Closer Look

MEMORANDUM

FDA Advisory Committee votes 13-1 and 14-0 to approve MannKind's Afrezza for type 1 and type 2 diabetes, respectively - April 3, 2014

Executive Highlights

- The FDA EMDAC voted 13-1 in favor of approval for MannKind's inhaled insulin Afrezza for type 1 diabetes, and 14-0 in favor of approval for type 2 diabetes.
- Overall, FDA presentations were uniformly negative. Specifically, the Agency was not convinced of a hypoglycemia benefit, interpreted Afrezza's results as falling short of A1c non-inferiority (in type 1), emphasized high study dropout rates, and suboptimal insulin titration, and characterized Afrezza's efficacy in type 2 as "modest" compared to oral agents. Panel discussion regarding discussion topics and questions was, by contrast, patient centered and more focused on the product's convenience, which we see as a positive since convenience is so associated with adherence.
- Much uncertainty remains regarding labeling (e.g., possible pulmonary function screening requirements) and positioning in the treatment paradigms of each disease.

After a busy day of deliberation in which the FDA was quite negative on MannKind's inhaled insulin Afrezza, the Endocrinologic and Metabolic Advisory Committee delivered a striking, nearly unanimous vote in favor of approval: 13-1 for type 1 diabetes and 14-0 for type 2 diabetes. Coming into the meeting, the FDA's briefing documents was on the negative side balanced (see our summary of the briefing documents), and following a highly negative set of agency presentations in the morning, approval looked much less likely, particularly in type 1 diabetes . In the afternoon, the panel engaged in fairly directed patient-centered discussion, balancing the drug's modest comparative efficacy to subcutaneous insulin and pulmonary safety concerns against the significant patient convenience factor of inhaled insulin and a possible hypoglycemia benefit. We understood the data and also understood the company may not have invested appropriately in trials - but from our view, the best "comparator" isn't sub-cu insulin since so many don't use that product appropriately (or at all) in the "real world". Though the near-unanimity of the votes sends a clear message to the FDA, it's also important to point out that the binary nature of the votes didn't reflect the complexity of the opinions. For example, some of the "yes" votes were delivered with only marginal confidence (e.g., pulmonologist Dr. James Stoller and oncologist Dr. Eva Szabo each stated that their confidence in a "YES" vote was only a "two" on a scale of one to ten" due to safety concerns). Similar to most FDA votes we have seen, a number of other votes were similarly accompanied by caveats and assumptions regarding contraindications, screening, and post-marketing monitoring. It's tough to call what the FDA will say come Afrezza's PDUFA date on April 15, or even if the Agency will make a final determination by then. Overall, we believe it is unlikely, given the number of label-related questions that that have emerged.

Although no single issue emerged as a deal-breaker for Afrezza, the agent's perceived modest comparative efficacy (by some panelists, along with the FDA) made balancing benefit versus risk a tougher proposition a harder decision for some. The FDA stated early that it saw no clear evidence of a hypoglycemia benefit with Afrezza, further reducing the compound's proposed value (we believe that a good CGM study using an accurate-in-hypoglycemia CGM will be far more valuable than the 7-point SMBG profiles that were used in the MannKind studies - better CGM wasn't available for testing when MannKind did studies). The pulmonologists on the panel expressed concern about the possibility of people with undiagnosed asthma and COPD ending up on the drug, especially since both diseases are quite difficult to diagnose; trials had found that if these patients used Afrezza, they would experience reductions in lung function. The panel generally

agreed that not enough data was available to conclusively decide on a lung cancer signal, and that post-marketing surveillance will be key. That was a very favorable decision for MannKind in our view - we were thinking FDA was stacking the panel with pulmonologists who might have a much more negative view and might be very risk averse.

Looking ahead, although approval seems much more likely at this point, several questions remain that could make or break the drug's potential on the market, most related to reimbursement, and MannKind's ability to partner. What the drug label will look like and how this therapy will fit into the diabetes treatment paradigm remain uncertain. Formulary status will be key, and obviously with just one product, MannKind is as a disadvantage compared to companies like BMS/AZ and Lilly/BI who have so many products. (Many big companies could benefit with such an easy product to prescribe and teach and use, though! To have a product that patients might actually consistently use would be a boon.) Some panelists wondered whether Afrezza's availability might actually delay patients' progression to basal insulin, which has proven strong efficacy (though this is a major question, we don't see it impacting reimbursement or partnering). In type 1, we could see Afrezza being used as a sort of "hyperglycemia rescue" for patients that need to quickly correct severe hyperglycemia or that are dosing too close to a meal for injectable insulin to be useful - while that seems unlikely to be reimbursed early on, there will definitely be key groups who should get reimbursement and who we expect will. Beyond these early questions, other important questions remain about reimbursement (Will payers accept Afrezza's efficacy?) and how strongly HCPs' negative experience with Pfizer's Exubera will weigh in considering this agent (unfortunately, inhaled insulin has some "baggage"). "Real world experience" will be absolutely key - payers have long wanted more people on insulin, and if Afrezza is priced the same as traditional insulin, which we expect, payer views may be better than expected if they see much better "real world" adherence (patients using and benefiting from the product). All in all, the Advisory Committee vote was a critical step along Afrezza's path towards successful commercialization, and a giant leap for MannKind (and innovator Mr. Al Mann).

Our coverage contains perspectives from the panel, MannKind, and the FDA on the biggest discussion points of the day, including (i) efficacy in type 1 diabetes; (ii) efficacy in type 2 diabetes; (iii) pulmonary safety and lung cancer; (iv) pharmacokinetic, pharmacodynamic, and dosing issues; (v) coverage of the open public hearing; (vi) discussion points and two voting questions, with a panelist-by-panelist rationale for each. We conclude the report with a discussion of several remaining key questions.

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I. Efficacy in Type 1 Diabetes

MANNKIND PERSPECTIVE

David Bregman, MD, PhD (Director, Clinical Development, MannKind, Valencia, CA)

MannKind's Dr. David Bregman summarized the design and results of the most recent phase 3 study of Afrezza in patients with type 1 diabetes - see our comprehensive report on this study here. The 24-week trial randomized 518 patients to use of Afrezza (either the Gen 2 [n=174] or original MedTone inhaler [n=174]) or insulin aspart (n=170); patients remained on their background basal insulin throughout the study (70% were on insulin glargine). Management emphasized that this trial was designed with input from the Agency, which served as a good reminder for panelists when trial design issues and questions came up in discussion (e.g., Should the study have been open label, or should dummy injections and dummy inhalers been used?). Overall, Afrezza demonstrated non-inferiority relative to insulin aspart in the primary analysis. Management emphasized that this was confirmed in "multiple sensitivity analyses" except with the "worst case imputations" - this did a good job of countering the FDA's concerns over non-inferiority (see below). Afrezza also showed a significant advantage on hypoglycemia - a 30% reduction in total hypoglycemia and a 43% reduction severe hypoglycemia (both p<0.05). MannKind devoted a few specific slides to some of the FDA's other main concerns with this study - sub-optimal insulin titration and whether the differences in A1c confounded Afrezza's apparent hypoglycemia advantage over aspart.

- **In the primary efficacy results, Afrezza was non-inferior to insulin aspart at the pre-specified A1c margin of 0.4%.** A1c declined by 0.2% in the Afrezza group vs. 0.4% in the insulin aspart group, both from a baseline of 7.9%. The treatment difference of 0.19% translated to a p-value of 0.016 and a 95% confidence interval of [0.02-0.36] - just sneaking under the non-inferiority margin of 0.4%. (As an aside, we'd note that the FDA's numbers (see below) differed slightly: a baseline A1c of 8.0% for the Afrezza group, a treatment difference of 0.22%, and a 95% confidence interval of 0.08-0.37. We assume the discrepancy results from different statistical approaches.)
    - **Dr. Bregman emphasized that non-inferiority was confirmed using mixed model repeated measures (MMRM), the "preferred approach to handling missing data in longitudinal clinical trials."** A per protocol assessment also supported non-inferiority, as did multiple sensitivity analyses. Only with the "worst case imputations" (see FDA's presentation below) was non-inferiority called into question.
- **Overall, Afrezza led to a 30% reduction in total hypoglycemia (9.8 vs. 14 events per subject-month) and a 43% reduction in severe hypoglycemia (8 vs. 14 events per 100**

subject months) vs. insulin aspart [p<0.05 for both]. Several subsequent slides on hypoglycemia countered the FDA's view that Afrezza's apparent hypoglycemia advantage was the result of lower efficacy vs. aspart.

    - **By A1c:** Over the 24-week study period, Afrezza had a lower total hypoglycemia event rate than insulin aspart for every A1c category (5.5-6.5%, 6.5-7%, 7-7.5%, 7.5-8%, >8%). The difference was greatest in the population with an A1c of 7-7.5%, where Afrezza led to a 40% reduction in hypoglycemia (10.5 vs. 17.4 events per subject-month). The smallest benefit of Afrezza on hypoglycemia came in those with an A1c >8% - a 13% reduction (8.6 vs. 9.9 events per subject-month).
    - **Post-meal**: Dr. Bregman showed the total hypoglycemia event rate stratified by study week and time post meal. Afrezza and insulin aspart had nearly identical rates of total hypoglycemia from 0-2 hours post meal; the clear advantage for Afrezza came in the 2-5 hour post-meal window, where it had a much lower rate of hypoglycemia for all 24 weeks of the study. Importantly, during the study's follow-up period (weeks 25-28) - when Afrezza use was discontinued and all patients reverted to insulin aspart - the 2-5 hour hypoglycemia advantage disappeared. This supports the conclusion that Afrezza's shorter tail of insulin action reduces the occurrence of delayed post-meal hypoglycemia.

- **Dr. Bregman's slides specifically addressed the FDA's concerns about basal and prandial insulin titration in the type 1 trial.** While the FDA's plots of insulin use over time (see Dr. Yanoff's talk below) showed a clear divergence in titration between the Afrezza and insulin aspart groups, MannKind's plots made the groups look quite similar. We noticed a key difference that made the data look much less concerning in MannKind's case - the company's plots showed the *mean total daily* basal and prandial insulin doses over the course of the trial (a y-axis scale of 25-45 units for basal, 20-30 units for insulin aspart, and 70-130 units for Afrezza), while the FDA's plots showed the *change in insulin doses* over the course of the trial. A clear reminder of how the same data can be used to argue opposing sides, simply due to the way it is presented.
- **Dr. Bregman briefly discussed Afrezza's 1.3 kg weight advantage** (-0.4 kg of weight loss in the Afrezza group vs. a 0.9 kg weight gain in the insulin aspart group), though it was hardly mentioned during the rest of the day's discussion. It did not emerge as a key advantage of Afrezza or a reason to vote in favor of it.

FDA PERSPECTIVE - A1C

Lisa Yanoff, MD (Clinical Reviewer, FDA)

FDA Clinical Reviewer Dr. Lisa Yanoff discussed the clinical efficacy of Afrezza, severely calling into question many aspects of the most recent phase 3 study in type 1 diabetes. The Afrezza arm had much higher dropout rates (25% vs. 11% on insulin aspart), and the worst-case scenario sensitivity analysis performed to evaluate the effect of these dropouts caused Afrezza's non-inferiority to insulin aspart to disappear. In addition, Dr. Yanoff shared concerns about the insulin titration in the study - insulin aspart was "minimally titrated" in the comparator arm, and the average daily basal and prandial doses used in the Afrezza group were consistently higher than those used in the aspart group (in the face of a lesser improvement in A1c) - this further called into question the evidence for any glycemic effectiveness of Afrezza in type 1. Following this FDA presentation, an approval for type 1 diabetes seemed far less likely than our impression entering the day. Despite the Committee's ultimately supportive 13-1 vote for an approval of Afrezza in type 1 diabetes, it is certainly possible the FDA could ask for more pre-approval data in type 1 diabetes, given that the Agency is not convinced Afrezza has a hypoglycemia advantage. We would love to see a CGM study, though don't believe that should be required before approval.

- **In the primary efficacy results, Afrezza was non-inferior to insulin aspart at the pre-specified A1c margin of 0.4%.** However, given that the lower bound of the 95% confidence interval exceeded zero, Dr. Yanoff highlighted that Afrezza was statistically worse than aspart on A1c change. The upper bound of 0.37% was also very close to missing the 0.4% margin, a point that

came up again and again throughout the day. Dr. Yanoff further reminded listeners of MannKind's original phase 3 study in type 1 diabetes (#009) was also borderline for the treatment difference, with an upper CI bound of exactly 0.40%.

	Afrezza	Insulin Aspart	Treatment Difference	95% CI
Baseline A1c	8.0%	7.9%		
Change in A1c	-0.2%	-0.4%	0.2%	0.08-0.37

- **Dr. Yanoff's review of the phase 3 trial in type 1 diabetes immediately drew attention to study dropouts and missing data.** Dropouts were 21-25% in the two Afrezza arms (MedTone and Gen 2 inhalers) vs. 11% on insulin aspart. Dr. Yanoff noted that the observed dropout rate in the aspart arm was "more consistent with the expectation in such a trial." She noted, "The degree of missing data raises issues on the reliability and confidence of the results."
    - **Dr. Yanoff showed two concerning A1c plots over time, separated by completers and dropouts.** While A1c declined in parallel in the two completer groups, the A1c trends in those who dropped out of the study diverged - type 1 patients on Afrezza experienced a slight rise in A1c between weeks four and 12 of the 24-week study, and A1c at 16 weeks showed no change from baseline. By contrast, those who dropped out of the study in the aspart arm saw a continued decrease in A1c over the 16 weeks.
- **In the FDA's worst-case scenario sensitivity analysis, Afrezza's non-inferiority to insulin aspart disappeared.** The analysis added 0.4% in A1c to every discontinued Afrezza subject assuming all subjects were "missing not at random" (MNAR). This increased the treatment difference between Afrezza and aspart from 0.2% to 0.38%, and widened the confidence interval from [0.08-0.37] to [0.15-0.48]. While this analysis was clearly a challenging bar to meet, the FDA was concerned that it pushed the upper bound of the confidence interval (0.48) over the pre-specified margin of 0.40%.
- **Dr. Yanoff raised multiple concerns with the insulin titration in the type 1 study**. She noted that the population studied in the type 1 trial was generally healthy, without severe complications, and not selected to be at high risk for cardiovascular disease. She said, "One may argue that the investigators should have been comfortable following the titration algorithms." Based on the data, this did not seem to be the case.
    - **Prandial titration was much less aggressive in the insulin aspart arm of the study.** Dr. Yanoff showed a plot charting the change in prandial insulin dose over time in the two study groups. At every point, the change in the prandial insulin dose in the Afrezza arm was much higher vs. the aspart arm. In cutting the data by meal, patients on Afrezza reached the prandial titration target at a much greater rate than in the insulin aspart arm - 37% vs. 12% at breakfast, 36% vs. 20% at lunch, and 36% vs. 9% at dinner. Given the open label nature of the trial design, Dr. Yanoff called this "an important finding." She said that the inadequate titration of insulin aspart casts doubts on whether the trial judged Afrezza against an optimal comparator ("a crucial aspect of a non-inferiority trial).
    - **Basal insulin titration appeared more aggressive in the Afrezza arm of the study.** Dr. Yanoff showed another plot over time charting the change in basal insulin dose - at every time point, those in the Afrezza arm had a larger change in basal insulin dose. We would note that this might be expected, given that Afrezza's faster profile has a shorter tail and would thus require more background basal insulin in between mealtime doses - Dr. Yanoff did not acknowledge this fact, which was a disappointment.
    - **Only a small percentage of subjects reached the basal insulin titration target by week 12 -** 10% in the Afrezza arm vs. 13% in the insulin aspart arm. We're not sure why

the FDA chose week 12, as the basal optimization phase ended at week four, followed by a 12-week prandial titration phase. In addition, we'd note that the basal insulin titration targeted an very challenging fasting glucose target of 100-120 mg/dl - given the day-to-day variability of type 1 diabetes, we were not surprised to see that so few patients met the targets.

- **The insulin aspart arm saw more patients reach glycemic target (A1c ≤7% or ≤6.5%) who were above target at baseline.** Dr. Yanoff pointed out that the relatively low responder rates suggest that both groups were inadequately titrated to reach glycemic goals. Again, we'd note that the titration targets were quite challenging to meet (basal: 100-120 mg/dl; prandial: 110-160 mg/dl 90 minutes post-meal).

	Afrezza	Insulin Aspart	P-value
A1c ≤7% at week 24 and >7% at baseline	10%	21%	0.01
A1c ≤6.5% at week 24 and >6.5% at baseline	5%	11%	0.1

FDA PERSPECTIVE - HYPOGLYCEMIA

Lisa Yanoff, MD (Clinical Reviewer, FDA, Silver Spring, MD)

Dr. Lisa Yanoff presented on the non-pulmonary safety of Afrezza, devoting just three slides to hypoglycemia. Her remarks were again quite negative, headlined by the statement that there is "no clear, consistent evidence of a hypoglycemia benefit with Afrezza." Rather, she suggested that Afrezza's apparent hypoglycemia advantage in the type 1 diabetes trials "is consistent with the finding that Afrezza was less effective than the comparator" - in other words, the Agency's perspective is that Afrezza's smaller A1c-lowering efficacy would result in less hypoglycemia. We would argue that the opposite causal flow is also true - less hypoglycemia in the Afrezza arm would raise A1c and make Afrezza look worse. Indeed, the latter seems more likely, given all we have heard from key opinion leaders like Dr. Lois Jovanovic and Dr. Steve Edelman (both of whom spoke compellingly in favor of Afrezza in the Open Panel Hearing) about the "fast in, fast out" nature of Afrezza. In the clarifying questions that followed her talk, the FDA's Dr. Jean-Marc Guettier (Acting Division Director, Division of Metabolism and Endocrinology Products) went as far to say that it would be "very, very challenging for any sponsor to claim a hypoglycemia benefit for any product." To do so, the Agency would want to see a dedicated hypoglycemia study where A1c was matched between the two groups. As a result, we would be quite shocked to see a hypoglycemia benefit claim in the Afrezza label, should it be approved.

- **In the clarifying questions, Dr. Guettier also highlighted that "hypoglycemia is a very difficult thing to capture in a clinical trial,"** as it relies on the patient to capture the event (vs. A1c, which is centrally measured). This was of course a major point of contention at the insulin degludec advisory committee, where the FDA also called into question that insulin's hypoglycemia advantage. In our view, this is a prime example of where CGM can collect the data and truly establish a hypoglycemia benefit or not.

PANELIST PERSPECTIVES

Regarding the efficacy of Afrezza in type 1 diabetes, some panelists seemed to side with the FDA on its questionable non-inferiority to insulin aspart - Dr. Erica Brittain called it "borderline at best" and Dr. Robert Smith shared his "concerns that the efficacy may be less than subcutaneous insulin." Others were more accepting of Afrezza's usefulness - Dr. Ed Hendricks called the effectiveness evidence in type 1 diabetes "convincing" and Dr. William Calhoun felt that the efficacy was "close" to meeting the prespecified margin, and even in the worst case fell within the FDA's guidance. Panelists who addressed hypoglycemia did not seem completely convinced that a benefit had been fully demonstrated - Dr. Abraham Thomas said that

there was "potentially less hypoglycemia," and Dr. Erica Brittain noted that she was "not completely sure how to interpret the hypoglycemia data." Despite the less-than-enthusiastic tone on the efficacy data, panelists were very willing to trade it for the many patient advantages of Afrezza. Many panelists cited clear value of Afrezza in several subgroups of patients - patients with needle phobias, those who miss doses of insulins (e.g., factory workers who cannot stop to take an injection), patients who might need insulin between meals, those with visual impairment, and manual dexterity issues. Below, we've included the eloquent thoughts from patient representative Ms. Rebecca Killion on the value of Afrezza in type 1 diabetes:

- **"From a patient perspective, I've always found that physicians are more enamored with A1c than patients.** I find that as a patient, and I think I speak for the population in general, that there is fear of hypoglycemia. It's an immediate consequence of your condition vs. long-range concerns if my numbers are too high. Patients survive the now to worry about the later. There is a tension between patients and doctors. That should not be forgotten or underestimated. You could be buying a pretty decent A1c with a series of highs and low. That affects patients every single day. Diabetics dance with the devil every single day. There are peaks and valleys, and often you're in transit time, coming in and out of zone. It's very, very frustrating. The message is that patients are failing. But it's not patients that are failing. It is patients being failed by their treatment options. There are things that are not measurable like A1c, but they are incredibly important to patients that have the disease.

II. Efficacy in Type 2 Diabetes

MANNKIND PERSPECTIVE

In the same presentation, Dr. David Bregman also presented on Afrezza's clinical efficacy in type 2 diabetes. In trial 175, the recent pivotal phase 3 trial for Afrezza in type 2 diabetes, Afrezza (on top of oral agents) led to a 0.8% mean A1c reduction compared to 0.4% with oral drugs alone (baseline A1c = ~8.25%). Dr. Bregman emphasized that the results were confirmed by multiple sensitivity analyses, to account for missing data (which the FDA listed as a major concern). He also presented data from the older trial 102, in which Afrezza plus basal insulin was compared to a biphasic rapid-acting (BPR) 70/30 insulin mix. Here, Afrezza was statistically non-inferior, with an A1c reduction of -0.59% vs. -0.71% with BPR; the point estimate for the treatment effect was statistically significant, but fell within the non-inferiority margin. Dr. Bregman next highlighted "compelling" findings from secondary analyses. Nearly 40% of patients on Afrezza in trial 175 reached an A1c goal of 7.0%, compared to only ~15-20% of those on oral drugs alone. Other analyses showed improvements in seven-point glucose profiles (a clear blunting of postprandial hyperglycemia), as well as mean body weight compared to BPR (but not oral agents). A dose-response analysis of trial 175 found a fairly linear reduction in postprandial glucose excursions with linear Afrezza dose increases - we saw this as a way to pre-empt the "atypical dose response" concern that the FDA had mentioned in its briefing documents. Dr. Bregman's overarching message on efficacy in type 2 diabetes was that Afrezza provided a superior A1c reduction compared to oral drugs alone, and was non-inferior relative to an active comparator.

- **Dr. Bregman's presentation also touched upon the hypoglycemia benefit seen with Afrezza (relative to an active comparator) in type 2 diabetes.** In trial 102, Afrezza was associated with a 33% reduction in total hypoglycemia and a striking 68% reduction in severe hypoglycemia versus BPR. The slide on hypoglycemia only shared the results of trials with active comparators, and (as a result) did not show the hypoglycemia results from trial 175 - Afrezza plus oral drugs was associated with a significantly higher incidence of mild/moderate hypoglycemia compared to the group on oral medications only (67% vs. 30%, $p<0.0001$). That finding is of course not particularly surprising, especially since oral drugs in the Afrezza group could not be changed without *discussion between the principal investigator and the medical monitor.*
- **Earlier in the series of sponsor presentations, Dr. Janet McGill (Washington University in St. Louis, MO) discussed the unmet medical need in diabetes, setting the stage for Dr. Bregman's discussion of Afrezza's clinical efficacy.** She highlighted the

clinical inertia in type 2 diabetes, citing a Kaiser Permanente study that found a five-year average gap between failure on oral agents and initiation on insulin. Fear of weight gain and hypoglycemia, along with convenience factors, are causes and/or contributing to this inertia - they are also factors that appear to improve with Afrezza.

FDA PERSPECTIVE

The FDA's Dr. Lisa Yanoff acknowledged that Afrezza proved superior to oral medications alone in type 2 diabetes patients in trial 175, but stated that the "efficacy of Afrezza for type 2 diabetes may be considered modest compared to some other available antidiabetes therapies, including non-insulin oral antidiabetes drugs." We thought this was a remarkably negative spin on some of Afrezza's more unquestionably positive data. Dr. Yanoff argued that, while Afrezza was compared with placebo in trial 175 (on a background of oral type 2 diabetes drugs), a comparison against an active comparator such as insulin would be more clinically relevant. Showing a summary slide of the placebo-adjusted A1c benefit seen with other diabetes drug classes (including DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 agonists, and bile acid sequestrants), which ranged from -0.5% to -1.1%, she suggested that a ~0.4% placebo-adjusted benefit in trial 175 could be considered unimpressive, especially for an insulin. Further supporting this argument, in her view, is the fact that less than a third of patients on Afrezza in trial 175 who started with an A1c above 7.0% ended with an A1c at or below that goal after 24 weeks (although that proportion is greater than the 15% of placebo patients who achieved a goal of 7.0% or less). As opposed to the FDA's analyses for the type 1 trial, the agency's sensitivity analyses to account for missing data in trial 175 did not change the primary outcome of superiority.

- **Dr. Yanoff reviewed other parameters measured in trial 175, including fasting plasma glucose and body weight.** There was no clinically meaningful difference in fasting plasma glucose between the two arms (-11 mg/dl with Afrezza vs. -4 mg/dl with orals alone); this result was more in line with expectations, relative to the significant and somewhat surprising FPG reduction seen in trial 171 in type 1 diabetes (-25 mg/dl vs. +10 mg/dl in the insulin aspart group; p=0.0027). There was a slight average weight gain (0.5 kg) with Afrezza plus orals in the 171 trial, while the placebo group on orals only lost weight slightly (-1.2 kg), another unsurprising finding.
- **The FDA's analysis of trial 175 found a very slightly larger effect size as compared to the sponsor analysis (-0.42% vs. -0.40%).** This difference did not appear to affect statistical significance or the superiority analysis.

PANELIST PERSPECTIVES

Despite the differing efficacy comparisons in trial 175 in type 2 vs. 171 in type 1, many panelists felt that much of what had been said in the discussion of Afrezza's use in type 1 diabetes applied to type 2 diabetes, especially the subgroups that might be a particularly good match for Afrezza (patients with frequent or severe hypoglycemia, needle phobia, difficulties taking injections in daily life, and weight management issues). Additionally, Dr. Abraham Thomas noted that Afrezza's simplicity and convenience could be a good option for elderly type 2 diabetes patients managed by a family member or caregiver rather than at a nursing home. Patient representative Ms. Rebecca Killion summarized Afrezza's role in the type 2 diabetes treatment paradigm well when she noted that the drug "may be inferior to injectable insulin, but it is far superior to no insulin" in patients that require treatment intensification. A critical concern raised during discussion was whether the commercial availability of Afrezza could reduce intensification to basal insulin (which most agreed is a very valuable and effective treatment option, particularly in those struggling with fasting glucose). This is a particular concern with primary care physicians, who might be swayed by the relative simplicity of training a patient on Afrezza. The FDA specifically asked the committee whether Afrezza should only be used as an add-on to a basal insulin or if it would also be appropriate for patients on oral therapy alone. Dr. Smith responded that both cases are appropriate, as the data does not currently exist to answer this question. Although patient fear of needles has frequently been cited as a factor favoring Afrezza, Dr. Thomas felt that needle-phobia is fading as needles get smaller (32 gauge) and given strong patient acceptance of GLP-1 agonists (in his experience). Despite these questions and concerns, the panel

voted unanimously in favor of approval in type 2 diabetes, and had a much higher level of confidence in that vote than in the vote for type 1 diabetes.

- **Dr. Smith and other panel members were concerned with the use of large doses of Afrezza in highly insulin resistant type 2 diabetes patients, since the candidate's effectiveness at these levels seems to diminish.** Dr. Smith suggested that pharmacovigilance programs could help address this issue. Overall, this did not seem to be a critical voting issue for any panelist - if a patient started "maxing out" on Afrezza (assuming there is indeed a diminishing effect at higher doses), we imagine they could switch to injectable rapid-acting insulin.
- **Dr. Abraham Thomas emphasized the need for a treat-to-target trial for Afrezza in type 2 diabetes.** In his view, without a trial with forced titration that examines whether Afrezza can help patients and providers achieve a given target (whether or not Afrezza proves more effective than a comparator), all we have are "hypotheses and feelings" in his view. A successful treat-to-target study would likely bolster provider confidence in Afrezza's efficacy, and help to better inform risk/benefit assessments for the drug.
    - **Later in the afternoon, while justifying his "YES" vote for type 2 diabetes, Dr. Thomas also called for a trial testing Afrezza against a rapid-acting injectable insulin as an add-on to basal insulin.** We would want to see that data as well, given that Afrezza would occupy an obvious place in type 2 diabetes patients as an add-on to basal insulin, a use that has not yet been fully tested. He also called for more data on Afrezza in the elderly, expressing hope that Afrezza might be able to help elderly patients (who generally have greater problems with hypoglycemia) get closer to their targets safely.

III. Pulmonary Safety and Lung Cancer

MANNKIND PERSPECTIVE

Dr. Nikhil Amin (VP, Clinical Development, MannKind) delivered the sponsor presentation on Afrezza's clinical safety, focusing on pulmonary safety and lung cancer. The lung-related safety issues included (i) cough, (ii) reductions in lung function, (iii) contraindication in patients with lung disease, and (iv) lung cancer. Comparisons between the first generation MedTone inhaler and the newer Gen2 inhaler found the two to be equivalent, meaning that MannKind could leverage data from trials using the MedTone inhaler to support safety. The company's clinical development program included ~6,500 diabetes patients and healthy volunteers. In the overall safety population (type 1 and type 2 diabetes; phase 2 & 3), the incidence of treatment-related adverse events was slightly higher in the Afrezza group than the comparator group (64.9% and 60.8%, respectively), as was the incidence of adverse events leading to discontinuation (7.2% and 1.1%, respectively); both imbalances were driven primarily by the increased incidence of cough seen with Afrezza (26.9%) vs. the comparator arm (5.2%). Dr. Amin emphasized that most of the pulmonary safety issues seen during Afrezza's clinical testing were either mild, statistically insignificant, relatively clinically insignificant, preventable, or some mix of those characteristics.

- **Although the incidence of cough was greatly increased with Afrezza, Dr. Amin shared a number of factors that provided some comfort on the issue.** The incidence of cough was highest during the first week of treatment, and decreased with time. Cough was generally mild, occurred within ten minutes of dosing, and was not associated with any changes in pulmonary function or insulin dose. Cough lead to discontinuation of 2.8% of subjects on Afrezza, which (in our view) means it was a fairly significant side effect in at least some patients. Interestingly, the incidence of cough in patients only exposed to the Technosphere powder (with no adsorbed insulin) was relatively high (19.7%), indicating that at least some of the cough is due to the excipient (FDKP), or simply due to the inhalation of a powder.
- **Slight reductions in lung function were seen with Afrezza, but Dr. Amin pointed out that these changes generally emerged early in treatment (first three months), did not worsen over two years of treatment, and were reversible after treatment cessation.**

The differences in lung function, measured as forced expiratory volume in one second (FEV_1), between the Afrezza and comparator groups (~0.04 L) were not necessarily very clinically relevant in and of themselves, but they raise questions about the longer-term effect the drug may have. Long-term changes in lung function, in some cases, are irreversible, a fact that was brought up during the afternoon discussion.

- **MannKind suggested that Afrezza be contraindicated in patients with asthma or chronic obstructive pulmonary disease (COPD) or other chronic pulmonary diseases.** Afrezza treatment in these populations led to moderate, transient reductions in lung function as well as wheezing and bronchospasms in asthma patients. MannKind would also recommend screening of patients for pulmonary conditions before initiating treatment (the company would probably prefer this to be a recommendation rather than a mandate), and would communicate the potential pulmonary risks of Afrezza to potential prescribers as part of a REMS program.
- **Unsurprisingly, on lung cancer, Dr. Amin stuck to the statistics (which do not show a significant increase in overall cancers or lung cancers).** There were two cases that emerged in the Afrezza group during trials, and another two cases that emerged during follow-up, as compared to no cases reported in the comparator group. Dr. Amin noted that the observed incidence of lung cancer in the Afrezza group (though higher than with placebo) was less than the expected incidence of lung cancer in the background population. The company has suggested a post-marketing study to provide additional data on the issue.
- **Dr. Amin ended by outlining MannKind's proposed comprehensive risk management plan for Afrezza.** Label contraindications would include the lung conditions mentioned previously, and warnings would encourage screening for lung disease and recommend against prescribing Afrezza in smokers. A fairly light REMS program would involve communicating potential pulmonary risks to potential prescribers. A prospective, long-term, post-approval observational study would evaluate the risk of lung cancer, respiratory events, and other long-term outcomes. Finally, an enhanced pharmacovigilance program would be put in place. As we saw during discussion, panel members generally felt that more precautions would be needed to ensure safety if the drug is approved.

FDA PERSPECTIVE

Dr. Miya Paterniti (of the FDA's Division of Pulmonary, Allergy, and Rheumatoid Products, or DPARP) was the senior-most pulmonology expert on the FDA side, and delivered the FDA perspective on the pulmonary safety issues associated with Afrezza. Dr. Lisa Yanoff (of the FDA's Division of Metabolism and Endocrinology Products) discussed lung cancer concerns. Overall, we felt that their presentations were not as overtly negative as many of the other FDA's presentations on other subjects - their approach was to lay the facts on the table in a neutral, open-ended manner. Our high-level takeaway from her presentation was that the FDA thought Afrezza's pulmonary safety concerns are certainly worth examining more closely, and data is limited, but that most of the issues are well characterized, consistent between the earlier and most recent regulatory submissions, and consistent between the Gen2 and MedTone inhalers. Notably, the FDA dedicated an extensive presentation to the results of Exubera's FUSE study, which evaluated whether Exubera exposure increased lung cancer incidence. Ultimately the trial was not entirely conclusive (15 vs. 3 cases of primary lung cancer mortality in Exubera vs. control, but 14 of the 15 cases were in former smokers), and investigators could not rule out that Exubera promoted the progression of existing tumors.

- **None of Dr. Paterniti's remarks about cough, asthma and COPD, or decreased lung function suggested that pulmonary safety issues would impede approval.** She noted that the major limitation of MannKind's data were that they only followed patients for two years, and she seemed open to further investigation in a post-marketing setting.
- **Notably, during the afternoon panel discussion, Dr. Paterniti shared that the FDA is considering recommending lung function evaluations every six months (via spirometry) in patients on Afrezza.** This could certainly help catch cases of emergent or

worsening lung function, but would be quite burdensome for patients and prescribers of Afrezza, given the lack of familiarity among PCPs and endocrinologists with measuring lung function by spirometry. Pulmonologist Dr. Erik Swenson pointed out that it is unlikely that most providers would actually be able to conduct such rigorous and regular follow-ups. Dr. Paterniti acknowledged that the FDA is well aware of these limitations, and is open to suggestions on the matter.

- **Dr. Yanoff reviewed lung cancer concerns, matter-of-factly stating that there was a numerical 4-0 imbalance observed.** She noted that the two patients who developed lung cancer during trials had a history of heavy smoking, while the two patients who spontaneously reported cases after the trials ended had no history of smoking. From panelists' remarks later, we gleaned that the two post-trial cases were quite rare (they were cases of squamous non-small cell lung cancer), so it was a bit suspicious that both of the cases in people with no history of smoking had been squamous NSCLC. Overall, her presentation tacitly implied that the lung cancer findings were curious, but that they were not damning enough to warrant rejecting Afrezza.
- **The FDA's Dr. Patricia Bright (Division of Epidemiology) presented a detailed analysis of Pfizer's Exubera's FUSE trial, evaluating Exubera's risk of lung cancer mortality.** While there was a 15 to 3 imbalance in primary lung cancer mortality for Exubera vs. control, there was also a trend towards a benefit in all-cause mortality for Exubera. In addition, 14 of the 15 Exubera cases were in people with a history of heavy smoking, and the rate of lung cancer was not out of the range for what you would expect in former smokers. There was the chance that Exubera exacerbated cancer in people already at high risk.

PANEL PERSPECTIVES: PULMONARY SAFETY (EXCLUDING CANCER)

Many panelists' primary pulmonary safety concern was whether patients with COPD and asthma could be properly identified so that they would not be exposed to Afrezza. The diagnosis of these two conditions can be quite nuanced and complicated. COPD is estimated to be as prevalent as diabetes, yet most people are undiagnosed. That gives a fairly high risk of undiagnosed COPD patients ending up on Afrezza and experiencing more rapid (and perhaps irreversible) deterioration in lung function. A consensus emerged that some form of screening and/or continued evaluation of pulmonary disease would be necessary, but pulmonologist Dr. James Stoller pointed out that the quality of spirometry (a means of evaluating lung function) measurements are variable in clinical practice, and most primary care physicians and endocrinologists are not familiar with spirometry. Regarding the early decreases in pulmonary function seen in the broad study population (in those without pre-existing pulmonary disease), pulmonologists felt that studies lasting two years were not long enough to provide definitive conclusions on whether lung function would continue to decline beyond two years, and if the decline might be irreversible in the long-term. On a positive note, most panelists accepted the older MedTone data as biologically equivalent to the Gen2 device, based on the clinical trials comparing the two devices, meaning that they accepted the longer two-year data for the MedTone as applicable to the to-be-marketed Gen2 (for which there only exist six-month data). Although the panel overwhelmingly voted in favor of approval during both voting questions, it was apparent that not all panel members were fully confident in Afrezza's pulmonary safety, and had voted "YES" with the expectation of rigorous safeguards and post-marketing programs to monitor for pulmonary safety.

- **Panelists proposed a series of possible solutions to improve pulmonary safety monitoring with Afrezza.** Drs. William Calhoun and Peter Wilson suggested that patients take their first dose of the drug under supervision, at their provider's office, in order to catch early incidences of bronchospasm. However, pulmonologist Dr. James Stoller countered that the effect of Afrezza in patients with chronic pulmonary disease might not be acute, and therefore might not be evident at the first administration. Of course, many panel members emphasized the need for screening and/or continued evaluation, but there was broad doubt on whether such programs could be effectively implemented by Afrezza's likely prescribers (primary care physicians and endocrinologists), who have little experience evaluating lung function. Reconciling this limitation

with the clear need for some sort of safeguard to monitor for lung function changes will be a particular challenge for the FDA in the coming weeks.

PANEL PERSPECTIVES: LUNG CANCER

The pulmonologists on the panel uniformly voiced their concern with the limited data on the numerical imbalance of lung cancers in the Afrezza arm, the theoretical mechanisms by which the high dose of insulin Afrezza delivers to the lung could drive tumor formation or progression, and the poorly designed preclinical carcinogenicity studies. In a quick back-of-the-envelope calculation, Dr. David Cooke demonstrated that the insulin concentration delivered to the pulmonary epithelium could be ten to a thousand times higher than the circulating levels of IGF1, a level that (theoretically) could activate the IGF1 receptor and promote tumor growth. The panel's pulmonologists uniformly expressed their desire for better preclinical studies (i.e., studies in diabetic rodents or in animals with tumor cells injected). Chair Dr. Robert Smith (who has done extensive research on IGF1) countered that we already know that high insulin concentrations can drive tumor growth, and that the real question is whether there is a real risk increase in humans. We think the panel's focus on the poor preclinical studies and basic science was in part due to the inability to draw conclusions from clinical studies, which begs the question of whether a mechanistic link is plausible (which, with insulin being a growth factor, is). Indeed, while oncologists Dr. Eva Szabo and Dr. Antoinette Wozniak (among other panelists) noted that the two post-trial cases of squamous cell carcinomas in non-smokers were quite unusual and disconcerting, they acknowledged that it is likely not possible to confirm a cancer risk pre-approval based on relatively short-term studies. Thus, the pulmonologists focused their energy on urging and re-urging the FDA to make sure the post-market surveillance is robust (measuring cancer incidence and severity so that conclusions can be drawn on Afrezza's impact on the formation of tumors and the progressions of existing tumors).

- **Oncologist Dr. Antoinette Wozniak opened the discussion by discussing data from the FUSE follow-up study, which found an increased incidence of lung cancer with Pfizer's inhalable insulin Exubera.** She agreed with previous presenters that most cases appeared to be linked with smoking, but underscored that the acceleration of pre-existing tumors is still a major drug safety issue. Later in the discussion, Dr. Cooke pointed out that even the relatively low incidence rate of lung cancer in FUSE should still be seen as worrying, given that inhaled insulins could be used by very young type 1 diabetes patients who might face exposures of 50 years or more. We knew that Exubera's trouble history would come up during this phase of the discussion - in many ways, we were surprised that the issue was not discussed more, given how great a focus it was in the FDA's presentations.
- **Dr. William Calhoun raised the possibility that the FDKP carrier/excipient particles, rather than Afrezza's insulin component, could have a tumor-promoting effect.** FDKP is a derivative of piperazine, a dinitrogen-substituted hydrocarbon, which is believed to have possible tumor-promoting effects. Though mechanistically plausible, this would be a hard hypothesis to test, as very few patients have (or will be) exposed to the Technosphere powder alone.
- **Ultimately, while lung cancer was one of the top few safety concerns during discussion, the lack of conclusive data in either direction and the small number of events kept most panelists from denying Afrezza approval.** Many panelists did cite uneasiness regarding the uncertainty over lung cancer in their post-vote speeches as a factor that reduces their confidence in their "YES" vote. Lung cancer was a major factor behind the day's single "NO" vote, from Dr. David Cooke, who said that he would prefer to see better preclinical data on the issue. As with non-cancer pulmonary safety, we believe that most candidates' "YES" votes were delivered with an implicit understanding that rigorous post-marketing monitoring will be implemented.

IV. Clinical Pharmacology

MANNKIND PERSPECTIVE

- **MannKind highlighted Afrezza's clinical pharmacology as a unique and favorable feature of the drug**, noting that the time-action profile has a faster onset and shorter duration than rapid acting insulin (Afrezza reaches peak concentrations in 12-15 minutes and has a peak glucose lowering effect [as measured by glucose infusion rate during a glucose clamp] at 30 minutes, while rapid acting insulin analogs have a peak concentration at ~60 minutes and peak glucose lowering effect at ~120 minutes). While Afrezza demonstrated dose-linear pharmacokinetics (concentration of insulin in the bloodstream rose proportionally with dose increases), it exhibited an attenuated pharmacodynamic dose response that was less-than-dose-linear. Specifically, at Afrezza doses higher than about 60 units (roughly 20 units of subcutaneous insulin), the incremental glucose-lowering effect of adding additional Afrezza decreased. MannKind noted that this saturation effect is characteristic of all insulins because insulin's pharmacodynamic response is driven by the amount of insulin in "effect compartments" (e.g., liver, muscle, adipose tissue), and not by levels in systemic circulation. Once these sites are saturated, adding additional insulin does not confer more of an effect.

FDA PERSPECTIVE

- **The FDA's Dr. Lokesh Jain came down negatively on Afrezza's clinical pharmacology, and he seemed to misunderstand the positive implications of Afrezza's faster on-off profile.** Indeed, Dr. Jain's presentation implied that Afrezza's rapidity and shorter duration of action compared to rapid acting analogs was a bad thing. He later corrected himself in Q&A (following an incisive question from a panel member), stating this his intent was merely to point out the difference and seek to explain the lower efficacy in type 1 diabetes.
    - **He was particularly concerned about the implications of the dose attenuation at ≥60 units for MannKind's proposed dosing regimen for converting subcutaneous insulin doses to doses of Afrezza.** The less-than-linear dose response calls into question whether MannKind's proposed conversion factor is valid (a constant 3.4 multiplier from the subcutaneous insulin dose). At high doses, this conversion factor would underestimate the amount of Afrezza needed and increase risk for DKA (indeed there was an increased rate of DKA for patients on Afrezza in early type 1 studies, but no cases have been seen in more recent studies). We do not see the pharmacokinetic/ pharmacodynamic concerns as an approvability issue, but they may be something that would need to be addressed with another trial to establish a better subcutaneous insulin-to-Afrezza conversion relationship.

PANELIST PERSPECTIVES

- **The committee members were very positive about Afrezza's pharmacokinetics/ pharmacodynamics and were not too concerned about the attenuated response at high doses.** As Dr. Morris Schambelan remarked, a strict linear dose-response is not necessary for a titratable drug where patients are constantly adjusting the dose based on feedback from glucose readings. Most panelists recognized the advantages of Afrezza's faster onset and offset of action, identifying many subgroups of patients who would benefit from this pharmacologic profile. As Dr. Abraham Thomas noted, patients with gastroparesis (decreased stomach motility; a diabetes complication) often struggle with timing their insulin doses because their food is digested so slowly. In addition, he thought that Afrezza could be a useful tool for quickly correcting hyperglycemia in between meals when prandial insulin would be too slow.

V. Open Public Hearing (OPH)

The 17 speakers during the Open Public Hearing (OPH) - the biggest OPH ever for diabetes - all advocated for Afrezza's approval either openly or indirectly (e.g., "we need more options"). This was by far the most powerful OPH sessions we have ever attended. While some KOLs maintain strongly that panelists are never affected by OPH speeches, we would have a hard time believing that to be the case this time around. Surprisingly, Dr. Sidney Wolfe did not participate; he surely would have voiced a negative vote.

- **Dr. Aaron Kowalski (JDRF, New York, NY) emphasized the need for insulins that more closely mimic physiology in people without diabetes.** He explained that type 1 diabetes is a unique disease in which the majority of patients do not reach their glycemic goals. The evidence shows, he maintained, that this is mainly due to the inadequacy of available tools. He cited data from the JDRF CGM trial, in which the average participant spent one third of each day with a blood glucose above 180 mg/dl and 90 minutes each day below 70 mg/dl. Dr. Kowalski particularly called for insulins with better PK/PD profiles, which would be a huge asset to the artificial pancreas. As a type 1 patient and one of the world's foremost experts on closing the loop, his comments added enormously to the Open Public Hearing.
- **ADA Chief Scientific and Medical Officer Dr. Robert Ratner, did not advocate specifically on behalf of Afrezza (in line with the ADA's policy), but did emphasize the need for new, improved agents.** Dr. Ratner underscored the large American population that requires insulin, and that rapid acting insulin analogs have an "unacceptable delay in onset." He noted that while it is easy to take supplementary insulin doses, once insulin is on board it cannot be removed. Dr. Ratner suggested that efforts to tightly control glucose have led to more hospitalizations for hypoglycemia than hyperglycemia, and that hypoglycemia is a "critically important hard endpoint." Dr. Ratner called for the development and approval of insulin preparations that allow people with diabetes to integrate diabetes care into their daily living - every meal, every day, for a lifetime. Though Dr. Ratner's overall message was positive for Afrezza, he did stipulate that people with diabetes must be confident in knowing the precise amount of insulin they are administering, perhaps referencing the FDA's concerns over the robustness of the dosing scheme proposed by MannKind. This was a very impressive talk to come from ADA and we believe panelists listened closely to Dr. Ratner given his reputation and the visibility of ADA.
- **On behalf of "people with diabetes willing to accept the risk/benefit of Afrezza," Dr. Steve Edelman (UC San Diego, CA) asked the panel to consider approving Afrezza.** As a person with type 1 diabetes for 44 years, an endocrinologist, and founder of TCOYD, Dr. Edelman emphasized to panelists the degree to which Afrezza fills an unmet need. One such need is the inability of currently available insulins to limit postprandial excursions and hypoglycemia - major barriers to achieving A1c goals. Dr. Edelman also argued that Afrezza's rapid-on and rapid-off profile could be important in reducing the variability of glucose levels. He told the panel that for CGM users, a frustrating thing to see is how slow currently available insulins are. He vividly (and humorously) illustrated the only perfect way for type 1s to keep their blood glucose levels steady - "I don't eat anything and I stand perfectly still." Dr. Edelman expressed that for many patients, Afrezza could make life with diabetes much easier, and that it would help adherence, a major problem associated with virtually all diabetes therapies.
- **Dr. Lois Jovanovič (Sansum Diabetes Research Institute, Santa Barbara, CA) focused on the importance of controlling postprandial glucose, using pregnancy as a vivid example.** She characterized post-prandial blood glucose as "the most important blood sugar" in pregnancy, as it causes macrosomia (large babies) and predicts diabetes later in life. She noted that with subcutaneous insulin, patients get frustrated because they have to wait "forever" for the insulin to kick in. Making insulin more responsive for diabetes patients (including gestational diabetes patients) will make a difference in terms of outcomes for both this generation and the next one.
- **Our own Ms. Kelly Close spoke on several big-picture trends that Afrezza could help address: the poor state of diabetes control and care in the US, the need to get PCPs on**

board with insulin, and the opportunity to reduce the stigma tied to insulin. See her slides here and commentary on behalf of Close Concerns here. Ms. Close cited *NEJM* data (Ali et al., 2013) showing that diabetes control has not improved over time in the US; people reaching an A1c <7% has actually dropped from 57% to 52% in the two most recent NHANES surveys, and the parentage of people with an A1c >9% has stayed flat at 13%. This poor control is coming at a heavy financial cost: last year the US spent $245 billion on diabetes, demonstrating the need for new products that help keep people out of the hospital where the biggest bills are acquired. Turning her attention to HCPs, Ms. Close underscored the need for PCPs to have therapies that are simple to prescribe and treat. Patients have very little time with their doctor - maybe one hour a year - which does not give physicians much time to learn about their patients' needs or educate them on a new agent. She emphasized the biggest challenge PCPs cite when explaining why they delay prescribing an insulin - needles/injections. On the patient side, Ms. Close reminded attendees of the rampant stigma against diabetes that exists, and how Afrezza's discrete administration could help alleviate this stigma.

- ***diaTribe*** **Managing Editor Mr. Adam Brown spoke on the impact Afrezza could have on his daily life, and the need for glycemic metrics better than A1c** - see Adam's slides here. Adam shared some of his own personal recent CGM readings to illustrate how challenging it can be to manage one's glucose, even with access to the best tools available. In one case, he overate to correct nocturnal hypoglycemia, spiking him to 275 mg/dl by the morning. In another, he woke up hyperglycemic and ended up overcorrecting for morning insulin resistance, which led to a severe crash around noon. Mr. Brown emphasized that even with access to the top therapies and devices, these examples are a peek into how he "still gets it wrong everyday." In light of this, Mr. Brown characterized an insulin with a faster onset and offset (as a "really attractive option" from a patient perspective. Mr. Brown also criticized A1c as a sole metric for glycemic control, arguing, "A1c does not tell the full story. An A1c of 7% is not an A1c of 7%" (to which EMDAC Patient Representative Ms. Rebecca Killion nodded emphatically). Through a series of colorful charts, he demonstrated to panelists how patients could achieve an A1c of 7% spending 100% of the time in zone, or by averaging a series of highs and lows. Mr. Brown urged the panel and FDA to expand the metrics to emphasize *the quality* of a person's A1c, not just the absolute number. Mr. Brown concluded his speech pressing, "Anything we can do to help patients not feel like they are walking a tight rope with their diabetes is huge" and underscored the need to "get rid of the treat-to-failure model."
- **Speaking via webcast, Mr. Manny Hernandez (Diabetes Hands Foundation, Berkeley, CA) made a powerful case for Afrezza's approval, quoting English- and Spanish-speaking users of TuDiabetes.** Mr. Hernandez has been on insulin for over a decade, and in that time, available methods for delivering insulin have improved significantly. However, a needle is still ultimately involved in these methods. Mr. Hernandez recounted how starting insulin was daunting. Ten-thousand shots and thousands of infusion set insertions later, he continues to accept them "only because [he] needs them to survive." Meanwhile millions of people with type 2 diabetes are not on insulin that should be. Indeed, on TuDiabetes, Mr. Hernandez has read thousands of stories of people living with type 2 diabetes who are frightened to start injections, but want to do better. Several users have also offered testimonials on what Afrezza would mean to them: "I think the product has the ability to change the world" and "As a type 2, I can see myself dumping my pump entirely for this solution." Mr. Hernandez closed by noting that while people are concerned about Afrezza's affordability, at least needles will no longer stand in their way to taking insulin.
- **Diabetes advocate Mr. Bennett Dunlap (StripSafely Campaign for Accurate Diabetes Testing) supported the approval of Afrezza from the perspective of a person with type 2 diabetes and the father of two children with type 1 diabetes.** Mr. Dunlap reminded the panel that the diabetes status quo is associated with significant risk, and that insulin is a very dangerous drug. He highlighted a recent *JAMA* study showing that insulin was associated with ~97,000 ER visits and ~29,000 hospital admissions each year in 2007-2011. To put this in

perspective, methamphetamine resulted in 93,000 ER visits - "that insulin beats *Breaking Bad* is evidence that real world solutions are needed."

- **Dr. David Klonoff (Mills Peninsula Medical Center, San Francisco, CA) discussed a series of objective and subjective benefits associated with Afrezza, which he has witnessed firsthand as an investigator from MannKind's clinical trial program.** MannKind paid for his travel to the Advisory Committee meeting. On the objective, data-driven side, he noted that the agent's speed and predictability help reduce postprandial hyperglycemia and hypoglycemia, and cuts down drastically on glycemic variability. On the subjective side, he pointed out that Afrezza is more convenient, less painful, does not require a sharps container, and reduces the likelihood that patients will be accused of being a drug addict (a very real possibility, he noted, on the streets of San Francisco). He emphatically encouraged the panel to vote in favor of approval.
- **Dr. Sandra Connolly (Celerion, Neptune, NJ), a primary care physician and investigator in MannKind's phase 1 program, provided a pragmatic perspective on Afrezza.** Primary care physicians, she emphasized, are more likely to take a compromising stance with regard to managing their patients' chronic diseases, which leads to clinical inertia. This treat-to-failure paradigm stems from a number of factors, including the time required to train patients to administer insulin, limited access to CDEs, and a fear of accidental overdoses. In her experience, training patients on Afrezza takes less than an hour, and overdoses are unlikely (due to clear cartridge marking). From a patient perspective, Afrezza gets around the issue of needle-phobia, and reduces the stigma of insulin injection.
- **Dr. Leddy, representing AACE, shared that the organization welcomes the development of agents that are safe, effective, reduce the risk of hypoglycemia, are easy to administer, and do not cause weight gain.** She focused on hypoglycemia and emphasized that the short and long-term consequences are devastating. Patients fear hypoglycemia almost as much as they fear blindness and kidney disease (the risk is certainly more immediately tangible), and often reduce their insulin dose after a hypoglycemic event. This ultimately reduces adherence, she said, and results in worse outcomes. Although (as expected) Dr. Leddy's talk did not vehemently and explicitly argue for approval, it provided reasons why Afrezza's benefits are worth taking very seriously.
- **A gentleman with type 1 diabetes for over 12 years movingly urged the FDA to approve Afrezza, citing his "life changing experience" participating in Afrezza's phase 3 trial for type 1 diabetes (171).** He movingly stated that one of the hardest points in his life was having to give up Afrezza when the trial ended. He recounted for the panel how his friend's mom died from hypoglycemia when he was very young, and that he has come close to the same situation several times. In the trial, he "could not believe [his] eyes" when Afrezza began lowering his glucose levels "in a matter of minutes," and was out of his system in an hour. Over the course of the trial, his A1c dropped from 8.5% to 7.1% and then into the low sixes. However, he emphasized that A1c does not capture the time in zone he experienced - he did not experience a single severe low over the trial's six months and had only two moderate lows. Additionally, he could take Afrezza as late as 9 PM without fearing nocturnal hypoglycemia. He found it easy to adhere to Afrezza, and could take it discreetly. He also brought two letters for the panelists to read, which were written by family members (including his son who was 14 years old when the trial was ongoing) on witnessing the elimination of his lows during the trial.
- **Ms. Anna Ortiz was a 27-year-old woman with type 1 diabetes who had a very positive experience in an Afrezza trial** - MannKind had paid for her travel to the Advisory Committee meeting. Ms. Ortiz opened by describing how maintaining good glycemic control over the 15 years she has had type 1 diabetes has been a "struggle" despite trying six different types of insulin. She expounded on how college was a particularly difficult time for her diabetes management, and that "late nights, binging on pizza makes [her] hate being diabetic." In the trial, Ms. Ortiz was surprised how easy it was to take Afrezza and highlighted that it did not have a bad taste, and that her blood glucose numbers responded well to it. She appreciated not having the bumps and bruises of

injections, that Afrezza made it much easier to go to restaurants, and that with Afrezza her blood glucose numbers were much more forgiving if she forgot a dosing and took it late. Notably, Afrezza helped Ms. Ortiz control her glucose during her pregnancy - her daughter Celeste is now a happy, healthy 11-month old. Ms. Ortiz concluded by stating that she thinks millions of people with diabetes would benefit from Afrezza, and that "as much research has been done on curing diabetes, nothing has looked as optimistic as this for improving our daily lives."

- **A woman who was diagnosed with diabetes 14 years ago noted that taking five shots of insulin a day caused her to feel like a human pincushion** - a small price to pay, she said, for her health. The best part of being in the Afrezza trial, she pressed, was the drop in her A1c from 8.2% to ~7%. Her frustration was palpable as she noted that her A1c has since risen to 7.9%. Another benefit of Afrezza was how much easier it made it for her to take insulin in public. Additionally, prior to the study she had bruises on her stomach from the inject1ions, and it was "nice to get rid of that abuse." Her travel and hotel expenses were paid for by MannKind.

VI. Voting Questions

TYPE 1 DIABETES APPROVAL

Despite the very negative tone of the FDA's morning presentations, the committee voted 13-1 in favor of Afrezza's approval for a type 1 diabetes indication. Many panelists, however, noted that they were not very confident in their "yes" votes, citing uncertainty with regards to efficacy, DKA, long-term lung safety, and lung cancer. The sole "no" vote for type 1 diabetes came from pediatric endocrinologist, Dr. David Cooke, whose biggest concern related to Afrezza's cancer risk. Most ultimately voted yes because they were convinced that Afrezza would indeed offer a valuable improvement to patients' quality of life, even if that had not been measured in trials, and because they thought safety concerns could be addressed in rigorous post-marketing trials.

YES Votes:

- **Dr. Katherine Flegal (Senior Scientist and Distinguished Consultant, CDC, Hyattsville, MD) voted yes, remarking, "I think that we do not have quite enough information, but perfect is the enemy of the good."** Dr. Flegal characterized Afrezza as a "useful addition" for type 1 diabetes care, though certainly not for everyone. She cautioned that some people might be unresponsive to the agent, and that more practical experience is needed using Afrezza to determine its proper use. Her concern was that the ease of using Afrezza could result in its overuse, by which we think she meant people who should be using subcutaneous insulin will instead use Afrezza, potentially worsening their glycemic control. In terms of Afrezza's lung safety, Dr. Flegal favored the FDA's suggestion of a post-marketing surveillance program that includes an internal comparator group (rather than MannKind's proposed registry lacking a control group). Dr. Flegal did not make many comments or questions throughout the day, so her explanation was one of the few windows into her thinking on Afrezza.
- **Similarly, the astute Dr. Abraham Thomas (Endocrinologist, Henry Ford Hospital, Detroit, MI) voted yes despite a lack of some desirable data.** In particular, Dr. Thomas pressed that a treat-to-target trial of Afrezza is needed. He saw some patient subgroups (e.g., those with reduced dexterity or vision) benefiting the most from Afrezza. The agent's great strength, in his view, is its short action, which might make it a good insulin for lowering glucose levels between meals when a subcutaneous insulin is not a good option for fear of stacking. On the safety side, Dr. Thomas expressed concern about Afrezza's potential association with DKA. Consequently, he called for the FDA to provide good guidelines for patients and providers on when they should use subcutaneous insulin instead of Afrezza to avoid DKA.
- **Patient representative Ms. Rebecca Killion seconded Drs. Flegal and Thomas's comments, acknowledging that while "Afrezza is not a perfect drug...insulin is far from a perfect drug."** Ms. Killion reminded the FDA that "too often [patients] struggle for

glycemic control and it leads to hypoglycemia." She noted that a person does not need to be needle-phobic to want an alternative; multiple injections everyday "are more than a burden…[they are] frustrating and at this point inescapable." Similar to Drs. Flegal and Thomas, Ms. Killion acknowledged the unanswered questions on Afrezza. In particular, she expressed concern about the drug's pulmonary risks. However, on balance, she saw it as an important step for type 1 diabetes care. Earlier, during the panel discussion portion of the day, Ms. Killion made several points that were sharp as a tack that we believe greatly moved other panel members. She lamented physicians' veneration of A1c as the end-all-be-all glycemic measure when "you could be buying a pretty decent A1c with a series of highs and lows," as she found herself doing when she finally got access to a CGM. She emphasized that despite patients' best efforts, they often still feel like they are failing when in fact it is "patients being failed by their treatment options." She drove home the point that while patient empowerment and adherence are not easy to measure, they are incredibly important to patients who have the disease.

- **Dr. Ed Hendricks (Obesity Specialist, Center for Weight Management, Roseville, CA) was convinced that Afrezza is "effective and useful."** On the flip side, Dr. Hendricks did not find the data on Afrezza's "shortcomings" convincing enough to think that its approval should be withheld. While Dr. Hendricks did not speak much throughout the day, his past history of votes at diabetes/obesity EMDAC meetings have demonstrated him to be a fairly liberal voter (5-0 in favor of other drugs prior to Afrezza).
- **Acting Chair Dr. Robert Smith's (Endocrinologist, Alpert Medical School of Brown University, Providence, RI) strongest motivation for voting yes was that Afrezza's inhaled delivery would benefit some patients who were currently not effectively served by current options.** However, Dr. Smith suggested that injectable insulin would likely serve most people with type 1 diabetes better than Afrezza. Though unfortunately, we do not currently have the data to resolve which patients should and should not be on Afrezza. Regarding safety, Dr. Smith felt the data about potential serious adverse events are not strong enough to require pre-approval trials. However, he stressed that he still has several concerns including cancer risk and deteriorating pulmonary function.
- **As she always seems to say, it was a close call for Dr. Erica Brittain (Statistician, NIAID, NIH, Bethesda, MD), because Afrezza is "not as good" as currently available options.** She explained that the primary outcome (A1c change from baseline compared to insulin aspart) in the type 1 diabetes trial was statistically "borderline at best" and that Afrezza has an unknown cancer and pulmonary risk. Still, she decided to vote yes, as she did feel that the prespecified 0.4% A1c margin for non-inferiority was "sort of" met and that Afrezza could be given some leeway on the margin due to its other advantages over subcutaneous insulin. She pressed that patients and HCPs must be educated on Afrezza likely not having the same efficacy as available insulins, and on it not being a good option for everyone. In addressing safety, Dr. Brittain was realistic about the available options for a post-marketing study, acknowledging that "there aren't any wonderful options." While she "would love a randomized controlled trial…that does not seem feasible." Instead, Dr. Brittain recommended the FDA require a surveillance program that has an internal comparator and incorporates a comparison to SEERs (a national database of lung cancers).
- **Consumer representative Ms. Diana Hallare (Visalia, CA) briefly commented on her yes vote.** She liked that Afrezza has a short action profile, can help patients with their glycemic control, and has an alternative route of administration. She would like to see further research with regards to Afrezza's cancer and pulmonary risks, and possible interactions with other medications - we note that no concerns about interactions with other medications came up during the day's discussions, but Ms. Hallare usually raises this concern at every meeting she attends. Ms. Hallare's brief explanation reflected the few comments and questions she made throughout the day.
- **Dr. William Calhoun, MD (Pulmonologist, University of Texas Medical Branch, Galveston, TX) voted yes and quickly listed Afrezza's strengths.** Dr. Calhoun thought that Afrezza's efficacy was close to meeting the pre-specified margin, noting that even in the worst-case

scenario it fell within the FDA guidance of "0.3%" (we were a bit confused by his use of "0.3%," as the pre-specified non-inferiority margin had clearly been 0.4%, a mark Afrezza met in the primary analysis but not in the pessimistic sensitivity analysis. If he was referring to the conventional arbitrary A1c-lowering threshold that diabetes drugs are informally expected to meet according to the ADA, that would be 0.5%). Additionally, Dr. Calhoun cited Afrezza's hypoglycemia benefit (which he thought was a "real finding"), reduced weight gain, and reduced injection burden. We also appreciated Dr. Calhoun's recognition that Afrezza "empowers patients" while giving providers another option. Like other panelists, Dr. Calhoun called for close monitoring of Afrezza's pulmonary and cancer safety.

- **Dr. Morris Schambelan's (Endocrinologist, University of California, San Francisco, CA) positive decision was "a little closer than [he] thought it would be."** His hesitation was because "the cancer signal began to dwell on [his] mind." However, unlike Dr. Cooke, Dr. Schambelan felt that Afrezza's efficacy was sufficient for him to vote yes. Dr. Schameblan liked Afrezza's PK, and thought it might mitigate some hypoglycemia. Echoing nearly every panelist before him, Dr. Schameblan emphasized that a rigorous post-marketing surveillance program needs to ensure "we don't do harm" by prescribing Afrezza.
- **While Dr. James Stoller (Pulmonologist, Cleveland Clinic, Cleveland, OH) voted in favor of Afrezza's approval for type 1 diabetes he noted that his confidence level was only a two on a scale of one to ten.** The reason for Dr. Stoller's yes vote was because he was "impressed by the unmet needs" of some patient subsets. He expressed low confidence in approving the agent due to his concerns for users' pulmonary safety. Dr. Stoller was realistic about the limited power that restrictions on a label can have on clinical behavior saying, "We sometimes take solace thinking the label will ensure proper use; irrespective of what it says on the label, I'm not sure what will happen in clinical practice."
    - **In particular, Dr. Stoller was concerned about patients with undiagnosed COPD receiving Afrezza** (even if the label were to require screening for COPD prior to Afrezza prescription, many providers lack the tools or expertise to do so) - during open discussion, Dr. Stoller noted that about as many American adults have COPD as have type 2 diabetes and that more are undiagnosed than diagnosed. Due to his "suspicion" as to whether providers would follow through on lung function screening, Dr. Stoller recommended that Afrezza be contraindicated in anyone who had ever smoked (not just current smokers) and people who have alpha-1 antitrypsin deficiency (a risk factor for COPD).
    - **We took note of Dr. Stoller's comment that he was "impressed by the inadequacy of A1c" -** he called for a better way to assess diabetes agents' impact on quality of life, a major win for patients to hear from a advisory committee member. Dr. Stoller was also surprised that diabetes did not have a validated quality of life metric, which exists in pulmonary medicine. On this latter point, Dr. Stoller made "kind of a plea" that such a metric be invoked, inviting "a budding clinical epidemiologist" to get to work on it.
- **Following Dr. Stoller's lead, Dr. Eva Szabo (Pulmonary Oncologist, National Cancer Institute, Rockville, MD) also tempered her affirmative vote with a confidence level of "two."** Dr. Szabo also cited the uncertainty with regard to Afrezza's pulmonary and cancer risks as her reasoning. She indicated that researchers will be able to determine the full extent of these risks post-marketing, and she was reassured knowing that people with COPD would be excluded. Furthermore, she highlighted that she could think of "lots of reasons to approve" Afrezza, though she did not go into detail on these and prior panelists already had.
- **Dr. Antoinette Wozniak (Pulmonary Oncologist, Karmanos Cancer Institute, Detroit, MI) indicated that her "internist self" was more confident voting yes than her "oncologist self."** As an internist, she saw that Afrezza would benefit some people. However, as an

oncologist she was a "little less" confident due to theoretical - though unproven, she noted - cancer risk. She explained that it is going to take "a while" to see if Afrezza has a cancer risk, and that a robust registry study must be performed to flesh this out.

- **Dr. Peter Wilson (Cardiologist, Emory University School of Medicine, Atlanta, GA) stressed that providers and the FDA are "supposed to provide hope."** Dr. Wilson's main concerns with approving the agent were the pulmonary and cancer risks. He noted that if he were prescribing this agent to a person with type 1 diabetes, he would strongly drive home the message of the dangers of smoking prior to or during treatment with Afrezza. He acknowledged that when prescribing Afrezza to a person who is 18 years old, we likely won't know if it is safe until he is 30 - Dr. Wilson felt "a lot better" about this situation if the 18 year old were never to smoke.
    - **Dr. Wilson seconded Dr. Stoller's request for a quality of life assessment in diabetes.** Dr. Wilson sees such a metric as particularly important when comparing different insulins against one another.

NO Votes:

- **Dr. David Cooke (Pediatric Endocrinologist, Johns Hopkins University School of Medicine, Baltimore, MD) cited similar benefits and risks as panelists voting "yes," but came to a different conclusion on the overall risk-benefit balance.** Dr. Cooke's biggest concern was Afrezza's cancer risk. Indeed, Dr. Cooke was the panelist whose back-of-the-envelope calculation estimated that Afrezza could elevate insulin levels in lung fluid to 10 to 1,000 times greater to that of the IGF1 growth factor, which he hypothesized would result in over activation of the IGF1 receptor and potentially promote tumor growth. Dr. Cooke acknowledged, though, that cancer data cannot be gathered in a "timely manner" for a decision on the agent's approval. However, he thought that because Afrezza's efficacy was not as good as subcutaneous insulin, the potential cancer risk was unwarranted, especially since the agent's hypoglycemia benefit was unproven in his view. In fact, Dr. Cooke indicated that if Afrezza's hypoglycemia benefit were proven, that would be enough to swing his benefit/risk appraisal in favor of approval. Dr. Cooke also acknowledged that Afrezza has several "unambiguous [...] personal benefits" such as the convenience and desirability of avoiding injections. He ended up voting yes for the type 2 diabetes indication, where the benefits seemed much clearer.

Non-voting

- **Dr. Erick Swenson (Pulmonologist, University of Washington, Seattle, CA) had to leave the Advisory Committee meeting before the voting occurred.**

TYPE 2 DIABETES APPROVAL

Panelists unanimously voted 14-0 to approve Afrezza for type 2 diabetes, and the audience broke out in a collective "Wow!" when the vote flashed across the screen. Most panelists had an easier time deciding "yes" for type 2 diabetes than type 1 diabetes given the stronger data supporting clinical efficacy in this population and slightly fewer safety concerns (for example, DKA is less of a concern). Many panelists expressed their appreciation of the fact that having a non-injectable insulin option available could combat some clinical inertia involved in delaying insulin initiation for type 2 patients. However, several panelists also remarked that the long-term lung safety and lung cancer concerns were still question marks in this population. A few also pointed out that we do not have efficacy data on Afrezza as an add-on to basal insulin, which may be the most common situation in which Afrezza is used in type 2 diabetes. Another concern expressed by Dr. Abraham Thomas was that the availability of Afrezza could delay initiation of basal insulin when the latter is actually warranted. Voting rationales were quite brief, as most panelists had little to add beyond what was said in the prior voting question.

YES Votes

- **Dr. Peter Wilson was convinced that Afrezza would be a "very safe drug" for type 2 diabetes patients.** A primary difference for the type 2 population compared to the type 1

population, in his view, was the "tremendous" delay in getting patients onto insulin from oral agents, and he thinks Afrezza will allow for earlier insulinization. He believes the special subgroups of people identified in the type 1 population (e.g., visually impaired, limited dexterity, needle phobic) are also highly represented amongst older type 2 patients.

- **Dr. Antoinette Wozniak said that she echoed Dr. Wilson's comments and had nothing further to add.**
- **Dr. Eva Szabo noted that her confidence in the "yes" vote for type 2 diabetes was much higher than her "yes" vote for type 1 diabetes.**
- **Dr. James Stoller echoed the sentiment based on safety concerns and said he had nothing to add.**
- **Dr. Morris Schambelan said he had nothing to add.**
- **Dr. William Calhoun thought the efficacy data were firmer in the type 2 diabetes trials than in the type 1 diabetes trials.** He thought that all of the safety concerns that had been articulated for type 1 diabetes (long-term pulmonary safety and lung cancer concerns) were relevant for type 2 diabetes as well.
- **Dr. David Cooke, the only panelist who voted "no" for type 1 diabetes approval, astutely justified why he voted differently for type 2.** He was more comfortable with approval in type 2 diabetes partly because exposure time would likely be shorter given patients' generally older age. That lowers the risk for longer-term complications due to pulmonary safety concerns as well as malignancy risk. He also expressed appreciation for Afrezza opening the door to insulinization for type 2 diabetes patients who might not otherwise initiate insulin if injections were the only option.
- **Ms. Diana Hallare emphasized the need for post-marketing studies** on the cancer and lung safety risks, interactions with other medications (which she brings up at nearly ever vote in which we have seen her participate), and use in pregnancy.
- **Dr. Erica Brittain said that while many of the concerns she expressed during her commentary on the type 1 diabetes vote still existed for type 2 diabetes, she recognized the need to put patients on insulin that wouldn't otherwise take it.**
- **Panel Chair, Dr. Robert Smith, said that the magnitude of his uncertainties about safety and efficacy were no different between the type 1 and type 2 diabetes populations, but that they differed in terms of specifics.** With regards to efficacy, he highlighted the lack of data on Afrezza on a background of basal insulin or "other agents." While he acknowledged Dr. Cooke's point about elderly patients having a reduced period of exposure, he pointed out that people with more advanced diabetes may be at higher risk of having pre-existing emerging tumors, and that Afrezza would enhance the progression of those tumors. His "yes" vote for type 2 diabetes came with the same level of tempered confidence as for type 1 diabetes.
- **Obesity clinician Dr. Ed Hendricks was more confident in his type 2 diabetes vote than his type 1 diabetes vote, mainly because of Afrezza's weight benefit for the generally obese type 2 diabetes population.** Afrezza's weight benefit was not a big focus of the day, so we appreciated this reminder during this discussion.
- **Dr. Abraham Thomas highlighted the need for a type 2 diabetes trial of Afrezza as an add-on to basal insulin -** he saw this as the most common situation in which Afrezza would be used. Additionally, he advocated for a specific geriatric trial for safety and efficacy, since the elderly are likely one of the subgroups that will most benefit from Afrezza's easier administration.
- **Dr. Katherine Flegal also expressed concerns about safety in the elderly as well as the high prevalence of undiagnosed COPD and the possibility of tumor progression.** She said that she was just as concerned about safety in the type 2 diabetes population as the type 1 diabetes population.

Non-voting

- **Dr. Erick Swenson (Pulmonologist, University of Washington, Seattle, CA) had to leave the Advisory Committee meeting before the voting occurred.**

VII. Key Questions

The meeting left us with multiple questions - few were answered through the course of the day. Afrezza has overcome the first regulatory approval hurdle, though the day's discussion seemed to suggest that a lot of the hardest work may lie ahead. We detail many questions that still remain here, in six categories.

1. COMMERCIALIZATION

- **What is the likelihood of a partnership for MannKind following approval?** A partnership agreement will almost certainly not be signed until after the April 15 PDUFA date, possibly well after, since the label (assuming approval) will represent a huge factor in deal valuation. Additional factors that might be considered are the number and intensity of post-approval trials required (reducing MannKind's resources to participate in a launch), the uncertainty that exists around the size of Afrezza's target population, reimbursement, and the timing of other ultra rapid acting insulins reaching the market. See our MannKind 4Q13 report for a list of 10 potential partners and their corresponding motivating/de-motivating factors.
- **Will payers be convinced that Afrezza is worth reimbursing?** Will they stipulate that people must have already tried and failed a subcutaneous rapid acting insulin?

2. AFREZZA'S LABEL

- **Will the label allow broad use in the general type 1 and type 2 diabetes populations,** or will it restrict use to specific subgroups that would benefit most (as suggested by many panelists)? There aren't any specific data to support segmentation, but there is perceived benefit in people who are non-adherent to injectable insulin and people who have other conditions making it difficult to inject themselves (reduced vision or dexterity) or other conditions that make the rapid onset and offset an attractive option (gastroparesis, proneness to postprandial hypoglycemia).
- **Is there a place for Afrezza in otherwise healthy people with type 1 diabetes?** Dr. Abraham Thomas suggested that Afrezza could be used in between meals to quickly correct for hyperglycemia when a prandial insulin may provide too much stacking - we like to think of this as sort of a *hyper*glycemia rescue dose of insulin, given the ultra-fast-acting profile of Afrezza. Still it remains to be seen how this would work in "real life." For example, Afrezza will first be available in increments of three or six units, meaning that it may not provide enough granularity for type 1 patients that are sensitive to insulin.
- **Will the label include the potential for a hypoglycemia benefit?** Given the FDA's straightforward statement that it is unconvinced of a hypoglycemia benefit and a lack of strong consensus among panelists on this point, we think it is unlikely the FDA will include such a benefit in Afrezza's label. This, of course, could hinder commercialization efforts for Afrezza, since it is one of the agent's most clinically important characteristics (as cited by nearly all of the patient and physician advocates for the drug during the Open Public Hearing).
- **Will MannKind run a trial dedicated to demonstrating a hypoglycemia benefit?** In the clarifying questions, the FDA said it would be "very, very challenging for any sponsor to claim a hypoglycemia benefit for any product." This also was quite surprising. The Agency would want to see a dedicated hypoglycemia study where A1c was matched between the two groups to be able to claim a hypoglycemia benefit. As mentioned above, we think it would be a boon for Afrezza's commercialization to be able to advertise a hypoglycemia benefit and wonder if MannKind or a partner will pursue such a trial.

- **How broad is the pool of people that will be excluded for pulmonary safety risks?** MannKind proposed the exclusion people with COPD and asthma. However, Dr. Stoller suggested excluding people who have ever smoked (~40% of US adults in 2009) rather than just current smokers (18% of US adults today) and people with alpha-1 antitrypsin deficiency (a risk factor for COPD; <1% of American adults). This recommendation was driven by Dr. Stoller's concern over the practicality of expecting providers to actually conduct a spirometry before prescribing the drug, and every six months thereafter, even if the label calls for it.

3. AFREZZA'S PLACE BE IN THE TYPE 2 DIABETES TREATMENT PARADIGM

- **Will Afrezza be seen as a replacement for rapid-acting insulin or as an add-on to oral antidiabetic agents?** We would venture to guess that it would not be effective enough to replace rapid-acting insulin for someone who is already on it (an early trial demonstrated inferiority to insulin aspart in type 2 diabetes), and that it would not necessarily offer enough of a convenience/ efficacy benefit to be used in place of any oral agents. We think it will most likely be used in patients already on basal insulin who would otherwise not be willing to intensify to rapid-acting injectable insulin.
- **Will a trial of Afrezza as an add on to a basal insulin be required?** MannKind did not study Afrezza as an add-on to basal insulin, which makes us wonder whether this indication can be claimed in the label.
- **Could Afrezza have the unintended consequence of delaying basal insulin initiation?** Several panelists including Drs. Thomas, Smith, and Wilson questioned if the availability of Afrezza could delay initiation of a basal insulin (e.g., patients who should actually initiate a basal insulin but prefer Afrezza's inhaled administration may opt for Afrezza instead). HCPs could also favor the easier-to-train treatment initiation.

4. POST-MARKETING REQUIREMENTS

- **What structure will a post-marketing surveillance program of cancer and pulmonary risk take?** MannKind recommended a registry of Afrezza users that would be compared against the SEER population (a cancer registry). The FDA indicated that this approach's strength might be that it is the quickest; however, one of its several limitations is that smoking is not measured in the SEER data. Thus, most panelists indicated their preference for a registry with an internal comparator (for example, comparing patients who remain on Afrezza for a long time vs. patients who started it but stopped right away). The FDA also noted that a randomized clinical trial theoretically could be performed but that it would probably need to enroll over 60,000 people in order to be adequately powered for determining lung cancer risk.
- **Will a post-approval treat-to-target trial be required?** Many panelists expressed a desire for more data on Afrezza's efficacy in both type 1 and type 2 diabetes. The highly respected Dr. Thomas repeatedly called for a treat-to-target trial at least in people with type 2 diabetes regardless of the approval decision. Dr. Thomas indicated that such a trial would help determine its real-life clinical value.
- **Will MannKind be required to further refine its conversion algorithm from subcutaneous insulin units to Afrezza units?** As we previously mentioned, a major point of contention was Afrezza's dosing and PK/PD. Afrezza appears to have a less-than-linear dose-response relationship, which calls into question whether MannKind's proposed conversion factor is valid (a constant 3.3 multiplier from the subcutaneous insulin dose). At high doses, this conversion factor would underestimate the amount of Afrezza needed and increase risk for DKA (indeed there was an increased rate of DKA for patients on Afrezza in early type 1 studies). Acting Chair Dr. Robert Smith questioned MannKind on whether requiring high doses of Afrezza was a predictor for DKA, and did not seem convinced with the company's data suggesting that it was not. We think Afrezza's

dosing may need to be addressed with another PD trial to establish a better subcutaneous insulin-to-Afrezza conversion relationship.

    - Dr. Abraham Thomas also voiced the need for MannKind to provide clarity to patients and HCPs on when a subcutaneous insulin rather than Afrezza ought to be used to avoid DKA. Relatedly, we wonder how useful Afrezza will be for very insulin resistant people who require very high doses of insulin.

5. FDA APPROACHES FOR RISK MANAGEMENT

- **How will the FDA ensure that people with asthma or COPD do not mistakenly receive Afrezza, and how will patients be monitored to ensure that long-term lung function is retained?** MannKind suggested that the label should recommend a spirometry test be performed before Afrezza use, and the FDA indicated that the label will likely call for a spirometry being performed every six months. However, several of the pulmonologists, particularly Dr. Stoller, expressed strong concern about whether these tests will actually be performed and interpreted well. Most PCPs and endocrinologists would need to refer patients to a pulmonologist for the test. We can see the FDA requiring a REMS program where a spirometry has to be performed (similar to the negative pregnancy test required for a woman to receive some highly teratogenic agents like Accutane).
- **Relatedly, how big of a burden would the requirement for pre-prescription and every-six-month spirometry be?** Those caring for people with diabetes most often - PCPs and endocrinologists - are not often equipped with spirometers or able to interpret the results. Thus, most patients would be required to see a pulmonologist every six months for these tests. This may add a barrier for some patients who do not want to go through this hassle (or pay the additional copays).

6. OTHER QUESTIONS

- **Will regulatory researchers and regulatory agencies be able to define a better measure of glycemic control than A1c?** We hope to see increasing use of time in zone, which is now possible with more accurate and reliable CGM.
- **Will researchers and the FDA begin to work on a quality of life measure?** Dr. Stoller and Dr. Wilson pressed that such a measure would be beneficial when evaluating agents (particularly when comparing insulins). Dr. Stoller indicated that this type of metric is already in use in pulmonary medicine.

-- by Adam Brown, Hannah Deming, Jessica Dong, Manu Venkat, and Kelly Close