manufacturer has said about the product all along: the hypoglycemia that was observed during the clinical trials was likely due to other medications the patients were taking.

Perhaps more important is the total absence of nocturnal hypoglycemia with Afrezza. It is clear from the PK/PD profile, that approximately 75% of the product is gone in an hour and about 90% in 90 min. We saw zero risk of hypoglycemia caused by Afrezza, beyond these points. There is just no excess insulin in the bloodstream to produce the hypoglycemia. As a result, if patients take Afrezza with their last meal and go to bed more than about an hour later, they simply have no risk of hypos from the Afrezza. We also observed no “stacking” of the insulin if doses were separated by about 90 minutes.

Communication with Liver Restored. Afrezza has an additional feature that distinguishes it from all other insulins and dramatically increases the safety of the product. Afrezza’s PK/PD profile is a near perfect match to the normal pancreatic response to food. (See Figure below) As such, Afrezza mimics the First-Phase insulin response which, in addition to supplying insulin to assist in the metabolism of blood sugar, also signals the hepatic supply of glucose to shut down. This results in less total glucose being present in the blood stream, requiring less insulin to metabolize it. Other insulins do NOT mimic this First-Phase response. With all other insulins, gluconeogenesis continues to occur in the presence of the meal, resulting in higher total glucose levels. At some later point, an hour or more, other insulins do finally arrest gluconeogenesis, but paradoxically, this may be just the point that the body needs its hepatic supply to be initiated.

HOW AFREZZA INSULIN COMPARES TO HEALTHY NONDIABETIC INSULIN RESPONSE

(THE RAA CURVES ARE A GRAPHICAL APPROXIMATE REPRESENTATION OF DATA STEMMING FROM SEVERAL STUDIES.)



Other insulins are unreliable in the communication with the liver and this can present a very dangerous situation. This is where Afrezza shines. It not only arrests gluconeogenesis, but appears to also alert the liver to the blood glucose level. If those levels start to go low, then hepatic glucose production begins to supply the needed glucose to “rescue” the person. How else to explain that one can take Afrezza insulin in the presence of NO MEAL and not become hypoglycemic?

We found there to be a broad safety margin with Afrezza as compared to injected insulins. For example, if a patient for whom a recommended dose was 4 units, instead took 8 units, he/she did not get into trouble. While the 8 units would lower blood sugar more, it did not push the patient into the hypoglycemic range. The activation of the hepatic supply of glucose seemed to prevent that, though we recommend more study on this point. Also, something as simple as the packaging of Afrezza further contributes to its safety. The maximum dose in a cartridge is 12 units. A person would have to consciously overdose himself with additional cartridges to deliver more

Could Afrezza Actually Prevent Hypoglycemia? It is axiomatic that insulins cause hypoglycemia. Every article written about insulin mentions the fear of hypoglycemia. The phenomenon has achieved a level of acceptance rivaling the law of gravity. It’s beyond debate. Except, it may not be so with Afrezza. It may actually be exactly the opposite: that Afrezza insulin PREVENTS hypoglycemia.

We investigated naturally occurring hypoglycemia in non-diabetic people. We observed that in response to a large, simple carbohydrate meal, subjects’ blood sugar would frequently drop into a severe hypoglycemic range in the hours following such a meal. We observed blood sugar levels frequently in the low 40s, and some perhaps in the upper 30s in our subjects. Of course, these subjects’ blood glucose levels naturally corrected, though some stayed in the severe hypo range for hours.

We then replicated such meals and administered Afrezza thereafter. We investigated different times of administration: synchronous with the start of the meal, slightly later, immediately following the meal, and hours after finishing the meal. In each case we observed the same phenomenon: LESS HYPOGLYCEMIA. In other words, **Afrezza prevented hypoglycemia that occurs naturally in nondiabetics.**

This very challenging finding could itself be a source of extensive study. We at Vdex are not prepared to investigate it further at this time, but we strongly encourage others to do so. We do not believe our observations are outliers. Afrezza is a quite different chemical than injected insulin and there is much to suggest that this salutary result will not only be replicated, but further supported by other studies.

Confusion Created by Experience With Other Insulins. This lack of hypoglycemia with Afrezza is such a contrast with standard injected insulin that experience with those products offers no helpful information in the use of Afrezza. If anything, physicians are unduly reluctant to use Afrezza based upon their knowledge and experience with traditional insulins. This is unfortunate for patients. We at Vdex have no reservations about the risk of hypoglycemia with Afrezza.

Further, the product label, which states, “The most common adverse reactions associated with AFREZZA (2% or greater incidence) are hypoglycemia, cough and throat pain or irritation,” may be factually accurate, but is highly misleading. The label goes on to state, “Hypoglycemia is the most common adverse reaction associated with insulins, including AFREZZA.” By associating Afrezza with other insulins, the label draws unwarranted attention to this concern, in our opinion.

Flatter Curves. With all subjects using Afrezza we saw flatter blood glucose curves in the CGM readouts. It is clear with Afrezza patients achieve lower highs and higher lows. Recent research has focused on the amplitude of blood glucose levels as a separate risk factor for complications from diabetes. There is growing evidence that greater amplitude in itself is a risk to patients, distinct from average HbA1c level, or the greater risk of hypoglycemia due to greater blood glucose fluctuation. This just adds to the overwhelming pool of data we have gathered supporting the use of Afrezza.

Other Safety Concerns. The other potential risks center mostly on concerns about damage to the lungs. Some have hypothesized a risk of lung cancer, others cite diminished pulmonary capacity and still others' concern is general irritation to the lungs. As stated above, we cannot meaningfully evaluate the carcinogenicity of Afrezza beyond the information supplied by the manufacturer. That data is persuasive to Vdex. In its development, Afrezza was more thoroughly studied from the perspective of carcinogenicity, than Pfizer's inhaled insulin product, Exubera. Those studies revealed no cancer risks. In addition, there are a number of patients who have been using Afrezza for more than a decade now and we have yet to hear a significant cause for concern in their experience. Further, given our understanding of the components of Afrezza, regular, bio-identical human insulin plus an inert carrier molecule, we don't believe there is cause for concern.

Efficacy

Speed

Clearly use of insulin is an effective way to reduce blood sugar, and since Afrezza is insulin, it does just that. In evaluating any prandial insulin, speed is a critical metric. A major issue in the use of injected prandial insulins has been timing the dosing so that the insulin is present and working when the meal is present. Mis-timing of the two is a very large factor in the incidence of hypoglycemia.

Afrezza goes to work very quickly and there are some nuances in its use as a result. Patients should NOT administer it before a meal. Doing so just results in the loss of some of the glucose-lowering ability of the product because it will be metabolized before the full glucose effect of the meal is reflected in the bloodstream. Blood glucose levels can actually become out of control as a result. The one qualifier to this is the situation in which a person plans to consume very simple carbohydrates, like soft drinks or candy. Because those products produce a rapid, dramatic rise in blood sugar, it is preferable to take Afrezza simultaneous with the start of such a meal or even a few minutes before. Afrezza will blunt the rise. Otherwise, we recommend administering Afrezza about 15 minutes after the start of a normal meal.

See Studies 3A – C on this point.

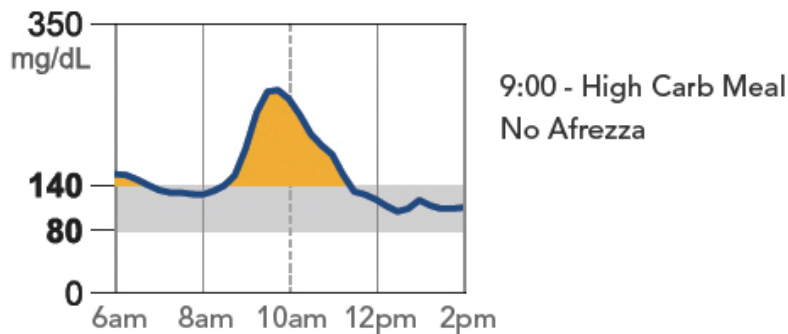
Study 6A – C: Use of Afrezza in Well-Controlled, Modest Meal

This series of studies involved the use of Afrezza in a well-controlled, diabetic patient with a current HbA1c of 6.1 on Afrezza ONLY.

Study 6A – Baseline

Design. The subject began eating a 6” turkey sub sandwich with a 16 ounce sugary drink at 9:00am without taking any Afrezza.

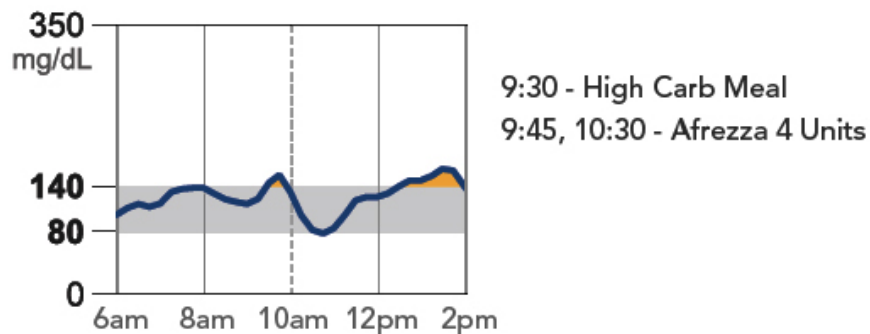
Results. The blood glucose excursion here is classic. The subject’s starting blood sugar was approximately 120, and over the course of about an hour, skyrockets to well into the 200s. The blood glucose stays elevated for several hours until the meal has been digested.



Study 6B – Initial + Follow-up dosing, 4 units

Design. This involved the same subject as Study 6A eating the same meal beginning about 9:30am. The subject administered a 4 unit dose of Afrezza 15 minutes after beginning her meal, with a follow-up dose 45 minutes later. She did not eat for more than 2 hours following her last dose of Afrezza.

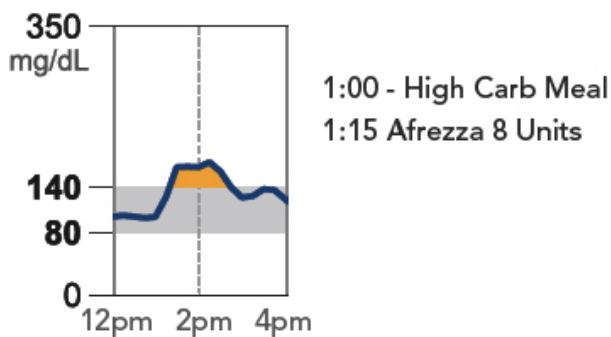
Results. Clearly, both doses eliminated the excursion that occurred in Study 6A, and drove down the blood sugar level. The subject did not become hypoglycemic, and the blood sugar recovered over the course of about 3-4 hours.



Study 6C – Use of 8 units, No Follow-Up

Design. The study involved the same patient consuming the same meal as in Study 6A, at about 1:00pm. The subject then took a single, 8 unit dose of Afrezza at 1:15pm. She did not eat for more than 4 hours.

Results. The Afrezza quickly brought the blood sugar down and kept it down for several hours despite there being no follow-up dose. Some of the rise of her blood sugar likely could have been averted if she took her Afrezza dose at the start of this high carb meal.



Comments

Afrezza's speed of action is both a blessing and a curse. Clearly, it is a large factor in the safety of the product, but for longer meals, you may need more Afrezza to keep the post prandial levels in check. We have recommended follow-on doses. For example, we advised with a standard meal to dose Afrezza 15-20 minutes after the start of the meal, and then another dose of the same size about 45 minutes later. With very long meals, we have even advised patients to administer two follow-on doses, for very tight control.

Another strategy is to dose more heavily in the initial dose and NOT do a follow-up. It appears this can be quite effective at keeping the post-prandial levels in check even several hours following the meal. Since Afrezza has such a broad safety margin, this should not concern patients or providers.

We have mentioned several times that Afrezza exits the blood stream very quickly. About 90% of it is gone in 90 minutes. The obvious question is, “How can it be controlling blood glucose levels hours later then?” We believe it is due to the interplay between pancreas and liver. To state it simply, it appears Afrezza normalizes physiology such that even though the Afrezza itself has been metabolized away, it’s influence through the pancreas and liver lives on. This is a feature of the product deserving much greater investigation.

Comparison to Injected Insulin

The product label recommends a conversion of doses of injected prandial insulin into Afrezza doses. Generally, patients need a little more Afrezza to get the same glucose-lowering effect as injected insulin produces, according to the label. Our experience is that one needs to give even more. The conversion chart on the Afrezza product label is insufficient to achieve the desired level of glycemic control. It should be noted, however, that as we became comfortable with the safety of the product, we were inclined to dose more aggressively to achieve better control than one might seek with injected insulin.

Also, insulin resistance varies by average glucose levels. Above about 200, a lot more insulin is required to achieve the same amount of glucose lowering as compared to a blood glucose level of say, 150. As one’s average glucose level comes down with continued use of Afrezza, one can expect to see a greater effect with the same dose.

It is clear that the current professional guidelines recommending an HbA1c goal of 7% or less are insufficient to forestall the long-term complications of diabetes. Even if patients could get to goal, and recent research indicates that fewer than 30% of patients reach that point, they will still have long-term complications. An HbA1c of 7 translates into an average blood sugar level of about 155-160. It is well-established that microvascular damage BEGINS to occur at blood sugar levels of 140. The damage gets progressively worse the higher the level. Also, the increase in damage is NOT a straight-line function with blood sugar. Rather it is more like a geometric progression. Patients with an average of 155-160 spend a great deal of time above this point. As a result, they are inevitably experiencing significant damage.

Summary of Efficacy Findings

There never has been any doubt about the efficacy of insulin in lowering blood glucose. After all, this is how the body does it normally. We did not investigate direct comparison between doses of injected insulin and Afrezza. We can clearly state that Afrezza is very effective at lowering blood glucose levels and goes to work much quicker. The real advantage of speed is in timing: the ability to have insulin present and active when the sugar is present in the blood. Afrezza has a huge advantage here.

Relative Utility

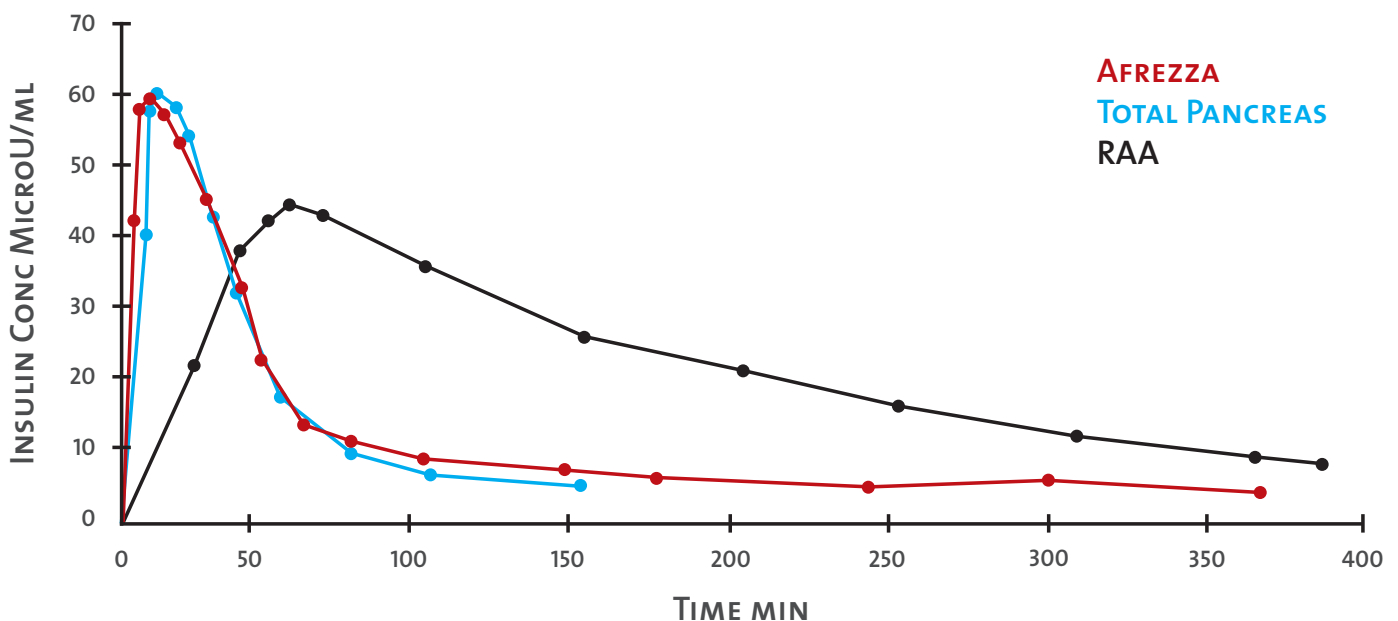
It is beyond the scope of this document to review all diabetes therapies. Hence, we will address the comparison of Afrezza to the most commonly prescribed medications today.

Type 1

Type 1 patients need both basal and prandial insulin. Since Afrezza is a prandial insulin, we will confine our comparative remarks to other prandial insulins. There is simply no comparison between Afrezza and the fastest prandial insulins, so-called Rapid Acting Analogs (RAA). As you can see in the figure below, Afrezza begins to work much more quickly and, perhaps more importantly, leaves the system much more quickly as well. This results in three, key benefits. First, there is very little chance of mis-timing the dosing since one begins dosing Afrezza typically at the start of, or several minutes into a meal. Second, one avoids the problem of mis-dosing. Prandial insulin doses need to be adjusted according to the carbohydrate content of a meal. For example, if a person plans on having a pasta dinner, he or she will typically dose more insulin that if having a protein-based meal of similar size. With RAA, patients typically dose 30-60 minutes before a meal. As such, they really should not change from what they intended to eat when they dosed. They're locked in as a result of their dosing. While Afrezza dosages can also vary somewhat with the carb content of a meal (but it appears less so than with injected insulin), those doses aren't taken until one actually begins to eat. So, the person already knows how much product to administer. Third, and most importantly is the reestablishment of communication between pancreas and liver that occurs with Afrezza. This communication is what alerts the liver to supply glucose if the body gets low, just as happens with normal, non-diabetic physiology.

HOW AFREZZA INSULIN COMPARES TO HEALTHY NONDIABETIC INSULIN RESPONSE

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Type 2

The major classes of non-insulin drugs are described briefly below.

Metformin (Biguanide). Clearly the most common treatment for people with Type 2 diabetes is metformin. In fact, at the first sign of the disease as prediabetes, many physicians put their patients on the drug. Metformin is inexpensive, easy to take and modestly effective in the early stages of the disease. Its primary mode of action is to decrease hepatic glucose production and increase glucose uptake in muscles. Approximately 30% of people prescribed metformin report GI distress, typically cramping and diarrhea, and discontinue the medication. More recent research has focused on a suspected link between long-term metformin use and Alzheimers disease.

Limitations: metformin doesn't act on the primary physiological deficiency of diabetes, beta cell dysfunction. It is a gateway drug leading to larger and larger doses and later, to new oral medications as patients' blood sugar control declines.

Sulfonylureas. This class of drugs increases insulin secretion from beta cells. It is effective, carries a risk of hypoglycemia, and can promote weight gain. Like metformin, sulfonylureas lose their effectiveness over time as there is further beta cell decline, leading to patients adding another medication to maintain blood sugar control.

TZDs. These drugs increase insulin sensitivity, are relatively safe but carry a risk of weight gain, bloating, heart failure and bone fractures. They too lose effectiveness over time.

DPP-4 inhibitors. The mode of action for these drugs is to increase insulin secretion, and decrease glucagon secretion, thereby decreasing glucose production. They are safe and well-tolerated but again, temporary. As beta cell failure progresses, these medications become less effective.

GLP-1 receptor agonists. These drugs act similarly to DPP-4 inhibitors. They are not particularly well-tolerated however, with a significant percentage of patients experiencing nausea and vomiting, and the class of drugs has been implicated in pancreatitis.

SGLT-2 inhibitors. This relatively new class of medications acts by decreasing reabsorption of glucose by the kidneys resulting in more glucose being excreted in urine. There appears to be little hypoglycemic risk and the drugs are effective. However, there are many side effects associated with the drugs, among them urinary tract and kidney infections, polyuria, dehydration and pancreatitis. Further, there is a new Black Box warning on Invokana, a popular drug of this class.

Each of these classes of medications has some utility in the spectrum of diabetes treatments, but each also works indirectly on the primary problem of beta cell dysfunction. Most exacerbate beta cell failure leading to the addition of other medications. At some point, typically late in the disease progression, all these drugs seem to lose their effectiveness (we don't have enough data to say that definitively about the SGLT-2 inhibitors). It is said about diabetes therapies that, "all roads lead to insulin." Eventually that is the last resort when everything else fails.

Insulin

Insulin is the most effective, and direct way to lower blood sugar in the body. Unfortunately, injected insulin has a dangerous history. Dosed incorrectly, insulin can lead to extreme hypoglycemia resulting in coma and even death. The problem is that exogenous insulin does not mimic the action of endogenous insulin. Referring to prandial insulins specifically, all exogenous insulins fail to achieve the first-phase insulin response that we observe with insulin excreted by the pancreas in response to a meal.

Additionally, insulin use is inconvenient. It must be injected and kept refrigerated when not used. Beyond the pain of injections is the hassle factor of carrying supplies such as alcohol wipes, blood sugar testing supplies. Insulin use for some also carries a stigma.

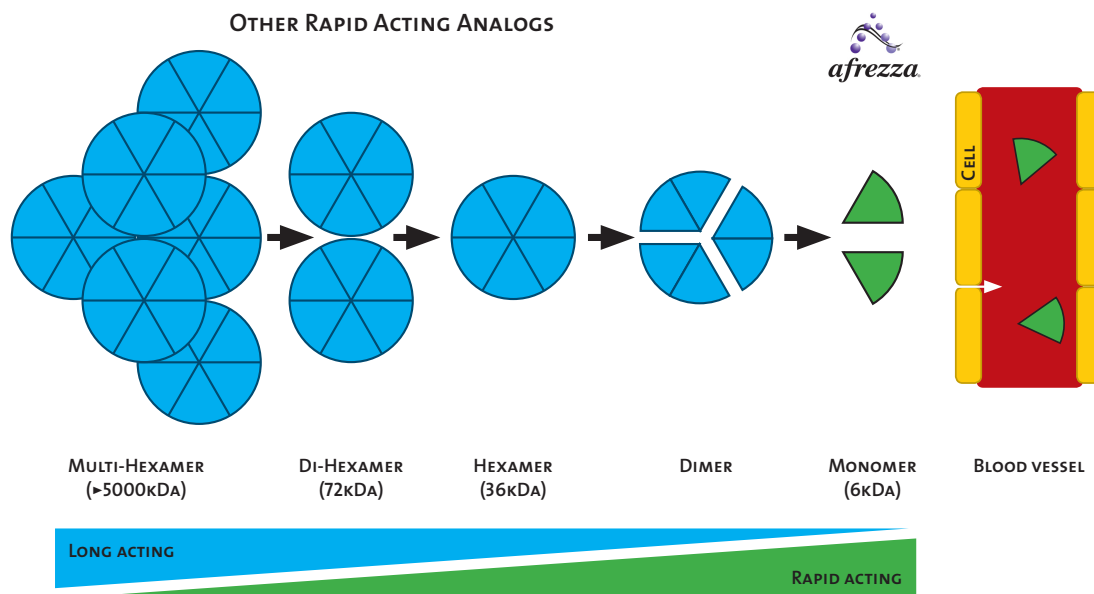
Quest For Speed. Scientists have long understood the need for fast-acting insulin. They have understood the need to produce an early, first phase insulin response to mimic normal physiology, and to deliver the host of benefits that flows therefrom. This is the Holy Grail of prandial insulin development. And, there has been very significant progress in this area over several decades. Today's "rapid-acting analogs," for example Novolog and Humalog, are much faster than their predecessors, and are successful products. Nevertheless, patients are still advised to inject their prandial insulin in advance of their meal in hopes of timing the presence of insulin with the presence of glucose. The RAAs achieve peak concentration in about an hour. So, while much better than the older insulins, the RAAs fail to reproduce the first-phase insulin response characteristic of normal physiology.

Rapid Elimination. As important as the speed of onset with insulin is the speed at which the insulin is eliminated from the body. Since the typical person digests a meal in about three hours, ideally the insulin would be gone at that time too. Excess insulin in the blood stream simply drives blood sugar lower, risking hypoglycemia. This continues to be a significant limitation in the use of insulin today. The RAAs remain in the blood stream for hours after the meal is digested. Further, the elevated insulin levels keep gluconeogenesis arrested, thereby increasing the risk of hypos.

The Magic of Afrezza. As stated elsewhere in this report, Afrezza does not suffer from the deficiencies of other insulins. In fact, the PK/PD profile seems to be almost an identical match to normal pancreatic insulin. So, what causes this? The two properties that contribute to Afrezza's rapid "on-off" action are the molecular structure Afrezza and the route of delivery of the product.

Afrezza's Molecular Structure. Afrezza insulin is the only insulin in the world that has a monomeric molecular structure. All other insulins are hexameric. The body cannot use hexameric insulin. It needs monomeric insulin. So, the body breaks the injected hexamer molecule (6-molecule chain) into three, dimers (2-molecule chains) and then into six, monomers (single molecule chains). This process of breaking down the insulin takes time. By contrast, Afrezza is delivered as monomeric insulin (see Figure below). As soon as it reaches the bloodstream, it's ready to do its job

INSULIN COMPARISON



Afrezza's Route of Delivery. Further contributing to the delayed action of injected insulin is the fact that insulin has to diffuse through tissue (usually fat) to get into the bloodstream. This also takes time. Afrezza is inhaled and upon contact with the aveolar surface of the lungs, at the pH of the tissue, liquefies and immediately diffuses into the bloodstream. The insulin quickly dissociates from the carrier molecule, Technosphere, and is available for use by the body. Injected insulins are associated with injection site lipodystrophy, scarring and resulting unreliable uptake.

Combining the molecular structure of Afrezza and the route of delivery, produces dramatically different action in the body as our studies have demonstrated. Clearly, Afrezza enjoys the additional advantage of being easier and more convenient to use. We saw little difficulty with compliance.

Summary of Findings on Relative Utility

A review of the existing diabetes therapies for Type 2s is sobering. In many ways, the current approach is primitive or backwards. The most effective therapy is the most shunned, ie insulin. Everything else is essentially an attempt to avoid using insulin. Some of the drugs have miserable side effects, some are minimally effective and all are temporary. We forestall the inexorable march to insulin with other therapies. But, even worse, when the medical community finally concedes defeat and embraces the use of insulin, it's already too late. The disease has won. Permanent damage has been done. Life, at best, becomes a battle of minimizing the dysfunction of diabetes. Patients are then forced to other medications or procedures to deal with the dysfunction created by diabetes. They take medications for neuropathy. They get laser procedures for the leaky blood vessels in their eyes. They visit a dialysis center three times a week and get hooked up to a machine to cleanse their blood. What a way to live.

One obvious question presents itself: in any battle, **why would you save your best weapon until you've already suffered huge losses?** Does that make any sense? Wouldn't you use your best weapon first?

Usage Guidelines

At this writing, Vdex is one of the largest prescribers of Afrezza. Beyond just prescribing the product, we have studied it extensively, as evidenced in the early pages of this report. We have closely monitored patients while taking the medication and feel very confident that we understand how it works. As a result, we offer the following guidelines to any provider desiring to incorporate Afrezza into their practice.

Forget everything you ever knew about insulin. Insulin has a reputation, a bad one. It works well to lower blood sugar but is really regarded as the last therapy (Type 2) to try after everything else has failed. Why? Hypoglycemia. Doctors fear insulin. The best thing a provider can do is forget everything he/she knows about insulin. All the usual fears about insulin simply do not apply to Afrezza.

Need to think and talk about it differently. Patients also fear insulin. When they hear insulin they think injections and severe disease. Some patients feel ashamed in having to finally begin using insulin. Research indicates that compliance with insulin therapy is not good. A better approach is to not initially even mention insulin. Discuss how with a new therapy, you can safely manage blood sugar just **the way the body does naturally**. Discuss some of the key ancillary benefits of Afrezza such as sleeping through the night, something we have seen regularly with patients once they start on the medication. Mention how Afrezza is a supplement to what the pancreas is already doing. Break the association between Afrezza and other insulins. Establish a new association between Afrezza and the normal functioning of the pancreas.

Be careful about getting into the position of having to defend the use of Afrezza. The product needs no defense. You simply have to explain how it works (naturally) and how there are essentially no side effects, as compared with all other diabetes therapies.

Dose more aggressively. Afrezza has a self-reinforcing quality to it. When patients see results and experience how easy the therapy is to administer, they become excited about it. Many patients express that they feel more in control of their disease. This phenomenon will occur more quickly if you dose more aggressively. With Afrezza you can do so safely. As the studies mentioned above make clear, it's difficult to induce hypoglycemia with Afrezza. You really have to try.

Use a continuous glucose monitor. Feedback further assists compliance and that's just what a CGM will give you and the patient. The technology in this area is advancing rapidly so there will be more choices. At Vdex, we have used both the Dexcom and Abbott systems. Both are excellent, but the Abbott system has a significant cost advantage.

CGMs are not just for people with Type 1 disease. We recommend temporary use in Type 2s. With the Free-Style Libre system, patients can wear the sensor for 2 weeks while getting titrated on Afrezza and then not worry about finger sticks at all thereafter. For others it may take a little longer. They might opt to wear another sensor for two more weeks. In any case, **eliminating all finger sticks is a very significant advantage.**

Our approach at Vdex is to give the prescription for Afrezza and install a CGM at the first meeting. We have the patient return in one week, review the CGM readings which we share with the patient. We then typically increase the dosing (see "Step Therapy" below).

Step Therapy. People with diabetes tend to be fearful of change. Many have had bad experiences with their disease, principally hypoglycemia, so if they're stabilized on a medication, they'll likely not be highly motivated to change. When initiating Afrezza, it's best to follow "Step Therapy." Start a patient with 4 or 8 units at dinner only, a single inhalation for the day. Do not change their other medication unless they are taking a prandial insulin. If they are using a prandial insulin, substitute Afrezza according to the label but dose a little more aggressively. Otherwise, keep the patient on all the other medications, being mindful of any drug interactions. Bring the patient back in a week, observe the CGM data and adjust dosing as needed. The next step is to add dosing at breakfast if the patient is now comfortable with the evening dosing. You may also want to add a follow-up dose in the evening. Later you may add a lunch time dose.

In time, you can begin to wean the patient off some of the oral medications. By that point, patients tend to be "hooked" on Afrezza and will only feel better as other medications are removed from their treatment regimen. Very soon after patients begin using Afrezza they have much better sleep. This is a huge benefit that will further incentivize patients to stay on the medication.

Practice how to inhale. It seems obvious how to use Afrezza, but you cannot assume it is to the patient. You must use "dummy" cartridges, allowing patients to load the cartridge and practice inhaling. Some patients are timid and need instruction about how aggressively to inhale. A few minutes of practice is time well spent.

A New Treatment Paradigm in Diabetes

At the time of first diagnosis, doctors invariably start patients on oral medications, usually metformin. Those drugs eventually fail as the patients' conditions worsen so the doctor gives them other medications in addition to what they were taking. As the disease continues to progress they then add on powerful, injected medications. Later still they move on to insulin and all its risks. At this point, patients now are taking injections and fistfuls of pills. They feel terrible, but that's life for them. Around this time, many patients are having complications from their disease so they get other medications for their neuropathy, or hypertension, or cardiac issues, or retinopathy, etc. These patients' bodies are cauldrons of drugs. Who really knows what all this stuff does or how it interacts? And, is this really any way to live?

All along this progression, we ask patients to stab themselves daily with sharpened pieces of steel to test their sugar levels. Their bodies become a mass of scar tissue, they lose feelings in their finger tips from all the abuse, if they actually comply with all the instruction. We give them meters and test strips and pens along with all sorts of other diabetes paraphernalia.

With all that, the average person with diabetes will die about 10 years sooner than a non-diabetic. And, likely the last five years of that already shortened life will be debilitating. So, maybe the diabetes sufferer really loses 15 years of life.

Really?

Can we do better than this?

Yes, we can.

The normal, healthy body controls blood sugar by expressing insulin in response to a meal to metabolize glucose and fuel the body. Over the past several hundred years, our diets have evolved from hundreds of calories of high protein and roughage daily, to thousands of calories of fast food burgers and sugary soft drinks. Our lifestyles, once very active, are now sedentary. Our diets and lifestyles have evolved, but our pancreas has not. The result is that our pancreas is overworked and failing. That's diabetes. What we need is a supplement to our pancreas, additional capacity to handle the increased load.

The Pocket Pancreas

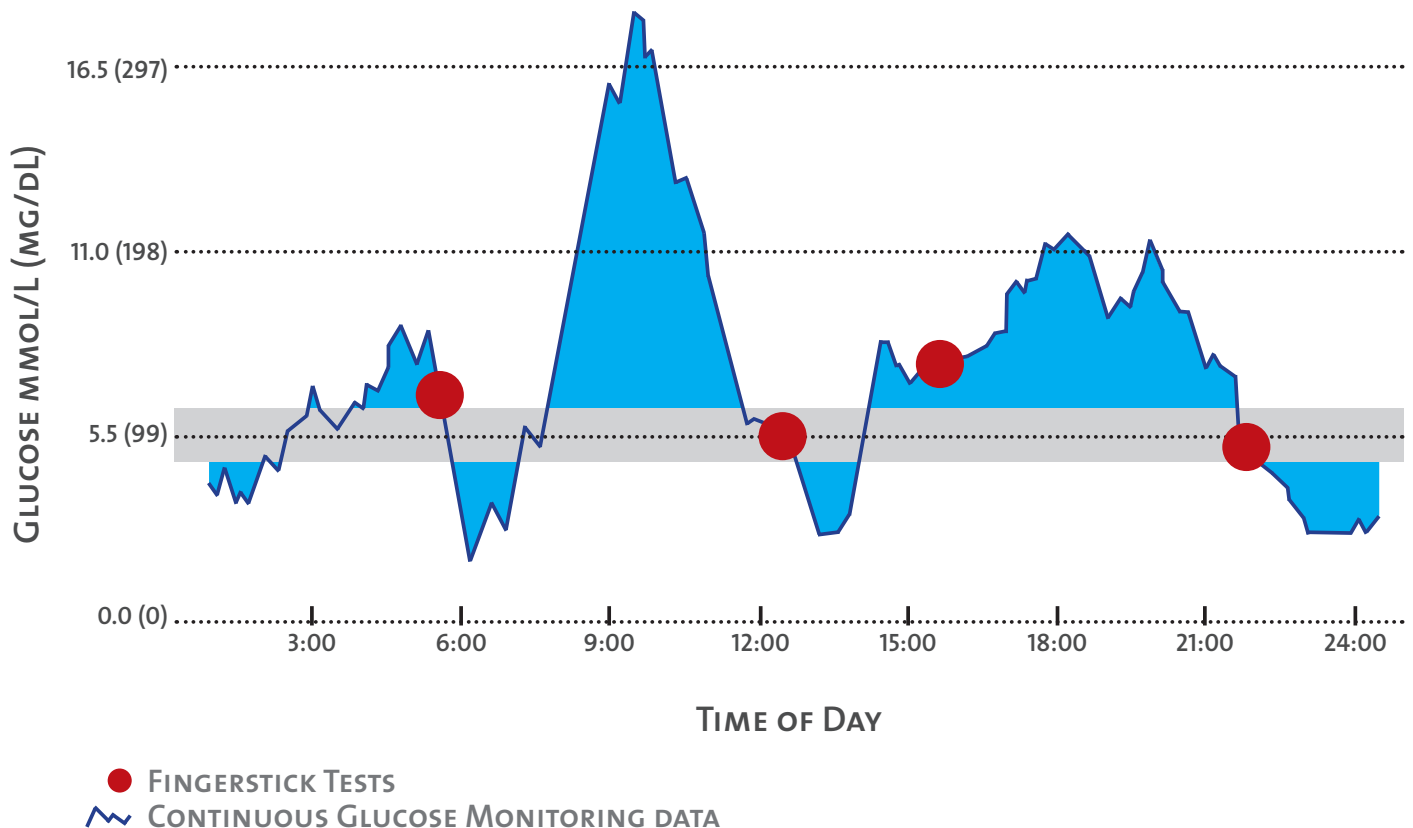
Afrezza contains chemically identical insulin to what the pancreas expresses. The body can't tell the difference. The PK/PD profile is an almost perfect match to normal pancreatic PK/PD. It is also why the pancreas-liver symphony is restored with use of Afrezza, but with no other insulin. With the pancreas and liver communicating again, hypoglycemia becomes rare.

If we could manage blood sugar the way the body does naturally, wouldn't that be the best way to do it? We can. Afrezza is essentially a "Pancreas In Your Pocket," a "Portable Pancreas." You use it when you need it, when your internal pancreas needs an assist. **The question now becomes, why use anything else?**

2 things to manage any variable...

To manage any variable, even variables as diverse as blood sugar and a golf swing, takes two things: the ability to observe that variable in real time (or close to real time), and the ability to effect it, also in real time. If you can observe a variable, but do nothing about it, you cannot manage it. If you can affect it, but you can't observe where it is, you cannot manage it. Until very recently, in managing blood sugar, we could do neither.

Observing Blood Sugar. Historically, we have observed blood sugar via finger stick tests performed by patients on themselves. Only the most diligent patients would perform them daily and few would do them multiple times per day. The figure below shows a tracing of actual blood sugar as recorded by a CGM. The red dots represent the points that the patient performs finger stick tests. Note that for this patient he/she only sees the data represented by the four red dots. He/she is blind to the CGM data. Based upon this, the patient would conclude he/she has very good control. The reality, represented by the blue tracing of a CGM, is quite different. The finger stick readings fail to capture the highs or lows of this patient's blood sugar throughout the day. The patient, making decisions based upon the finger stick data is woefully uninformed, even misinformed. Note also how, by varying the testing time even by only several minutes, you can get dramatically different glucose readings. It's really probably better not to have this data at all. And, for those patients who take maybe one or two blood sugar reading per day or fewer, it's probably better to do nothing. This graph is typical of diabetic blood sugar fluctuations.



The answer is, of course, continuous glucose monitors. The technology is rapidly improving and costs have come down substantially. With CGMs we have, for the first time, the ability to observe blood sugar in near real time and throughout the day, including while the person is asleep. This gives us much more data with which to make treatment decisions. A diligent patient might take 4 blood sugar readings per day. With a CGM (Abbott FreeStyle Libre Pro) you get 96 readings per day, and the all-important nighttime readings. Imagine how much more accurate that picture is. Also, because of the benefit for controlling blood sugar, insurance coverage for CGMs is steadily improving.

Affecting Blood Sugar. As the popularity of CGM has increased, the remaining problem has been the ability to affect blood sugar in real time. Other than Afrezza, there are no therapies that do this. None of the orals or injected medications work quickly enough. And since diabetic blood sugar levels are so rapidly vacillating, you must be able to affect the level quickly or you run the risk of exacerbating the fluctuations. You might give injected insulin when blood sugar levels are high, but by the time that insulin reaches peak concentration and peak effectiveness, the blood sugar could have already dropped substantially. The insulin is then making the problem worse. This has been part of the trouble with injected insulins.

Afrezza First, Afrezza Instead, Afrezza Always

Given our extensive, direct experience with Afrezza, we have confirmed the safety of the product. Given that this is insulin, and a bio-identical insulin at that, we have confirmed the efficacy of the product. In fact, it is well-established by the medical community that insulin is the best way to manage blood sugar. It is also quite clear in the mounting evidence that use of insulin earlier in the disease process can forestall, and even reverse, the disease progression.

Our protocol is simple, yet revolutionary: Afrezza First, Afrezza Instead, Afrezza Always.

Afrezza First. We believe the single best way to manage blood sugar is the way the body does naturally. We know that the sooner a patient begins using insulin the better, and the major impediment to injected insulin use up to now has been safety and convenience. Since neither is an issue with Afrezza, we use it as first therapy. In fact, we believe use of metformin first, which is the accepted protocol, is counterproductive.

Metformin may be easy to prescribe, inexpensive to use, and moderately effective for a time, but it does nothing to combat the underlying disease process of progressive beta-cell failure. In fact, if patients tolerate the medication well, and about 30% of patients don't, then those patients who stay on it may live with a false sense of security. They may be living with elevated blood glucose levels which insures long-term, irreversible damage to the body. The beta cell failure will simply continue. Why would we subject patients to that? How could we ethically?

Afrezza Instead. There are literally dozens of medications used to manage prandial blood sugar, most of which are foreign molecules. Most have side effects. Some severe. While these medications may have FDA approval, do we really know what they do with decades of use? The FDA clinical trials don't last long enough to know. Further, since current diabetes protocols call for stacking new medications on top of old as blood sugar control continues to worsen with time, how can we possibly know what the interactions of all these chemicals causes? Afrezza is not a foreign molecule to the body. It is chemically identical to what the pancreas secretes. We recommend using Afrezza instead of anything else.

Afrezza Always. With Afrezza we're able to bring blood sugar levels down to a normal range for many patients. If we do so successfully, we will avoid the monstrously expensive complications that beset those with long-term elevated glucose levels. Afrezza should be used always when blood sugar becomes elevated.

It's time to think differently about diabetes and insulin. Diabetes has exploded as our diets have evolved to contain high levels of sugar and our activity levels have declined. Our pancreas has not evolved to the point that it can keep up to the work load. What we need is an additional pancreas, a Pancreas In The Pocket.

For those patients in the prediabetes range, Afrezza is perfectly appropriate as well. Dispensing with the anodyne title of prediabetes is something we strongly recommend. The research is clear that in the so-called prediabetes range, significant dysfunction is already occurring. "Prediabetes" is just early stage diabetes. Afrezza will be effective in preserving normal blood sugar control.

Afrezza + CGM. Combining Afrezza with modern continuous glucose monitoring technology allows for the management of glucose down to levels previously unattainable. We can literally bring many patients into the non-diabetic range with no increased risk of hypoglycemia. In fact, we can both bring glucose levels down AND reduce the incidence of hypoglycemia at the same time. We think a more appropriate way to live with a Western lifestyle is to combine Afrezza with periodic use of a continuous glucose monitor and to dispense with finger stick readings altogether. Many patients don't comply with the finger stick testing protocols their physician recommends anyway.

Why save your best weapon in a battle until you've already suffered lots of losses? Wouldn't it make more sense to use your best weapon first, especially since it likely means you won't need others? Unfortunately for many people with diabetes, the advance of Afrezza + CGM came after they suffered permanent damage. Despite this, both can be used to more easily manage the disease at any stage. In fact, as diabetes progresses, the management of the disease becomes more difficult. Patient compliance becomes worse, and the decline accelerates. With Afrezza + CGM, compliance will be dramatically better, control will be dramatically better, and quality of life will be dramatically better.

For those newly diagnosed with diabetes, the argument for Afrezza + CGM becomes even stronger. We simply cannot find a better way to manage the disease at present.

A Final Word...

We shouldn't be surprised that this product is the outgrowth of Alfred Mann's genius. He was innovative, brilliant, and more than a touch stubborn, qualities of all successful entrepreneurs. He counseled, "take care of the patient and the business will take care of itself." For him, success was a byproduct of delivering value to others. He brought the world the insulin pump for Type I diabetic patients, understanding the need for a better solution to the multiple daily injections that preceded the pump.

Decades ago Al saw the ravages of Type 2 diabetes as well. He felt compelled to turn his prodigious talents toward finding a solution. He saw the development of many treatments and the glaring deficiency that remained: a truly physiologic prandial insulin. The pharmaceutical industry saw the problems with insulin and developed a myriad of drugs to circumvent the use of insulin. Al Mann saw the problems with insulins and said, "We need to develop a better insulin." Of course he did. And, he gave us Afrezza.

To all medical providers in diabetes: you should heed Al Mann's advice, "take care of patients..." In fact, that is your duty, your ethical and moral obligation. With that as your guide, you simply cannot ignore the facts presented herein, safe in the knowledge that consensus currently supports you. Current care is substandard. Afrezza is a quantum leap forward. Of course, we encourage others to conduct their own studies. Develop the data for yourselves. Challenge our conclusions. We are quite confident what you will find.

We know our protocol sounds revolutionary, some might even say irresponsible. But those who say such things do so without the benefit of the facts. They are responding to emotion not data, habit not science. Our interest is in the facts, and the best possible care for diabetics, not fealty to precedence, consensus opinion, or political or economic pressure. Doctors considering our recommendations might benefit from the advice of the renowned, German mathematician, Carl Jacobi, who counseled in trying to solve a difficult dilemma, "Invert, always invert." So, imagine, if Afrezza had been developed first, would anyone bother with all the other medications currently in use?