Closer Look

MEMORANDUM

MannKind 2Q13 - Phase 3 results for ultra-rapid inhaled insulin Afrezza; superior to oral therapy in type 2, non-inferior to insulin aspart in type 1 - August 15, 2013

Executive Highlights

- In 353 type 2s, Afrezza added to oral therapy led to a significantly greater decline in A1c over 24 weeks vs. those on orals alone plus a placebo inhalation powder: -0.8% vs. -0.4% ($p<0.0001$; no baseline provided). Twice as many patients on Afrezza reached an A1c <7% (38% vs. 19%; $p=0.0005$). This was a spectacular result in our view given that there is such a need for more type 2 patients to be on insulin (fewer than 30% of people with type 2 diabetes are on any kind of insulin even though approximately 50% are not at goal).
- In 518 type 1s, Afrezza led to a non-inferior decline in A1c vs. insulin aspart over 24 weeks: -0.2% in the Afrezza group vs. -0.4% in the insulin aspart group. Afrezza had significant benefits on hypoglycemia, weight change, and fasting blood glucose. We assume CGM would have shown more "time in zone" but this data was not measured.
- An amendment to Afrezza's NDA will be submitted to the FDA "early in the fourth quarter of this year." Management continues to expect a six-month Agency review.

Yesterday, MannKind reported 2Q13 financial results along with long-awaited phase 3 results for its ultra-rapid inhaled insulin, Afrezza (Technosphere Insulin). Management expressed obvious pleasure with the outcome of these trials, and indeed, both studies met their primary endpoints and we were particularly impressed with the results in the type 2 trial. In the type 2 study, Afrezza added to oral therapy was superior to oral therapy alone plus a placebo inhalation powder: A1c declined by 0.8% in the Afrezza plus orals group vs. a decline of 0.4% in those on orals alone ($p<0.0001$; no baseline A1c provided). In the type 1 study, Afrezza was non-inferior to insulin aspart after 24 weeks: A1c declined by 0.2% in the Afrezza group vs. a decline of 0.4% in the insulin aspart group (no baseline A1c or p-value provided). As expected, the data in type 2s was much stronger, given that these were very early stage type 2s and the comparator was orals alone - while some may object to this, it was appropriate in our view since so many type 2 patients refuse to take insulin. Study highlights and detailed results are presented below, along with the call's Q&A, financials, and the latest partnership update.

Notably, the studies were designed ("carefully designed," in management's words) to address the FDA's questions in the last Afrezza complete response letter. Importantly, the type 1 study showed that the Gen 2 Dreamboat and Gen 1 MedTone inhaler are comparable, allowing MannKind to leverage a large body of previously collected pulmonary safety data. This was great news for MannKind. Importantly, there did not seem to be any major safety red flags in either study. Consistent with previous trials, the use of Afrezza was associated with a "clinically insignificant decrease in lung function that appeared at the onset of therapy, did not progress during therapy and resolved fully upon cessation of therapy." There were also no cardiovascular concerns over the 24-week type 2 study: two events in the Afrezza arm vs. three events in the orals-only arm (there were zero events in the type 1 study). Said management, "In all of the clinical trials involving a total of more than 6,700 subjects…we've seen nothing to raise concern for safety with Afrezza."

An amendment to Afrezza's NDA will be submitted to the FDA "early in the fourth quarter of this year." This suggests an October resubmission at the earliest, which is ever so slightly behind previouscestimates of "late

September/early October." Previously, management has expected a six-month Agency review, meaning approval could come as soon as March or April 2014.

On the partnership side, the release of the phase 3 data enables MannKind to resume partnership discussions - some parties have already done some due diligence, while others were presumably waiting for the phase 3 results. The company's current preference is for a global partner, though MannKind may elect to retain co-promotion rights in the US (consistent with previous commentary). Financially speaking, MannKind is confident it can "comfortably" fund operations into 2014.

Table of Contents

Executive Highlights

HIGH-LEVEL TAKEAWAYS

- **Broadly speaking, MannKind's phase 3 data looks encouraging and shows clear benefits of Afrezza for both type 1 and type 2 diabetes.** Beyond the significant improvements in A1c in type 2 diabetes and the hypoglycemia/weight/fasting glucose benefits in type 1 diabetes, there is a lot to be said for the convenience of inhaled insulin - injection adherence is challenging for many patients, especially type 2 patients, and we would not be surprised to see Afrezza do much, much better in a real-world, non-clinical trial setting.
- **The fact that Afrezza's label could include early stage type 2s represents an extremely valuable market opportunity for MannKind and one with lots of potential to help HCPs intensify therapy sooner**. We believe that there are many sub-optimally controlled patients that currently stay on oral therapy to avoid injections. In our view, Afrezza has important potential to help those patients get to goal faster and to stay at goal.
- **Afrezza is poised to become the first ultra-rapid-acting insulin to come to market.** Next closest to market is Novo Nordisk's ultra-rapid-acting aspart, slated to enter phase 3 in 3Q13. Biodel's BIOD-123 ultra-rapid-acting recombinant human insulin is set to report phase 2 results this calendar quarter. As a reminder, Afrezza levels peak within 12 to 14 minutes, a big improvement over the typical 60-90 minutes with Humalog, Novolog, and Apidra.
- **Said Al Mann: "After 30 years in the business, I can say that I cannot speak for the FDA…We have addressed their questions. We believe that has opened the door to an effective review by the agency."** It is indeed very tough to predict what the FDA will do, especially with a history of two previous complete response letters (CRL) for Afrezza and the recent CRL for insulin degludec. MannKind has clearly had lots of dialogue with the agency and deliberately designed the phase 3 studies to answer the questions from the last CRL. Broadly, there do not seem to be any significant safety signals.
- **One of our biggest takeaways from the call and the phase 3 results was the importance of getting beyond A1c to measure drugs' efficacy.** There was somesuggestion that rates of hypoglycemia were driving the A1c differences between Afrezza and the comparator groups. This was especially critical in the type 1 study, where insulin aspart had a slight A1c advantage over Afrezza (-0.4% vs. -0.2%), but with rates of hypoglycemia that were significantly higher by about 50% (14 events per subject-month for aspart vs. 9.8 events with Afrezza; $p<0.0001$). Interestingly, Afrezza had a huge advantage in terms of fasting glucose levels (-25 mg/dl in the Afrezza group vs. +10 mg/dl in the insulin aspart group), perhaps suggesting that the overall glycemia was indeed

improved in the Afrezza arm but was not reflected in A1c. We hope to see post-hoc analyses that help clarify this question, and in the future, use of CGM to avoid it entirely.

- **There was a lot of data not given in the call that we'd like to have. MannKind said because it plans to publish the phase 3 results, they would not share any further data beyond the topline data published in the company's simultaneous press releases.** We most look forward to post-hoc analyses/data that:
    - Provide baseline A1c at the start of the treatment period (we were extremely surprised this was not included!);
    - Better assess and characterize the impact of hypoglycemia on change in A1c in both studies;
    - Stratify the type 2 data based on oral therapy use at baseline (e.g., number of oral therapies, type of oral therapy, etc.);
    - Provide more detail on the titration of oral medications in the Afrezza arm of the type 2 study (e.g., How many patients, if any, had their oral doses titrated down?);
    - Disclose the seven-point profiles to better compare the effect of Afrezza throughout the day;
    - Quantify and further explain the meal-time dosing, especially in type 1s; and
    - Dig deeper into the superior fasting glucose improvements with Afrezza that were not borne out in A1c superiority in the type 1 study.
- **MannKind is planning "several phase 3b and 4 studies…to further differentiate Afrezza."** No details were shared, and presumably a partner would pay for these. We see potential for lots of follow-on studies: using CGM, use of Afrezza in later-stage type 2s on basal insulin, use of Afrezza in very early stage type 2s (e.g., those who cannot tolerate metformin, those in whom metformin doesn't work), and perhaps those with prediabetes.

PHASE 3 STUDY HIGHLIGHTS - TYPE 2

- **The type 2 study compared oral therapy alone (1-3 orals) plus a placebo powder/ inhaler (n=176) to use of Afrezza added on to oral therapy (n=177). Those in the Afrezza group experienced a significantly greater decline in A1c over the 24- week treatment period: -0.8% vs. -0.4%** ($p<0.0001$; baseline A1c was not provided for the treatment phase, though patients had a mean A1c ~8.6% prior to the run-in phase).
- **Notably, after 24 weeks of treatment, twice as many patients on Afrezza reached an A1c <7% vs. those on orals alone** (38% vs. 19%; $p=0.0005$), and a striking four times as many reached an A1c <6.5% (16% vs. 4%).
- **The incidence of mild/moderate hypoglycemia was twice as high in the Afrezza plus orals group vs. those on orals alone (67% vs. 30%; p<0.0001)**. We wonder how rates of hypoglycemia would have been different if the Afrezza arm had orals stopped entirely or at least titrated down aggressively (see study design note below). The incidence of severe hypoglycemia was not significantly different, though it trended in favor of the oral therapy-only group: nine events for Afrezza vs. three events in those on orals alone ($p=0.09$).
- **Patients on Afrezza gained an average of 0.5 kg (1 lb) over the treatment period compared to an average loss of 1 kg (2 lbs) in patients on orals alone (p<0.0001).** We would guess that the extra hypoglycemia drove much of the weight gain. In Q&A, management emphasized that Afrezza is really "weight neutral," and the weight loss observed in the orals-only arm was due to 1) patients in overall worse glycemic control and 2) diabetes education/lifestyle modification. Since the latter was consistent across both arms, this did not strike us as a valid reason for weight loss.

- **We would strongly emphasize that subjects "*could not adjust or alter the doses of their oral medications during the study without discussion between the principal investigator and the medical monitor.*"** In the call and supporting materials, it was not clear how many patients on Afrezza had their oral medications changed/titrated down during the study. Assuming very few did (given the strict criteria for doing so), this could explain the much higher hypoglycemia rate and weight gain in the Afrezza plus orals arm vs. the orals-only arm. We look very forward to seeing further post-hoc data that clarifies this point.
- **"In general, treatment with Afrezza was well-tolerated over 24 weeks by subjects with type 2 diabetes."** The incidence of serious adverse events was lower in the Afrezza group (2.8%) compared to the comparator oral-therapy group (5.1%). The nature of these events was not specified. The incidence of serious cardiovascular events was balanced between the groups: two events in the Afrezza arm vs. three events in the oral therapy-only arm. The incidence of adverse events resulting in discontinuation was also balanced between the treatment groups: 4% with Afrezza vs. 5% in those on oral therapy only.
    - **The most common adverse event was cough, occurring with comparable incidence in both the Afrezza group (24%) and the oral therapy-only (20%) group (who were also taking a placebo inhalation powder).** Cough was "predominantly dry, intermittent, and usually occurred within 10 minutes of inhalation." The incidence of cough in both treatment groups was highest during the first week of the treatment period and diminished thereafter. We don't think this will be a big deal with patients.
- **This study is registered under the ClinicalTrials.gov Identifier: NCT01451398.** After a six-week run-in period during which all patients received dietary counseling and initiated blood glucose monitoring while continuing their oral medications, patients entered a 24-week treatment period in which they were randomized to one of two groups where, in addition to their oral medication, they received either: Afrezza with the Gen 2 inhaler (177 patients) or Technosphere Inhalation Powder (placebo) administered using the Gen 2 inhaler (176 patients). The treatment period was divided into 12 weeks of prandial insulin titration followed by 12 weeks of relatively stable dosing. There was also a safety follow-up visit four weeks after completion of the treatment period, during which all subjects returned to oral therapy only.

PHASE 3 STUDY HIGHLIGHTS - TYPE 1

- **In the type 1 study, use of Afrezza over 24 weeks was non-inferior to insulin aspart - A1c declined by 0.2% in the Afrezza arm vs. 0.4% in the insulin aspart arm** (no baseline A1c or p-value provided in the press release). The 95% confidence interval for the between-group difference (0.02%-0.36%) was just below the predetermined threshold of 0.40%. Both groups added Afrezza or aspart on top of their pre-study basal insulin - 70% were on glargine and the remaining 30% were split between NPH and insulin detemir.
    - **The proportion of subjects achieving A1c target levels ≤7.0% or ≤6.5% at the end of the 24-week treatment period was less in the Afrezza group than in the insulin aspart group** - management said in Q&A that this was statistically significant, but did not share the actual numbers. Importantly, among patients who achieved A1c levels ≤7.0% and ≤6.5% at the end of the 24-week treatment period, the event rates for overall hypoglycemia (mild, moderate and severe) were all significantly lower in the Afrezza group than in the insulin aspart group. To us, this suggests hypoglycemia may have played an important role in the better A1c-lowering efficacy with insulin aspart.
- **Said CEO Al Mann, "Afrezza reduces A1c at least as well as Novolog, but with the additional benefit of lower fasting glucose, lower hypoglycemia, and no weight gain. That is a compelling story."** We agree. We found these secondary endpoints to be the most valuable aspect of the type 1 data - all shed lots more light on the A1c data.

    - **Patients on Afrezza had significantly less total hypoglycemia**: 9.8 events per subject-month with Afrezza vs. 14 events with insulin aspart (p<0.0001).
    - **Notably, there was also a strong trend towards less severe hypoglycemia with Afrezza**: 8 events per 100 subject-months vs. 14 events with insulin aspart (p=0.10).
    - **Afrezza use was also associated with significant improvements in fasting blood glucose**: -25 mg/dl vs. +10 mg/dl in the insulin aspart group (p=0.0027). During Q&A, this was a point of confusion, as one would have expected a bigger A1c improvement with such fasting glucose improvements (i.e., a 35 mg/dl in fasting glucose roughly translates to ~1% improvement in A1c).
    - **Afrezza had a significant weight advantage over insulin aspart** - those on Afrezza lost 0.4 kgs (1 lb) vs. a weight gain of 0.93 kg (2 lbs) with insulin aspart (p=0.01).
- **Importantly, the type 1 study also established a bridge between the Gen 2 inhaler and the large body of pulmonary safety data that was previously collected for Afrezza using the MedTone inhaler.** As a reminder, the FDA originally requested the new phase 3 studies in part because MannKind changed the Afrezza inhaler from the MedTone to the Gen 2 Dreamboat. Therefore, the type 1 study randomized 518 patients to use of Afrezza with the Gen 2 Dreamboat inhaler (n=174) or the MedTone inhaler (n=174) vs. use of insulin aspart (n=170). Efficacy results were only presented for the Gen 2 group, though management said in Q&A that the results were comparable between the two inhalers.
- **The decrease in forced expiratory volume in one second (FEV1 - the study's main safety objective) seen in the Afrezza Gen 2 inhaler group was slightly greater than that seen in the aspart group (0.03 L; no p-value provided).** However, after cessation of the treatment period, FEV1 values in both Afrezza groups increased, so that by the follow-up visit at week 28 there were virtually no differences in FEV1 among the Afrezza MedTone inhaler,Afrezza Gen 2 inhaler, or insulin aspart treatment groups (no specific results or p-values provided). This suggests that the "clinically insignificant" decrease in lung function resolved upon discontinuing use of Afrezza. In comparing the inhalers to each other, there was an insignificant difference of 0.01 L in mean change in FEV1 between the MedTone and Gen 2 inhaler groups (p=0.5).
- **"In general, treatment with Afrezza was well-tolerated over 24 weeks by subjects with type 1 diabetes."** The incidence of serious adverse events (SAEs) related to study drug was similar in the Afrezza Gen 2 inhaler (2.3%), Afrezza MedTone inhaler (2.9%) and insulin aspart (1.8%) groups. These SAEs were not specified. There were no serious cardiovascular events reported in this study.
    - **The most common drug-related adverse event was cough, reported by 31% of Afrezza Gen 2 inhaler patients, 21% of Afrezza MedTone inhaler patients, and 0% of insulin aspart patients.** Cough was "predominantly dry, intermittent, and usually occurred within 10 minutes of inhalation." The incidence of cough was highest during the first week of the treatment period and diminished quickly thereafter. The discontinuation rate due to cough was 5.7% in the Afrezza Gen 2 inhaler group: 2.9% in the Afrezza MedTone inhaler group, and 0% in the insulin aspart group. We wonder if this will be a point of contention with the FDA as it reviews Afrezza's NDA.
- **This study is registered under the ClinicalTrials.gov Identifier: NCT01445951.** After a four-week run-in period to optimize their basal insulin, patients entered a 24-week treatment period in which they were randomized in one of three ways: 1) continuing on subcutaneous insulin aspart in combination with their pre-study basal insulin (170 patients); 2) switching to Afrezza administered using the Gen 2 inhaler in combination with their pre-study basal insulin (174 patients); or 3) switching to Afrezza administered using the MedTone inhaler in combination with their basal insulin (174 patients). The treatment period consisted of 12 weeks of prandial insulin optimization with continued basal titration followed by a 12-week period during which subjects maintained stable

doses of insulin (prandial and basal). There was also a follow-up visit four weeks after completion of the treatment period.

FINANCIALS AND PARTNERSHIP UPDATE

- **MannKind has enough financial resources on hand to "comfortably fund operations into 2014."** As of June 30, cash and cash equivalents totaled $29 million, up slightly from $28 million as of March 30. The cash balance does not reflect a July 1 $160 million debt financing agreement with Deerfield, through which MannKind received $40 million up front (with potential to receive three more tranches of $40 million if certain milestones are hit - one being the release of today's phase 3 data). The fact that Deerfield has invested says a great deal - they have been very successful with other diabetes deals such as Insulet (though perhaps less so with Arena). This year, MannKind has received proceeds of $30 million from the exercise of warrants, and another$65 million is expected from the exercise of remaining warrants that expire this October. MannKind also has up to $125 million available for future borrowing under the loan agreement with CEO Al Mann. In short, the company has access to financial resources well over $200 million.
    - **For context, MannKind had operating expenses of $42 million in 2Q13, including R&D expenses of $27 million.** Management would not speculate in Q&A on future spending, though suggested R&D spending will remain at the same level as thecompany gears up for commercialization. We anticipate this may be hard to do due to education demands alone and associated spending.
- **We assume the release of phase 3 data will prompt more partnership discussions, though we imagine given FDA random-ness, that most partners would want to see an approval before signing an agreement.** The preference is still a "global partner that will help launch and position the product globally." However, MannKind "may look to participate" in the US marketing of Afrezza, where a co-promotion arrangement might be set up.

CLOSE CONCERNS QUESTIONS

Q: How much did hypoglycemia drive the A1c reductions seen in both studies?

Q: Was CGM not used in the study due to expense or greater work for practices or another reason?

Q: In the type 2 study, how would efficacy data change when stratified by type of oral therapy?

Q: How would the type 2 results change - especially for hypoglycemia - if orals were titrated down in the Afrezza group?

Q: Given non-inferiority to insulin aspart, are the benefits of Afrezza on hypoglycemia, fasting glucose, and weight enough to support FDA approval for type 1 diabetes?

Q: Will FDA be concerned with the increases in cough or decreases in pulmonary function?

Q: Will FDA require a cardiovascular outcomes trial? If so, would this be pre- or post-approval?

Q: Will there be an advisory committee meeting for Afrezza?

Q: Should it be approved, what patients will the type 2 indication for Afrezza include?

Q: Will MannKind sign with a partner prior to FDA approval?

QUESTIONS AND ANSWERS

Q: In the type 1 trial, we saw a delta of almost three pounds of weight loss difference. In the type 2 trial, we saw a weight gain of 3.5 lbs. Do you have an explanation of why that may be?

A: In the type 1 trial, we believe it is because we are managing their glucose more effectively. So the weight loss there is actually related to the drug product. In the type 2 trial, we believe that what we see there is the impact of heavy diabetes education. As you know, with these type 2s early in their disease, many of them had not used glucose meters before. They also went to frequent visits to the clinical site. So we believe that that's the outcome - it was probably really due to lifestyle modification.

Q: So they put on weight because of lifestyle modification?

A**:** No. The amount of weight added in the type 2 study was very small, just over a pound. Where we saw the difference was there was weight loss in those that were in the control group. We believe that was due to the fact that they were not in as good of control and that we had also participated in increasing their knowledge of their lifestyle as diabetics. Keep in mind that the cause of weight gain in insulin therapy is because the people are eating snacks to avoid hypoglycemia and the liver is pouring out glucose as well to avoid hypoglycemic issues. We don't have those issues with Afrezza, so that my view is that Afrezza is really weight- neutral.

Q: Do you have the numbers in the type 1 study for the percentage of patients that achieved an A1c <7% and <6.5%?

A: I do not have those numbers presently. In the type 1 trial, those reaching <7% and <6.5% did favor the insulin aspart group. But I do not have the numbers with me; I'm sorry. [Editor's Note: we found this somewhat odd, since these numbers were disclosed for the type 2 study.]

Q: Has the FDA told you that if you meet the primary endpoints of these trials, you would get approval regardless of what else is in the package? Or what happens with secondary endpoints? Is it that cut-and-dry, or do you not have that level of clarity from the agency?

A: After 30 years in the business, I've learned that I cannot speak for the FDA. They told us that for them to consider approval of the product, we had to address the questions that came out of the complete response letters. We have addressed their key issues in those complete response letters. We believe that has opened the door to an effective review by the agency.

Q: In the type 1 trial, you provided us with A1c reductions for the second-generation inhaler and for the Novolog group. Can you give a comparison to how the first generation and second-generation devices performed relative to each other? Or tell us how first generation device performed relative to Novolog?

A: The MedTone device performed comparably to the Gen 2 device. We did not see an appreciable difference between those two.

Q: Did the FDA explicitly sign off on all aspects of these studies? Specifically about the size of Affinity 1, the three arms, and 170 patients in each arm. Regarding dropout rate, could the FDA use a different method for defining a dropout?

A: Regarding the size of the studies, all of the projections for the number of patients required for each treatment arm was vetted with the agency. They did review that and the protocols as well.

The dropouts are those who withdraw from the trial due to adverse event or other reasons. Withdrawing your consent is sufficient. So in some cases, we don't know all of the reasons for dropouts. The dropouts that occurred happened early in the trial. Especially in the Afrezza Gen 2 and Afrezza MedTone groups. It was related to the fact that it was a new route of delivery for them. And that the trials were becoming a burden to their lifestyle.

Q: In the type 1 study, can you talk about the use of basal insulin in the study? Was the dosing of basal balanced between the three arms?

A: Greater than 70% of patients were taking insulin glargine, with the remaining patients divided equally between NPH insulin and detemir. At the end of the trial, we evaluated the total basal insulin dose, and it was slightly lower in the insulin aspart group. It was comparable between the two Afrezza groups.

Q: Can you talk about the number of prandial insulin units? Was there anything to support that control and experimental insulins were being titrated to the same level?

A: Over the course of the titration period - the first 12 weeks post-randomization - both the MedTone and Gen 2 treatment groups had a significant increase in their dose of Afrezza. They were being effectively titrated. That was also being mandated by the titration management committee, which reviewed glucose values over various periods throughout the titration.

Q: On MedTone and the change in FEV1, can you comment on whether the change was similar to MedTone in previous studies?

A: Yes, that's correct. It was quite comparable to all of our previous type 1 studies.

Q: You mentioned that the number of patients reaching goal was more on Novolog vs. Afrezza. Did that reach statistical significance in any groups?

A: Yes, it was statistically different. There were a greater number of subjects reaching those levels in the insulin aspart group than in Gen 2 Afrezza group.

Q: You achieved your goal of lowering fasting glucose. Were you surprised by the magnitude of the A1c reduction in the type 1 diabetes study, given that you did get much lower fasting levels?

A: I wouldn't say I'm disappointed. That response in the type 1 diabetes trial was very, very consistent with what's been published for the last five, six years as people have gone through the DPP-4 inhibitors and other oral agents. [Editor's Note: We did not understand the pertinence of this latter comment to the type 1 trial.] The reduction in A1c that we saw in the aspart group - we did a very good job of titrating aspart as well as the Gen 2 Afrezza. We think those numbers fall right in line with very effective titration of both products. We're quite comfortable with the results.

Q: If the fasting glucose was lower in the Afrezza arm in the type 1 study, and you said that prandial insulin use was actually a little higher in the Afrezza arm, wouldn't both of those suggest that you could achieve a lower A1c level? And yet, the A1c level was higher in the Afrezza arm. Is the one thing that's different in the postprandial time period that you actually had more hypos in the Novolog arm? Thus, you had effectively lower blood glucose and that's what drove the A1c levels lower?

A: Let me see if I can bring this back here - you covered everything, including hypos there. What we did see is that at 24 weeks, there was a significant reduction in fasting plasma glucose in those subjects in the Gen 2 Afrezza group. There was no question - it was quite remarkable at greater than 35 mg/dl. Over the course of the day - looking at the seven point glucose profiles, pre- and post-meal all the way to bedtime - later in the day, there were lower glucose values in the insulin aspart group. We had pushed that dose very well. [In the Afrezza group, the glucoses] were slightly higher in the evening. However, the next morning, the fasting glucoses were lower. Throughout the day, the Afrezza Gen 2 group increased slightly, whereas the insulin aspart group did not.

Q: In the type 2 diabetes study, you had more hypos in the Afrezza arm. If those were in patients that had the lowest A1c levels, is it possible that for some of those patients, they were overly medicated?

A: The hypoglycemia incidence was greater - the number reporting a hypoglycemia event was greater. When we really looked at the ones that concerned us - the severe hypos - that wasn't at all correlated to their A1c level. I don't have in front of me the correlation of all hypos to A1c, but I can tell you - the ones that concerned us, the severe hypos, were not correlated to A1c. [Editor's Note: This would have been tremendously valuable data to include, and we thought this was an oversight not to release it with the topline results.]

Q: Were you able to detect differences in mild, moderate, or severe hypoglycemia according to type of orals the patient was on?

A: Very good question. I don't have that data. It's data that we will have to generate. As I mentioned earlier, there is some data that I won't disclose, because I don't want to exceed what would be too great a pre-publication disclosure. That's data we will be able to have, but I don't have it here today.

Q: How about baseline characteristics for hypoglycemia?

A: Nothing that stands out.

Q: In terms of cardiovascular events, was there any indication of what those were? Were they related to the study drug?

A: We had five cardiovascular events of which none were attributable to the study drug. They were balanced between the two groups. Two in Afrezza Gen 2 group and three in the comparator.

Q: Can you confirm for us - that the data you generated from these two trials is completely adequate to address the latest complete response letter from the FDA? Specifically as related to the device?

A: Related to the device - yes. As you would imagine, we've had a number of correspondences with the agency to ensure that we understood where they wanted information from the complete response letters. We are comfortable that the information we have generated on the device will satisfy the reviewing division.

Q: As you look to kickoff partnering discussions, what's your sense now that you have data in hand? How will that dictate how you go about partnering discussions? Can you remind us what you're looking for?

A: We have formed relationship with Greenhill and Company in regards to advising us on partnering discussions. We are putting together a formal process where we are going back to potential partners that have been in contact with us before. They have either proceeded with due diligence or some have decided to wait and resume due diligence upon the availability of phase 3 data. That starts as of today and we will go back and resume those activities. Following that, our preference is still a global partner that will help launch and position the product on a global basis. We may look to participate in marketing in the US, where we could have the right to co-promotion. Together with Greenhill and Company, we will look at who we believe will be the right partner in terms of experience and investment in the opportunity and that will determine the process going forward and the timing for any type of agreement.

Q: As you embark back on the clinical side on some phase 3b and other studies - what kinds of studies looking to do?

A: We are just planning those. It is too early to give any details. What these trials that we just reported, were constructed very carefully to meet the requirements of the FDA set forth in complete response letter. And in accordance with our discussions with the Agency. We want to do some trials that will further differentiate us in a significant way in glucose control in both primary and secondary endpoints. These trials were directed to the approval process. Now we want to target some marketing questions. This is one of the topics we would discuss with potential partners, and even hopefully have the potential partner pay for.

Q: For future trials, how should we be thinking about R&D spending going forward?

A: Obviously, you've already seen a slight decrease. I'm not going to project a lot. We have a lot of things coming to take place of the Affinity trials. We need to be pretty conservative there. We are planning to ramp up for commercialization, and that's going to require some expansion in our Danbury facility. You've seen some of that trickling in terms of capital spending, and you'll probably see more. I tend to be somewhat conservative. I'd say if may be shifting from R to D, or just preparation for commercial launch. But on balance, it's not going to change that much.

Q: Did this release of the data trigger the second tranche of [$40 million] financing agreement signed in July with Deerfield?

A: It's a fairly formal process with our friends at Deerfield. We're embarking upon that now. Ultimately, they'll have to make that decision, but our belief is that yes it will.

Q: Can you tell us a little bit about the range of A1c levels in patients enrolled in the trials? Were there any real differences between the two or three groups?

A: In the type 2 study, patients came in to the study, they averaged about 8.6-8.7% A1c. After the run-in phase, a six-week optimization phase, we saw a decline already occurring pre-randomization. At the point of randomization, they had comparable A1c levels. [Editor's Note: This was the only time baseline A1c was even approached in the call, and it still did not share what the baseline A1c was at the beginning of the treatment period. It's hard to ascertain the magnitude of effect without this.]

Q: Sometime back, you did a very well controlled, very small trial where you titrated patients not based upon the amount of insulin given, but based on the amount of food they were consuming. You came up with incredibly great success in avoiding hypoglycemic events, regardless of how much they ate. Was there anything in particular that you feel might be contributing to the hypo events that you saw in the type 2 diabetes trial? Things that are perhaps beyond the control that you could provide in the clinical setting that you used?

A: We have a host of data. We'll do considerable post-hoc evaluation. What we reported here were our pre-specified endpoints. The question you are asking is something we can address once we get into a post- hoc analysis. Looking at meals, frequency of meals, how many were skipped, etc. With more than 55,000 meals per group, we have lots of data to look at.

-- by Adam Brown and Kelly Close