Endocrinologic and Metabolic Drugs Advisory Committee Meeting on Afrezza: Introductory Remarks

April 1, 2014

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Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
Afrezza and Regulatory History

• Afrezza is a drug-device combination product consisting of a dry powder formulation of recombinant insulin (i.e., Technosphere Insulin) and an inhaler device (i.e., Gen2 inhaler)

• The product was not approved in two previous review cycles due to efficacy and delivery device issues

• With regard to efficacy:
  – Two out of three ≥ 6 months trials failed to meet their intended primary efficacy objectives (non-inferiority and equivalence)
    • In the two failed trials the efficacy of Afrezza was also demonstrated to be statistically inferior to standard of care active comparators
  – In general, interpretability of the phase III efficacy results was complicated by high and differential dropout rates, and concerns related to potential inadequate optimization of active comparator products

• The applicant was asked to complete two new trials to establish the efficacy and safety of Afrezza delivered using the device (Gen-2) intended for marketing
Objectives

• Review the intent of a non-inferiority (NI) trial
• Review the concept of the non-inferiority margin
• Review the concept of constancy assumption in a NI trial
• Review the importance of trial conduct quality in interpreting a NI trial
• Review interpretation of NI trial
• Review discussion points and voting questions.
Non-Inferiority Trial: Intent

• Comparison of a new agent to a known effective drug

• **Not** the intent of a non-inferiority trial
  • **to show that the drug is “no worse than” the comparator agent** (demonstrating superiority against the comparator would be needed to conclude this)

• The intent of a non-inferiority trial
  • “...to show is that **any difference between** the new drug and the known effective drug is small enough **to allow a conclusion that the new drug has at least some effect** or, in many cases, **an effect that is not too much smaller than the active control.**”

FDA Guidance for Industry Non-Inferiority Clinical Trials
Historical Effect: Comparator versus Placebo (Hypothetical case)

\[-0.8\% = \text{“M1 margin”}\]

Constancy Assumption:
In a new trial performed exactly the same way as the historical trials the comparator should be at least this effective.
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Deriving the Non-inferiority Margin

• New drug versus known effective drug

• The new drug may have an advantage other than enhancing effectiveness (e.g., convenience, safety)

• It may be reasonable to “tradeoff” some effect for this advantage

• How would one design a trial “to allow a conclusion that the new drug has at least some effect and that the effect of the new drug is not too much smaller than the effect of the active control”?

• To do this one must select a non-inferiority margin. Selection of a non-inferiority margin requires clinical judgment about how much loss of effect is “clinically acceptable”
Non-inferiority Margin

How much effectiveness are you willing to tradeoff for a benefit not captured in the efficacy assessment (e.g., convenience, safety etc.)?

10% of the active control’s effectiveness is preserved

M1 margin = 0.8%

Difference between comparator and new agent cannot exceed 0.72% = non-inferiority margin = M2 margin
Non-inferiority Margin

How much effectiveness are you willing to tradeoff for a benefit not captured in the efficacy assessment (e.g., convenience, safety etc.)?

- Difference between comparator and new agent cannot exceed 0.4% = non-inferiority margin = M2
- 50% of the active control’s effectiveness is preserved
- M1 margin = 0.8%
Non-inferiority Margin

How much effectiveness are you willing to tradeoff for a benefit not captured in the efficacy assessment (e.g., convenience, safety etc.)?

80% of the active control’s effectiveness is preserved

- Difference between Comparator and new agent cannot exceed 0.16% = non-inferiority margin = M2

M1 margin = 0.8%
Non-inferiority Margin:

- These last examples illustrate that selection of a NI margin involves, in part, clinical judgment.
- In selecting a margin one weighs the consequences of efficacy loss against the theoretical advantage of the product (i.e., unrelated to efficacy) to determine the amount of the comparator’s effectiveness that should be preserved.
- For diabetes in general and for insulin specifically FDA has sought to preserve at least 50% of the effect of the known effective comparator.
- For a comparator prandial insulin the FDA has allowed¹ an HbA1c difference of ~ 0.4%. 0.4% was the non-inferiority margin selected for the Afrezza trials.

¹ Guidance for Industry Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention
Objectives

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• Review interpretation of NI trials
• Review discussion points and voting questions.
Constancy Assumption:

Difference between Control and Comparator is zero (non-inferiority is met) but efficacy may not be “preserved”
Constancy Assumption:

Difference between Control and Comparator is zero (non-inferiority is met) but efficacy may not be “preserved”
Objectives

• Review the intent of a non-inferiority (NI) trial
• Review the concept of the non-inferiority margin
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• Review interpretation of NI trials
• Review discussion points and voting questions.
Poor Trial Quality Issues

• In a **superiority trial** the objective is **to show a difference** and defects in trial conduct that reduce the difference between the active control and the new drug tend to “bias toward the null” (i.e., a “failed” trial)

• In a **non inferiority trial** the objective is **to exclude a large difference** and defects in trial conduct that reduce the difference between the active control and the new drug tend to “bias toward the alternative” (i.e., a “successful” trial)

• Enrollment of inappropriate subjects, issues of adherence, withdrawals/dropouts, missing data, losses to follow-up and protocol deviation may bias towards a conclusion that the drug is effective when in fact it is not

• These issues have to be scrutinized when interpreting the results of a non-inferiority trial
Objectives

• Review the intent of a non-inferiority (NI) trial
• Review the concept of the non-inferiority margin
• Review the concept of constancy assumption in a NI trial
• Review the importance of trial conduct quality in interpreting a NI trial
• Review interpretation of NI trials
• Review discussion points and voting questions.
Possible Outcomes

Change in HbA1c (%)

versus placebo

Historical Control
Ex. 1 Comparator
Ex. 1 New Agent
Ex. 2 Comparator
Ex. 2 New Agent
Ex. 3 Comparator
Ex. 3 New Agent

Comparator

New agent
Non-inferiority Trial Results

Example: \(-0.4\% - (-0.9\%) = +0.5\%\)

Difference between new agent and comparator
Summary

• The intent of a non-inferiority trial is not to show a drug is “no worse than” an effective drug but rather to show that the new agent preserves some of the effectiveness of the comparator drug.

• By demonstrating a new agent preserves some of the effectiveness of the comparator one implicitly assumes the new agent has an effect against placebo. This is only true if the constancy assumption is maintained and trial operations do not yield a false positive result.

• Conclusions reached from a non-inferiority trial result can range from superiority to statistical and clinical inferiority (and everything in between).
1. Discussion

Trials in type 1 diabetes demonstrate that Afrezza provides numerically and statistically less HbA1c reduction than a comparator subcutaneous insulin. Discuss whether the applicant has demonstrated that Afrezza is an effective treatment for patients with type 1 diabetes mellitus. In your discussion, please address each of the following issues:

a. The impact of inadequate treatment optimization in the control arm on efficacy determination
b. The impact of missing data on efficacy determination
c. The relationship between Afrezza’s clinical pharmacology (e.g., extent and duration of action, dose-response, inhalation flow-rate dependence) to its effectiveness as a “prandial” insulin
d. Your level of concern with regard to how differences in efficacy will impact disease specific risks (e.g., risk of diabetic ketoacidosis) beyond achievement of therapeutic goals (i.e., prevention of diabetes related complications)
e. The importance of having an alternative route of insulin administration available
f. Comment on whether Afrezza is an appropriate substitute for subcutaneously administered mealtime insulin for most patients with type 1 diabetes or for a specific subgroup of individuals with the disease. If you believe the latter, describe this subgroup.
2. Discussion

Trials in type 2 diabetes demonstrate that Afrezza is superior to placebo but is less effective than a short acting subcutaneous insulin comparator. Discuss whether the applicant has demonstrated that Afrezza is an effective treatment for patients with type 2 diabetes mellitus.

a. Comment on the specific clinical setting where this agent is likely to be most useful.
b. Discuss your level of concern with regard to data suggesting a less than dose proportional glucose lowering response and its potential impact on achievement of glucose targets in this population.
c. Comment on any other issues discussed in the context of type 1 diabetes that you view as relevant to type 2 diabetes.
d. Comment on whether Afrezza is an appropriate substitute for subcutaneously administered mealtime insulin for most patients with type 2 diabetes or for a specific subgroup of individuals with the disease. If you believe the latter, describe this subgroup.
3. Discussion

Discuss the pulmonary safety findings in the Afrezza clinical development program (acute bronchospasm and pulmonary function decline over time).

a. Comment as to whether the pulmonary safety data (6 months with Gen2 device and 2 years with MedTone device) are sufficient to address the pulmonary safety of Afrezza.

b. Discuss your level of concern with the pulmonary risks.
4. **Discussion**

Discuss your level of concern with regard to the possible lung cancer risk with Afrezza use.
Discuss any other risk(s) which were not covered above.
6. Voting

Based on data in both the briefing materials and presented at today’s meeting, has the applicant demonstrated that Afrezza is safe and effective for the treatment of adult patients with type 1 diabetes mellitus to support approval?

a. DISCUSSION: If yes, please explain your rationale. Provide any recommendations you might have for post-marketing studies to evaluate identified safety signals.

b. DISCUSSION: If no, please explain your rationale. If appropriate, what further data should be obtained?
7. Voting

Based on data in both the briefing materials and presented at today’s meeting, has the applicant demonstrated that Afrezza is safe and effective for the treatment of adult patients with type 2 diabetes mellitus to support approval?

a. DISCUSSION: If yes, please explain your rationale. Provide any recommendations you might have for post-marketing studies to evaluate identified safety signals.

b. DISCUSSION: If no, please explain your rationale. If appropriate, what further data should be obtained?
Clinical Pharmacology Review

Endocrinologic and Metabolic Drugs Advisory Committee
Advisory Committee Meeting, April 1, 2014

Sang Chung, Ph.D.
Lokesh Jain, Ph.D.
Office of Clinical Pharmacology
Issues to be Addressed

- Lower efficacy compared to subcutaneous (SC) insulin
- Dosing regimen
  - For switch from SC to inhaled insulin
  - Dosing titration
Outline

- Pharmacokinetic (PK) and pharmacodynamic (PD) characteristics
- Dose-proportionality for PK and PD
- Between-subject variability
- Proposed dosing regimen
- Summary
Clinical Pharmacology Studies with Gen2 Device

• Study 176
  ▪ Euglycemic clamp PK and PD study in Healthy Subjects
  ▪ Dose-ranging study – 10, 30, 60, and 80 U (~4, 12, 24 and 32 IU Regular Human Insulin)
  ▪ Comparator – SC Regular Human Insulin – 15 IU

• Study 177
  ▪ Euglycemic clamp PK and PD study in T1DM
  ▪ Afrezza dose – 20 U (~8 IU Lispro)
  ▪ Comparator – SC Insulin lispro – 8 IU
Insulin Concentration – Time Profiles in Non-Diabetic Subjects

Outline

- Pharmacokinetic (PK) and pharmacodynamic (PD) characteristics
  - Dose-proportionality for PK and PD
  - Between-subject variability
  - Proposed dosing regimen
  - Summary
Pharmacokinetics – Afrezza vs. SC Insulin

**Study 176**

![Graph showing insulin concentration over time for Afrezza and SC Insulin doses.](image)

<table>
<thead>
<tr>
<th>Dose (IU)</th>
<th>Tmax (min)</th>
<th>Duration to baseline (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afrezza 10 U  (~ 4 IU RHI)</td>
<td>11.3</td>
<td>150-180</td>
</tr>
<tr>
<td>Afrezza 30 U  (~ 12 IU RHI)</td>
<td>13.1</td>
<td>180*</td>
</tr>
<tr>
<td>Afrezza 60 U  (~ 24 IU RHI)</td>
<td>14.5</td>
<td>180*</td>
</tr>
<tr>
<td>Afrezza 80 U  (~ 32 IU RHI)</td>
<td>16.7</td>
<td>180*</td>
</tr>
</tbody>
</table>

**Source:**
FDA Figures

*Data were only collected up to 180 minutes*
Pharmacokinetics – Afrezza vs. SC Insulin

### Table

<table>
<thead>
<tr>
<th></th>
<th>Afrezza</th>
<th>RHI</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>10 U</td>
<td>30 U</td>
</tr>
<tr>
<td>Tmax (min)</td>
<td>11.3</td>
<td>13.1</td>
</tr>
<tr>
<td>Duration to baseline (min)</td>
<td>150-180</td>
<td>180*</td>
</tr>
</tbody>
</table>

*Data were only collected up to 180 minutes

**Source:**
FDA Figures

**RHI = Regular Human Insulin**
Pharmacokinetics – Afrezza vs. SC Insulin

Study 177

<table>
<thead>
<tr>
<th>Source:</th>
<th>Afrezza</th>
<th>RHI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax (min)</td>
<td>11.3</td>
<td>13.1</td>
</tr>
<tr>
<td>Duration to baseline (min)</td>
<td>150-180</td>
<td>180*</td>
</tr>
</tbody>
</table>

Source: FDA Figures
Pharmacodynamics – Afrezza vs. SC Insulin

**Study 176: Healthy Subjects** (Afrezza vs. RHI)  
**Study 177: T1DM** (Afrezza vs. Insulin Lispro)

**Source:**  
FDA Figures

**GIR:** Glucose Infusion Rate  
**RHI =** Regular Human Insulin
Pharmacodynamics – Exubera vs. SC Insulin

Mean Glucose Infusion Rate (% of Maximum)

Mean GIR normalized to $GIR_{\text{max}}$ for each subject treatment versus time in healthy volunteers

Source: Exubera Prescribing Information
Outline

• Pharmacokinetic (PK) and pharmacodynamic (PD) characteristics

• Dose-proportionality for PK and PD

• Between-subject variability

• Proposed dosing regimen

• Summary
Dose-Proportionality – PK and PD of Afrezza (Study 176)

- PK: dose-proportional increase in exposures
- PD: less-than dose-proportional

![Graph showing GIR (mg/kg*min) vs Time (minutes) for different doses of Afrezza and SC RHI 15 U.](chart.png)

**Source:**
FDA Figures
Dose-Proportionality – PK and PD of Afrezza (Study 176)

- PK: dose-proportional increase in exposures
- PD: less-than dose-proportional
### HbA1c (%) Results for Phase 2 Study 005 in T2DM (MedTone Device)

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Baseline mean±SD</th>
<th>Change from baseline Adj. mean ± SE</th>
<th>Difference in adj. mean change with 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 14 units</td>
<td>43</td>
<td>8.9±1.4</td>
<td>-0.3±0.1</td>
<td>-0.5 (-1.0, 0.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>T1 28 units</td>
<td>43</td>
<td>8.6±1.4</td>
<td>-0.6±0.1</td>
<td>-0.8 (-1.3, -0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T1 42 units</td>
<td>41</td>
<td>8.7±1.2</td>
<td>-0.5±0.2</td>
<td>-0.7 (-1.2, -0.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>T1 56 units</td>
<td>42</td>
<td>8.8±1.2</td>
<td>-0.6±0.2</td>
<td>-0.8 (-1.3, -0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo</td>
<td>41</td>
<td>8.7±1.3</td>
<td>0.2±0.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Source:** Applicant data
Outline

- Pharmacokinetic (PK) and pharmacodynamic (PD) characteristics
- Dose-proportionality for PK and PD
- Between-subject variability
- Proposed dosing regimen
- Summary
Between-Subject Variability– PK and PD of Afrezza (Study 176)

- %CV for PK increased in a dose-related manner
- Conversely, %CV for PD decreased with dose

Source: FDA Figures

%CV = Coefficient of variation
Outline

• Pharmacokinetic (PK) and pharmacodynamic (PD) characteristics
• Dose-proportionality for PK and PD
• Between-subject variability
• Proposed dosing regimen
• Summary
## Dosing Regimen

### Proposed Prescribing information

<table>
<thead>
<tr>
<th>Meal time insulin dose</th>
<th>Afrezza dose</th>
<th>Aspart bolus dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>~ 3.4 times</td>
<td>Conversion</td>
<td>~ 2.5 times</td>
</tr>
<tr>
<td>0-3 IU</td>
<td>10 U</td>
<td>0-4 IU</td>
</tr>
<tr>
<td>4-6 IU</td>
<td>20 U</td>
<td>&gt; 4-8 IU</td>
</tr>
<tr>
<td>7-9 IU</td>
<td>30 U</td>
<td>&gt; 8-12 IU</td>
</tr>
<tr>
<td>10-12 IU</td>
<td>40 U</td>
<td>&gt; 12-16 IU</td>
</tr>
<tr>
<td>13-15 IU</td>
<td>50 U</td>
<td>&gt; 16-20 IU</td>
</tr>
<tr>
<td>16-18 IU</td>
<td>60 U</td>
<td>&gt; 20-24 IU</td>
</tr>
</tbody>
</table>

### Phase 3 trials

<table>
<thead>
<tr>
<th>Aspart bolus dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 IU</td>
</tr>
<tr>
<td>&gt; 4-8 IU</td>
</tr>
<tr>
<td>&gt; 8-12 IU</td>
</tr>
<tr>
<td>&gt; 12-16 IU</td>
</tr>
<tr>
<td>&gt; 16-20 IU</td>
</tr>
<tr>
<td>&gt; 20-24 IU</td>
</tr>
</tbody>
</table>

### Concerns

- Assumes same dose-response relationship between Afrezza and subcutaneous insulin
  - Not sufficient data to support this assumption (only one SC dose for comparison)
- Unknown whether less incremental benefit at higher dosage for Afrezza parallels that for SC insulin
  - Potential implications for dose titration
Applicant’s Justification for the Proposed Dosing Regimen

- Comparison of PK bioavailability between Afrezza and SC insulin
  - Does not consider non-proportionality in PD

- Comparison of the overall mean daily prandial dosage for Afrezza vs. SC insulin from the Phase 3 trial in type 1 diabetics
  - Different basal insulin doses and titration schemes between Afrezza and SC insulin
  - Generalizability of insulin aspart to RHI and other analogs
  - Study assumption of 1 : 2.5 conversion ratio
Outline

- Pharmacokinetic (PK) and pharmacodynamic (PD) characteristics
- Dose-proportionality for PK and PD
- Between-subject variability
- Proposed dosing regimen
- Summary
Summary

• **PK and PD profiles different than SC insulin**
  – Higher $C_{\text{max}}$ and Early $GIR_{\text{max}}$
  – Insulin concentrations decline to near baseline levels in about 2-3 hours and the duration of PD effect is relatively shorter

• **Less-incremental benefit with increase in dose**
  – Unknown if the diminishing benefit at higher dosage parallels to that seen with subcutaneous insulin

• **Assumptions for the proposed dosing regimen not well supported**
  – Similar dose-response relationship between Afrezza and SC insulin
Acknowledgements

- Manoj Khurana
- Afrezza Review Team
Clinical Efficacy of Afrezza

Endocrinologic and Metabolic Drugs Advisory Committee
Advisory Committee Meeting, April 1, 2014

Lisa B. Yanoff, M.D.
Division of Metabolism and Endocrinology Products
Topics for Presentation

• History of development program
  – Overview of results from previous studies

• Clinical efficacy evaluation
  – Trial 171 - T1DM
  – Trial 175 - T2DM

• Summary and Conclusions
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• History of development program
  – Overview of results from previous studies

• Clinical efficacy evaluation
  – Trial 171 - T1DM
  – Trial 175 - T2DM

• Summary and Conclusions
Regulatory History of Afrezza Program

2009
Original NDA
MedTone Device

2010
Resubmission
Gen2 Device

2013
Resubmission
Gen2 Device

Complete Response 1

T1DM – 1 trial
T2DM - 2 trials with duration of 6 months or greater

Complete Response 2

No major clinical trials with new device

Present

Two new Phase 3 trials
T1DM - 171
T2DM – 175

MedTone comparison
Difference in Change in HbA1c*
Afrezza vs. Comparator – Original NDA

Above 0 = Afrezza worse
Below 0 = Afrezza better
0.4 = Non-inferiority margin:
Below 0.4 = Afrezza non-inferior

*Primary analysis results
Topics for Presentation

• History of development program
  – Overview of results from previous studies

• Clinical efficacy evaluation
  – Trial 171 - T1DM
    • Missing data and insulin titration
  – Trial 175 - T2DM

• Summary and Conclusions
All patients switch to insulin aspart

4 week basal insulin optimization

Screening

Randomization

12 week prandial insulin titration

12 week stable phase

Afrezza Gen2 plus basal

Afrezza MedTone plus basal

Insulin aspart plus basal

24 weeks

Pulmonary safety
NI margin
0.4%
Basal Insulin Dosing and Titration

- Subjects stayed on pre-enrollment basal insulin
- Basal insulin dose adjustment
  - Subject-driven titration algorithms
  - Goal 100-120 mg/dL fasting glucose
- Algorithms should help subjects reach glycemic targets
Prandial Insulin Dosing and Titration

• Afrezza dose adjustment
  – 90 min post-prandial glucose (PPG)
  – Subject-driven titration algorithm
  – Titrated weekly

<table>
<thead>
<tr>
<th>Median 90 min PPG</th>
<th>Afrezza Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;110 mg/dL</td>
<td>Decrease by 10 U</td>
</tr>
<tr>
<td>≥110 mg/dL to &lt;160 mg/dL</td>
<td>Maintain current dose</td>
</tr>
<tr>
<td>≥160 mg/dL</td>
<td>Increase by 10 U at the same meal</td>
</tr>
</tbody>
</table>

• Aspart dose adjustment
  – Based on premeal glucose
# Subject Characteristics - Study 171

| Demographics | • Men 44%; women 56%  
|              | • Average age ~ 38 years  
|              | • >95% White |
| BMI          | • Mildly overweight (26 kg/m²) |
| Diabetes status | • Type 1 for at least 12 months  
|               | • Stable dose of basal/bolus for at least 3 mos  
|               | • HbA1c ≥7.5% and ≤ 10%  
|               | • Mean duration 16 years  
|               | • No recent severe hypoglycemia |
| General health status | • Generally healthy, no severe diabetes complications |
Subject Disposition - Study 171

Randomized Subjects n=518

- Afrezza Gen 2 n=174
  - Completed 75%
  - Withdrew 25%

- Afrezza MedTone n=174
  - Completed 79%
  - Withdrew 21%

- Insulin Aspart n=170
  - Completed 89%
  - Withdrew 11%

Lower completion rate in Afrezza arms than in insulin aspart arm
Subject Disposition - Study 171

Randomized Subjects n=518

Afrezza Gen 2 n=174
- Completed 75%
- Withdrew 25%

Afrezza MedTone n=174
- Completed 79%
- Withdrew 21%

Insulin Aspart n=170
- Completed 89%
- Withdrew 11%

May have implications for missing data considerations
## Discontinuations - Study 171

<table>
<thead>
<tr>
<th></th>
<th>Afrezza Gen2</th>
<th>Insulin Aspart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized subjects</td>
<td>174</td>
<td>170</td>
</tr>
<tr>
<td>Completed randomized treatment</td>
<td>130 (75%)</td>
<td>151 (89%)</td>
</tr>
<tr>
<td>Withdrew during randomized treatment</td>
<td>44 (25%)</td>
<td>19 (11%)</td>
</tr>
</tbody>
</table>

### Reasons for discontinuation

<table>
<thead>
<tr>
<th>Reason</th>
<th>Afrezza Gen2</th>
<th>Insulin Aspart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event (AE)</td>
<td>16 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>Physician decision</td>
<td>3 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Withdrawal by subject</td>
<td>21 (12%)</td>
<td>8 (5%)</td>
</tr>
</tbody>
</table>

- 5 dropouts ≈ inadequate efficacy
- 1 dropout ≈ adverse event

- Discontinuations more frequent with Afrezza vs. aspart; disproportionately more often for AEs and inadequate efficacy
- Similar to original NDA
Primary Efficacy Results Study 171

<table>
<thead>
<tr>
<th>LS Mean Change from Baseline</th>
<th>Afrezza Gen2</th>
<th>Insulin Aspart</th>
<th>Treatment Difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Randomized</td>
<td>8.0%</td>
<td>7.9%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Baseline HbA1c Value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in HbA1c</td>
<td>-0.20%</td>
<td>-0.42%</td>
<td>0.22%</td>
<td>0.08, 0.37</td>
</tr>
</tbody>
</table>

Change in HbA1c was analyzed using MMRM with terms for baseline, treatment, region, basal insulin type, visit, and treatment by visit interaction.
Missing Data Considerations
Change in HbA1c: Completers vs. Dropouts

Source: FDA graphs
# Sensitivity Analyses

<table>
<thead>
<tr>
<th>Method</th>
<th>Afrezza LS Mean Change in HbA1c</th>
<th>Aspart LS Mean Change in HbA1c</th>
<th>Treatment Difference LS Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA’s requested analysis</strong> “Analysis 1”: 0.4% was added to every discontinued Afrezza subject assuming all subjects MNAR</td>
<td>-0.07%</td>
<td>-0.38%</td>
<td>0.31%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Applicant’s analysis</strong> “Analysis 2”: 0.4% was added to MNAR Afrezza subjects* as adjudicated by the applicant</td>
<td>-0.14%</td>
<td>-0.37%</td>
<td>0.23%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Applicant’s analyses
Key: MNAR=Missing Not at Random (for analysis 2, defined as due to apparent lack of efficacy as adjudicated by applicant)
*N=5
Basal Insulin Titration

Source: Applicant’s graph
Was Basal Insulin Titration Adequate?

Percent at basal titration target by week 12

Source: FDA figure
Expressing ‘Afrezza Units’ as ‘Aspart Units’

<table>
<thead>
<tr>
<th>Afrezza 10 U Gen 2</th>
<th>4 IU insulin aspart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afrezza 20 U Gen 2</td>
<td>8 IU insulin aspart</td>
</tr>
</tbody>
</table>

Ratio of 2.5:1

Afrezza Gen 2 units divided by 2.5 gives “aspart equivalent units”

Example: 60 U Afrezza = 24 IU aspart (60 ÷ 2.5)
Prandial Insulin Titration

Source: Applicant’s graph
Was Prandial Titration Adequate?

<table>
<thead>
<tr>
<th></th>
<th>Treatment Arm Breakfast</th>
<th>Treatment Arm Lunch</th>
<th>Treatment Arm Dinner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afrezza</td>
<td>37</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Aspart</td>
<td>12</td>
<td>20</td>
<td>9</td>
</tr>
</tbody>
</table>

Source: FDA figure
Responder Rates Study 171

Patients who reached glycemic targets who were above target values at baseline

<table>
<thead>
<tr>
<th>FDA Analysis</th>
<th>Afrezza Gen2</th>
<th>Insulin Aspart</th>
<th>Difference</th>
<th>Fisher’s exact p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c ≤ 7.0% at week 24 and &gt;7.0% at baseline</td>
<td>10.2%</td>
<td>21.4%</td>
<td>-11.2%</td>
<td>0.01</td>
</tr>
<tr>
<td>HbA1c ≤ 6.5% at week 24 and &gt;6.5% at baseline</td>
<td>5.4%</td>
<td>10.5%</td>
<td>-5.1%</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Patients with missing data at week 24 were treated as non-responders
Efficacy Evaluation
Summary and Conclusions - Study 171

- Afrezza non-inferior to aspart in primary analysis
- Afrezza statistically worse than aspart
- Responder rates better with aspart vs. Afrezza
- High and differential dropout rates
  - Concern regarding missing data
  - Non-inferiority not demonstrated in FDA’s sensitivity analysis
- Non-inferiority studies rely on the assumption that the comparator worked as expected
  - Aspart was minimally titrated
  - Average daily basal and prandial insulin doses used in the Afrezza group were consistently higher than those used in the aspart group, in the face of a lesser improvement in HbA1c
Topics for Presentation

• History of development program
  – Overview of results from previous studies

• Clinical efficacy evaluation
  – Trial 171 - T1DM
  – Trial 175 - T2DM

• Summary and Conclusions
T2DM Trial - Study 175 Design

Patients continue on pre-enrollment OADs

6-week OAD run-in phase

Randomization

12 week dose titration phase

12 week stable dosing phase

Afrezza Gen2

Rescue therapy

Afrezza Placebo

Test for superiority

24 weeks

OAD=oral antidiabetic drug
Subject Characteristics Study 175

| Demographics | • Men 44%; women 56%  
|              | • Average age ~ 56 years  
|              | • >85% White, ~ 10% Black or African American |
| BMI          | • On average obese (32 kg/m²) |
| Diabetes status | • Type 2 for more than 12 months; no insulin  
|              | • Stable dose of optimal/maximally tolerated oral antidiabetic drugs (OADs) for at least 3 mos  
|              | • Metformin alone: 23%  
|              | • Two or more OADs 77%  
|              | • HbA1c ≥7.5% and ≤10%  
|              | • Mean duration 9 years  
|              | • No recent severe hypoglycemia |
| General health status | • Generally healthy, no severe diabetes complications |
Primary Efficacy Results Study 175

<table>
<thead>
<tr>
<th>FDA Analysis</th>
<th>LS Mean Change from Baseline</th>
<th>Treatment Difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Randomized</td>
<td>Afrezza Gen2</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Baseline HbA1c Value</td>
<td>8.3%</td>
<td>8.3%</td>
<td></td>
</tr>
<tr>
<td>Change in HbA1c</td>
<td>-0.84%</td>
<td>-0.41%</td>
<td><strong>-0.42</strong></td>
</tr>
</tbody>
</table>

- Change in HbA1c was analyzed using MMRM with terms for baseline, treatment, region, OAD type, visit, and treatment by visit interaction
- Data collected after initiation of rescue therapy were excluded from the analysis
## Efficacy of Non-titratable Antidiabetes Drugs on a Background of Metformin or at Least Two Other Drugs

<table>
<thead>
<tr>
<th>Class</th>
<th>Background Therapy</th>
<th>PBO-adj Δ HbA1c (%)</th>
<th>Treatment Duration (Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP4 inhibitor</td>
<td>Met</td>
<td>-0.8</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Met + SU</td>
<td>-0.7</td>
<td>24</td>
</tr>
<tr>
<td>SGLT2 inhibitor</td>
<td>Met</td>
<td>-0.8</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Met + Pio</td>
<td>-0.6</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Met + SU</td>
<td>-0.7</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.9</td>
<td></td>
</tr>
<tr>
<td>GLP-1 agonist</td>
<td>Met</td>
<td>-1.1</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Met + SU</td>
<td>-1.1</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Met + Rosi</td>
<td>-0.9</td>
<td>26</td>
</tr>
<tr>
<td>Bile acid sequestrant</td>
<td>Met</td>
<td>-0.5</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Met + Other OADs</td>
<td>-0.6</td>
<td>26</td>
</tr>
</tbody>
</table>

**Source:** Individual product PIs

**Key:** PBO=placebo; adj=adjusted; Δ=change in; Met=metformin; SU=sulfonylurea; Pio=pioglitazone; Rosi=rosiglitazone, OAD=oral antidiabetic drug

*Afrezza PBO-adj Δ HbA1c = -0.42%*
## Responder Rates Study 175

Patients who achieved glycemic targets who started above target value at baseline

<table>
<thead>
<tr>
<th>FAS Population</th>
<th>Afrezza Gen2</th>
<th>Placebo</th>
<th>Difference</th>
<th>Fisher’s exact p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c ≤ 7.0% at week 24 and &gt;7% at baseline</td>
<td>32.2%</td>
<td>15.1%</td>
<td>17.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c ≤ 6.5% at week 24 and &gt;6.5% at baseline</td>
<td>13.6%</td>
<td>3.4%</td>
<td>10.2%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Non-rescued patients with missing data at week 24 and rescued patients were treated as non-responders**
Efficacy Evaluation
Summary and Conclusions Study 175

- Afrezza superior to placebo on background of metformin or at least two other oral antidiabetes drugs
- Effect size -0.42% HbA1c
- Missing data rates and rescue therapy did not affect the primary efficacy analysis
- Responder analyses consistent with the primary efficacy analysis
- Efficacy of Afrezza for T2DM may be considered modest compared to some of the other available antidiabetes therapies, including non-insulin oral antidiabetes drugs
Assessment of Change in Fasting Plasma Glucose - Baseline to Week 24

### T1DM

**Study 171**

<table>
<thead>
<tr>
<th></th>
<th>Afrezza Gen2</th>
<th>Aspart</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG Change</td>
<td>-25 mg/dL</td>
<td>+10 mg/dL</td>
</tr>
</tbody>
</table>

- Not consistent with the primary efficacy analysis
- Reflective of higher basal insulin dose used in Afrezza vs. aspart arm?

### T2DM

**Study 175**

<table>
<thead>
<tr>
<th></th>
<th>Afrezza Gen2</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG Change</td>
<td>-11 mg/dL</td>
<td>-4 mg/dL</td>
</tr>
</tbody>
</table>

- Reflective of Afrezza’s use as a mealtime insulin which may not target fasting glucose?
Assessment of Change in Body Weight Baseline to Week 24

- **T1DM Study 171**
  
<table>
<thead>
<tr>
<th></th>
<th>Afrezza</th>
<th>Aspart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Weight Change</td>
<td>-0.4 kg</td>
<td>+0.9 kg</td>
</tr>
</tbody>
</table>

- **T2DM Study 175**
  
<table>
<thead>
<tr>
<th></th>
<th>Afrezza</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Weight Change</td>
<td>+0.5 kg</td>
<td>-1.2 kg</td>
</tr>
</tbody>
</table>

• Less effective insulin ≈ less weight gain?
Topics for Presentation

• History of development program
  – Overview of results from previous studies

• Clinical efficacy evaluation
  – Trial 171 - T1DM
  – Trial 175 - T2DM

• Summary and Conclusions
Difference in Change in HbA1c* Afrezza vs. Comparator – T1DM

Mean Difference in HbA1c (Afrezza – Control) with 95% CI

Above 0 = Afrezza worse
Below 0 = Afrezza better

0.4 = Non-inferiority margin:
Below 0.4 = Afrezza non-inferior

*Primary analysis results
Difference in Change in HbA1c* Afrezza vs. Comparator – T2DM

Mean Difference in HbA1c (Afrezza – Control) with 95% CI

-0.8 -0.4 0.0 0.4 0.8

Trial 014 (vs. aspart) Trial 102 (vs. 70/30) Trial 175 (vs. placebo)

*Primary analysis results

Above 0 = Afrezza worse
Below 0 = Afrezza better

0.4 = Non-inferiority margin:
Below 0.4 = Afrezza non-inferior
Acknowledgements

- Jean-Marc Guettier
- Cynthia Liu
- Todd Sahlroot
- Mark Rothmann
- Jennifer Pippins
- Trish Bright
- Rich Whitehead
- Mary Parks
- Ali Mohamadi
- Karen M. Mahoney
- Hylton Joffe
Afrezza Pulmonary Safety

Endocrinologic and Metabolic Drugs Advisory Committee
Advisory Committee Meeting, April 1, 2014

Miya Okada Paterniti, M.D.
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Outline

- Background
- Original Submission
- Re-submission
- Summary and Concluding Remarks
Technosphere Insulin (TI)

- Dry powder formulation of recombinant human insulin
- Novel excipient: fumaryl diketopiperazine (FDKP)
- FDKP self-assembles into Technosphere particles (TP) under acidic conditions
- Drug product is formed by adsorbing insulin onto the pre-formed TP
- Particles dissolve under physiological conditions, releasing the adsorbed insulin
Background

- **Original submission – March 2009**
  - TI delivered through MedTone Inhaler
  - 9 controlled trials spanning 11 weeks to 2 years

- **Re-submission #1 – June 2010**
  - TI delivered through Gen2 Inhaler
  - In vitro and clinical pharmacology data only; no clinical data provided

- **Re-submission #2 – October 2013**
  - Two Phase 3 clinical trials of 6 months duration with TI delivered via the Gen2 inhaler; pulmonary safety assessed.
A Change in Device

**MedTone**
(Original device)

**Gen2**
(To-be-marketed device)
# Characteristics of the MedTone and Gen2 Inhalers

<table>
<thead>
<tr>
<th></th>
<th>MedTone (Original)</th>
<th>Gen2 (To-be-marketed)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Device</strong></td>
<td>Breath actuated dry powder inhaler</td>
<td></td>
</tr>
<tr>
<td><strong>Formulation</strong></td>
<td>FDKP novel excipient as carrier for insulin</td>
<td></td>
</tr>
<tr>
<td><strong>Efficiency</strong></td>
<td>Less efficient</td>
<td>More efficient*</td>
</tr>
<tr>
<td><strong>Cartridge Strengths</strong></td>
<td>15 U (5 mg) 30 U (10 mg)</td>
<td>10 U (3.3 mg) 20 U (6.7 mg)</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>8 steps 2 inhalations per cartridge</td>
<td>4 steps 1 inhalation per cartridge</td>
</tr>
<tr>
<td><strong>Cleaning</strong></td>
<td>Weekly</td>
<td>No cleaning proposed</td>
</tr>
<tr>
<td><strong>Use period</strong></td>
<td>1 year</td>
<td>15 days</td>
</tr>
</tbody>
</table>

Source: MannKind Corporation EMDAC Briefing Document  
* 33% less Technosphere insulin needed with Gen2 inhaler to provide same insulin exposure as MedTone inhaler
Outline

• Background
• Original Submission
• Re-submission
• Summary and Concluding Remarks
### Original Submission: Clinical Studies with MedTone

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Study Duration</th>
<th>Treatment Arms</th>
<th>N*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1 DM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MKC-TI-101</td>
<td>R, OL</td>
<td>12 weeks</td>
<td>Afrezza Injected insulin</td>
<td>54</td>
</tr>
<tr>
<td>MKC-TI-009</td>
<td>R, C, OL</td>
<td>1 year</td>
<td>Afrezza Injected insulin</td>
<td>301</td>
</tr>
<tr>
<td><strong>Type 2 DM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MKC-TI-005</td>
<td>MC, R, DB, PC</td>
<td>11 weeks</td>
<td>Afrezza Inhaled Excipient (TP)</td>
<td>181</td>
</tr>
<tr>
<td>PDS-INS-0008</td>
<td>R, DB, PC, PG</td>
<td>12 weeks</td>
<td>Afrezza Inhaled Excipient (TP)</td>
<td>61</td>
</tr>
<tr>
<td>MKC-TI-026</td>
<td>R, C, OL</td>
<td>12 weeks</td>
<td>Afrezza Inhaled Excipient (TP)</td>
<td>75</td>
</tr>
<tr>
<td>MKC-TI-014</td>
<td>R, OL</td>
<td>24 weeks</td>
<td>Afrezza Injected insulin</td>
<td>151</td>
</tr>
<tr>
<td>MKC-TI-103</td>
<td>R, C, OL</td>
<td>24 weeks</td>
<td>Afrezza Oral anti-diabetic</td>
<td>358</td>
</tr>
<tr>
<td>MKC-TI-102</td>
<td>R, C, OL</td>
<td>1 year</td>
<td>Afrezza Injected insulin</td>
<td>334</td>
</tr>
<tr>
<td><strong>Type 1 and Type 2 DM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MKC-TI-030</td>
<td>MC, R, OL</td>
<td>2 years</td>
<td>Afrezza Non-inhaled Comparator</td>
<td>267</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Afrezza Non-inhaled Comparator</td>
<td>271</td>
</tr>
</tbody>
</table>

*Number randomized, R: randomized; OL: open label; C: controlled; MC: multicenter; DB: double blind, PC: placebo controlled, PG: parallel group; Source: Individual study CSRs.*
Original Submission: Safety database

<table>
<thead>
<tr>
<th>Subjects by Treatment Arm and Disease Type</th>
<th>Afrezza (TI)</th>
<th>Non-Inhaled Comparator</th>
<th>Inhaled Excipient (TP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>614</td>
<td>599</td>
<td>114</td>
</tr>
<tr>
<td>Type 1 DM</td>
<td>1795</td>
<td>1345</td>
<td>114</td>
</tr>
<tr>
<td>Type 2 DM</td>
<td>2409</td>
<td>1944</td>
<td>114</td>
</tr>
<tr>
<td>Total</td>
<td>2409</td>
<td>1944</td>
<td>114</td>
</tr>
</tbody>
</table>

Source: ISS 2009, Table 9, p 60; Table 10, p 61.
Original Submission: Key Pulmonary Exclusion Criteria in Phase 3 Studies

- COPD, asthma, or other significant pulmonary disease
- Current smokers or smoking history within the past 6 months
- Malignancy (within 5 years)
- Abnormal lung function defined via spirometry
Original Submission: Pulmonary Safety Findings

- FEV1 decline over time
- Bronchospasm in patients with asthma and COPD
- Cough
Spirometry

- **FEV1**: Forced expiratory volume in 1 second
  - Primary endpoint for many pulmonary trials
- **FVC**: Forced vital capacity
- **Best of 3 acceptable, reproducible efforts**
- **Lower limit of normal FEV1 and FVC is 80% predicted**
- **Afrezza exclusion criteria**: FEV1 or FVC < 70-80% predicted
# Original Submission: FEV1 Decline Over Time in Type 1 DM

## Change in FEV1 from Baseline in Type 1 DM with Technosphere Insulin via the MedTone Inhaler (Safety Population, Original Submission)

<table>
<thead>
<tr>
<th>Time point</th>
<th>FEV1 (L)</th>
<th>Treatment Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Afrezza Mean (SD)</td>
<td>Non-Inhaled Comparator Mean (SD)</td>
</tr>
<tr>
<td>6 months</td>
<td>-0.09 (0.01)</td>
<td>-0.05 (0.01)</td>
</tr>
<tr>
<td>N=370</td>
<td>N=437</td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>-0.07 (0.22)</td>
<td>-0.04 (0.17)</td>
</tr>
<tr>
<td>N=235</td>
<td>N=244</td>
<td></td>
</tr>
<tr>
<td>2 years</td>
<td>-0.13 (0.22)</td>
<td>-0.10 (0.19)</td>
</tr>
<tr>
<td>N=200</td>
<td>N=246</td>
<td></td>
</tr>
</tbody>
</table>

Source: Pulmonary CIR, ISS 2009, Table 51, p 159; DPARP NDA 2009 Review, Table 23, p. 69; Table 25, p. 71
FEV1 Decline Over 2 Years in Type 1 DM

Source: Figure 35, p 159, Pulmonary CIR, ISS, Module 5
### Clinical Studies in Patients with Underlying Lung Disease with Technosphere Insulin via MedTone Inhaler (Original Submission)

<table>
<thead>
<tr>
<th>Study Status</th>
<th>Design</th>
<th>Study Duration</th>
<th>Population</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetes</td>
<td>Asthma</td>
</tr>
<tr>
<td>MKC-TI-027</td>
<td>OL, SD(^1)</td>
<td>-</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Completed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MKC-TI-113</td>
<td>OL, 3-dose</td>
<td>-</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Completed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MKC-TI-015</td>
<td>OL, SD</td>
<td>-</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Completed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MKC-TI-134</td>
<td>R, OL</td>
<td>1 year</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OL = open-label, SD = single-dose, R = randomized, FEV1 = Forced expiratory volume in 1 second, COPD = Chronic obstructive pulmonary disease, non = non-asthmatic or non-COPD

\(^1\) SD applies to pulmonary function evaluation

\(^2\) Only 8 of these subjects had pulmonary function measured

Source: MKC-TI-027 CSR, MKC-TI-113 CSR, MKC-TI-015 CSR, 120-day safety update 2014
## Clinical Studies in Patients with Underlying Lung Disease with Technosphere Insulin via MedTone Inhaler (Original Submission)

<table>
<thead>
<tr>
<th>Study Status</th>
<th>Design</th>
<th>Study Duration</th>
<th>Population</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetes</td>
<td>Asthma</td>
</tr>
<tr>
<td>MKC-TI-027</td>
<td>OL, SD</td>
<td>- x</td>
<td>5 Asthma</td>
<td>15 non</td>
</tr>
<tr>
<td>Completed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MKC-TI-113</td>
<td>OL, 3-dose</td>
<td>- x</td>
<td>17 Asthma</td>
<td>13 non</td>
</tr>
<tr>
<td>Completed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MKC-TI-015</td>
<td>OL, SD</td>
<td>- x</td>
<td>18² COPD</td>
<td>20² non</td>
</tr>
<tr>
<td>Completed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MKC-TI-134</td>
<td>R, OL 1 year</td>
<td>- x x x</td>
<td>255 Asthma</td>
<td>255 COPD</td>
</tr>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OL = open-label, SD = single-dose, R = randomized, FEV1 = Forced expiratory volume in 1 second, COPD = Chronic obstructive pulmonary disease, non = non-asthmatic or non-COPD

1 SD applies to pulmonary function evaluation
2 Only 8 of these subjects had pulmonary function measured

Source: MKC-TI-027 CSR, MKC-TI-113 CSR, MKC-TI-015 CSR, 120-day safety update 2014
Bronchospasm in Patients with Asthma and COPD

- **Asthma (N = 17)**
  - Mean FEV1 15 minutes post-TI decreased by 400 mL
  - Return to baseline by 2 hours
  - 2 serious adverse events (SAEs) of bronchospasm
  - Bronchospasm and wheezing AEs (29%; 5/17) compared to no events in non-asthmatics

- **COPD (N = 8)**
  - Mean FEV1 18 minutes post-TI decreased by 200 mL
  - Return towards baseline by 8 hours
  - No SAEs
  - Respiratory AEs (cough, dry throat) similar for non-COPD
## Original Submission: Common Respiratory AEs

### Common Respiratory Adverse Events¹ (Safety Population, Original Submission)

<table>
<thead>
<tr>
<th>System Organ Class/PT</th>
<th>Afrezza N = 2409</th>
<th>Non-Inhaled Comparator N=1944</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Subjects with Respiratory AE</td>
<td>1088 (45)</td>
<td>606 (31)</td>
</tr>
<tr>
<td><strong>RESPIRATORY, THORACIC AND MEDIASTINAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>794 (33)</td>
<td>192 (10)</td>
</tr>
<tr>
<td></td>
<td>642 (27)</td>
<td>109 (6)</td>
</tr>
<tr>
<td>Crackles Lung</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>32 (1)</td>
<td>5 (&lt;1)</td>
</tr>
<tr>
<td>Lung Infiltration</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Pharyngolaryngeal Pain</td>
<td>56 (2)</td>
<td>20 (1)</td>
</tr>
<tr>
<td>Productive Cough</td>
<td>56 (2)</td>
<td>16 (1)</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>55 (2)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td><strong>INFECTIONS AND INFESTATIONS</strong></td>
<td>574 (24)</td>
<td>497 (26)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>45 (2)</td>
<td>24 (1)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>184 (8)</td>
<td>155 (8)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>26 (1)</td>
<td>19 (1)</td>
</tr>
</tbody>
</table>

¹Occurring at ≥ 1% in any arm, and more commonly with active treatment than comparator

Source: Pulmonary CIR, ISS 2009, Table 12, p. 53-7
## Original Submission: Respiratory SAEs

### All Respiratory SAEs (Safety Population, Original Submission)

<table>
<thead>
<tr>
<th>System Organ Class/Preferred Term</th>
<th>Afreza N = 2409</th>
<th>Non-Inhaled Comparator N = 1944</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with Respiratory SAE</td>
<td>13 (0.5)</td>
<td>9 (0.5)</td>
</tr>
<tr>
<td><strong>RESPIRATORY, THORACIC AND MEDIASTINAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>1 (0.04)</td>
<td>0</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>1 (0.04)</td>
<td>0</td>
</tr>
<tr>
<td>Bronchial obstruction</td>
<td>1 (0.04)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (0.04)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1 (0.04)</td>
<td>0</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1 (0.04)</td>
<td>0</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>1 (0.04)</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>1 (0.04)</td>
<td>1 (0.04)</td>
</tr>
<tr>
<td>Respiratory Failure</td>
<td>1 (0.04)</td>
<td>0</td>
</tr>
<tr>
<td>Hydrothorax</td>
<td>0</td>
<td>1 (0.04)</td>
</tr>
<tr>
<td><strong>INFECTIONS AND INFESTATIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (0.1)</td>
<td>5 (0.3)</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>1 (0.04)</td>
<td>1 (0.04)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>1 (0.04)</td>
<td>0</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>0</td>
<td>1 (0.04)</td>
</tr>
</tbody>
</table>

Source: Pulmonary CIR, ISS 2009, Table 10, p 49
Outline

- Background
- Original Submission
- Re-submission
- Summary and Concluding Remarks
## Resubmission: Clinical Studies with Gen2

### Sources of Pulmonary Safety Clinical Data for Technosphere Insulin (TI) via the Gen2 Inhaler

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Study Duration</th>
<th>Treatment Arms</th>
<th>N</th>
<th>Population</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MKC-TI-171</td>
<td>OL, R, C, FT</td>
<td>6 months</td>
<td>Insulin aspart</td>
<td>170</td>
<td>Type 1 DM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TI in <strong>Gen2</strong> Inhaler</td>
<td>174</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TI in <strong>MedTone</strong> Inhaler</td>
<td>174</td>
<td></td>
</tr>
<tr>
<td><strong>Type 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MKC-TI-175</td>
<td>R, DB, PC</td>
<td>6 months</td>
<td>TI in <strong>Gen2</strong> Inhaler</td>
<td>177</td>
<td>Type 2 DM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inhalation powder (excipient/TP) in <strong>Gen2</strong> Inhaler</td>
<td>176</td>
<td></td>
</tr>
</tbody>
</table>

OL = open-label, R = randomized, C = controlled, FT = forced titration, PC = placebo-controlled, DB = double-blind, TI = Technosphere Insulin (Afrezza), TP = Technosphere particles (excipient only), DM = diabetes mellitus
### Resubmission: Change in FEV1 in Type 1 DM

Change in FEV1 (L) from Baseline in Type 1 DM at 6 months in Resubmission Compared to Original Submission (Safety population)

<table>
<thead>
<tr>
<th>LS Mean (SE)</th>
<th>Treatment Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MKC-TI-171</strong></td>
<td></td>
</tr>
<tr>
<td><strong>TI Gen2</strong></td>
<td></td>
</tr>
<tr>
<td>-0.07 (0.01)</td>
<td></td>
</tr>
<tr>
<td>N=127</td>
<td></td>
</tr>
<tr>
<td><strong>TI MedTone</strong></td>
<td></td>
</tr>
<tr>
<td>-0.08 (0.01)</td>
<td></td>
</tr>
<tr>
<td>N=133</td>
<td></td>
</tr>
<tr>
<td><strong>Non-Inhaled Insulin</strong></td>
<td></td>
</tr>
<tr>
<td>-0.04 (0.01)</td>
<td></td>
</tr>
<tr>
<td>N=146</td>
<td></td>
</tr>
<tr>
<td><strong>TI Gen2 – TI MedTone</strong></td>
<td>0.01</td>
</tr>
<tr>
<td>(95% CI: -0.02, 0.04)</td>
<td></td>
</tr>
<tr>
<td><strong>TI Gen2 – Non-Inhaled Insulin</strong></td>
<td>-0.03¹</td>
</tr>
<tr>
<td><strong>TI MedTone – Non-Inhaled Insulin</strong></td>
<td>-0.04¹</td>
</tr>
<tr>
<td><strong>Original Submission²</strong></td>
<td></td>
</tr>
<tr>
<td>-0.09 (0.01)</td>
<td></td>
</tr>
<tr>
<td>N=370</td>
<td></td>
</tr>
<tr>
<td>-0.05 (0.01)</td>
<td></td>
</tr>
<tr>
<td>N=437</td>
<td></td>
</tr>
</tbody>
</table>

¹Numerical value, no analysis was done to determine statistical significance; ²Applicants 2009 Pooled Type 1 (MMRM)

Source: Study MKC-TI-171 CSR, Table 52, p 168; Summary of clinical safety 2013, Table 29, p. 67; Pulmonary CIR, ISS 2009, Table 51, p 159.
## Resubmission: Change in FEV1 in Type 2 DM

<table>
<thead>
<tr>
<th></th>
<th>MKC-TI-175</th>
<th>Original Submission*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TI Gen2</strong></td>
<td><strong>Inhaled Excipient (TP) Gen2</strong></td>
<td><strong>TI MedTone</strong></td>
</tr>
<tr>
<td></td>
<td><strong>LS Mean (SE)</strong></td>
<td><strong>Non-Inhaled Insulin</strong></td>
</tr>
<tr>
<td>-0.13 (0.01)</td>
<td>-0.04 (0.01)</td>
<td>-0.13 (0.01)</td>
</tr>
<tr>
<td>N=177</td>
<td>N=176</td>
<td>N=688</td>
</tr>
<tr>
<td></td>
<td>-0.08 (0.01)</td>
<td></td>
</tr>
<tr>
<td>N=765</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-0.09 (95% CI: -0.12, -0.05)</td>
<td></td>
<td>-0.05 (95% CI: -0.07, -0.03)</td>
</tr>
</tbody>
</table>

*Applicant’s 2009 Pooled Type 2 (MMRM)*

Source: Study MKC-TI-175 CSR, Table 43, p. 143; Pulmonary CIR ISS, Table 87, p 229-30.
Resubmission: Cough Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>MKC-TI-171</th>
<th>MKC-TI-175</th>
<th>Original submission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TI Gen2</td>
<td>TI MedTone</td>
<td>Inhaled aspart</td>
</tr>
<tr>
<td></td>
<td>N=174</td>
<td>N=173</td>
<td>N=171</td>
</tr>
<tr>
<td>Incidence</td>
<td>32%</td>
<td>23%</td>
<td>2%</td>
</tr>
<tr>
<td>Early d/c</td>
<td>6%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>TI Gen2</td>
<td>Inhaled Excipient Gen2</td>
<td>N=176</td>
</tr>
<tr>
<td></td>
<td>N=177</td>
<td>N=176</td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>24%</td>
<td>20%</td>
<td>27%</td>
</tr>
<tr>
<td>Early d/c</td>
<td>1%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>TI MedTone</td>
<td>Inhaled Excipient MedTone</td>
<td>N=114</td>
</tr>
<tr>
<td></td>
<td>N=2409</td>
<td>N=114</td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>27%</td>
<td>18%</td>
<td>6%</td>
</tr>
<tr>
<td>Early d/c</td>
<td>3%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Non-inhaled Comparator</td>
<td>N=1944</td>
<td></td>
</tr>
</tbody>
</table>

TI=Technosphere Inhalation Powder (active); TP=Technosphere Particles (excipient alone); d/c = discontinuation

Source: MKC-TI-171 CSR, Table 41, p 147, Table 43, p 151; MKC-TI-175 CSR, Table 39, p 136, Table 34, p 127; Pulmonary CIR, ISS 2009, Table 12, p 53-7, Table 11, p 50-1.

- One SAE of bronchial hyper-reactivity was reported in Study 171 in the TI Gen2 treatment group
Outline

• Background
• Original Submission
• Re-submission
• Summary and Concluding Remarks
Summary

• **Original Submission**
  – Pulmonary safety data up to 2 years with TI-MedTone
  – FEV1 mean decline 40 - 60 mL greater with Afrezza vs. non-inhaled comparators
    • Noted within first 3 months and persisted to 2 years, not progressive
  – Bronchospasm in patients with underlying lung disease
    • FEV1 decline in asthma (mean 400 mL) and patients with COPD (mean 200mL)
    • Bronchospasm and wheezing AEs (29%) in asthma
  – Cough: most common AE (27%) and reason for discontinuation (~3%)

• **Resubmission**
  – Pulmonary safety data up to 6 months with TI-Gen2
  – TI-Gen2 showed similar pulmonary safety profile compared to TI-MedTone inhaler
Concluding Remarks

• Significant change in device from MedTone to Gen2 (to-be-marketed)

• Shorter duration (6 months vs. 2 years) and smaller number of subjects (~12% of all TI)
Non-pulmonary Safety of Afrezza

Endocrinologic and Metabolic Drugs Advisory Committee Advisory Committee Meeting, April 1, 2014

Lisa B. Yanoff, M.D.
Division of Metabolism and Endocrinology Products
Topics for Presentation

• Non-pulmonary safety evaluation
  – Lung cancer
  – Diabetic ketoacidosis (DKA)
  – Hypoglycemia

• Closing remarks
  – Clinical risk benefit profile of Afrezza
Lung Cancer – Background

• Given mode of administration of Afrezza, and experience with Exubera® lung and bronchial cancers are a safety concern

• Human insulin may have potential mitogenic properties via insulin-like growth factor-1 (IGF-1) receptor binding

• Afrezza carcinogenicity studies negative
  – Limitations to methods used
  – Existing data do not address whether Afrezza may promote or enhance pre-existing, pre-malignant lesions
# Lung Cancer Cases – Afrezza-Treated Subjects*

<table>
<thead>
<tr>
<th>Subject Identifier</th>
<th>Age/sex/Country</th>
<th>DM Type</th>
<th>Smoking History</th>
<th>Afrezza Exposure</th>
<th>Diagnosis Time</th>
<th>Histology, Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>102/2909</td>
<td>61 / M Argentina</td>
<td>T2DM</td>
<td>40 pack-years</td>
<td>137 days</td>
<td>137 days</td>
<td>Neuro-endocrine oat cell type (small cell) lung cancer</td>
</tr>
<tr>
<td>005/407/3316</td>
<td>66 / M Czech Republic</td>
<td>T2DM</td>
<td>54 pack-years</td>
<td>627 days</td>
<td>627 days</td>
<td>Bronchogenic cancer, non-differentiated NSCLC, T4 N2 M0</td>
</tr>
</tbody>
</table>

### Spontaneous reports submitted after subjects had completed trial participation

<table>
<thead>
<tr>
<th>Subject Identifier</th>
<th>Age/sex/Country</th>
<th>DM Type</th>
<th>Smoking History</th>
<th>Afrezza Exposure</th>
<th>Diagnosis Time</th>
<th>Histology, Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0008/358</td>
<td>59 / M USA</td>
<td>T2DM</td>
<td>NS</td>
<td>3.5 years</td>
<td>2.5 years</td>
<td>Squamous NSCLC</td>
</tr>
<tr>
<td>030/618</td>
<td>73 / F Russia</td>
<td>T2DM</td>
<td>NS</td>
<td>1 year, 11 months</td>
<td>3.5 years</td>
<td>Squamous NSCLC, Stage II</td>
</tr>
</tbody>
</table>

NS=nonsmoker; M=male; F=female; NSCLC=Non-small cell lung cancer

*No cases of lung cancer were reported for comparator subjects.*
## Lung Cancer in Afrezza Program

<table>
<thead>
<tr>
<th></th>
<th>Afrezza</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pooled phase 2/3 safety database</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (SYE)</td>
<td>3017 (2052)</td>
<td>2488 (2250)*</td>
</tr>
<tr>
<td>Events of lung cancer</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Exposure-adjusted incidence (per 100,000 SYE)</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td><strong>Phase 2/3 controlled and uncontrolled studies of &gt;14 days duration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (SYE)</td>
<td>3283 (2747)</td>
<td>2494 (2267)</td>
</tr>
<tr>
<td>Events of lung cancer</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Exposure-adjusted incidence (per 100,000 SYE)</td>
<td>73</td>
<td>0</td>
</tr>
<tr>
<td><strong>All exposed patients^</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events of lung cancer</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

*Includes 290 subjects and 98 SYE exposed to Technosphere Placebo

^Incidence rates not calculated because two cases are spontaneous reports

SYE=Subject year exposure
Diabetic Ketoacidosis

• Original NDA experience
  – Imbalance in DKA events not favoring Afrezza (13 vs. 3)

• Narratives able to identify some triggers
  – Randomization should have balanced groups for predisposing factors

• Imbalance may be consistent with lesser efficacy of Afrezza
Hypoglycemia

• Original NDA submission
  – Incidence of hypoglycemia higher for Afrezza than placebo in placebo-controlled studies
  – Incidence of hypoglycemia lower for Afrezza than comparator in active-control studies vs. other insulin
    • Results confounded by differing efficacy
  – No clear, consistent evidence of hypoglycemia benefit

• Current submission
  – Results consistent with the original NDA
Hypoglycemia

Type 1 Diabetes Trial 171, Afrezza vs. Aspart

<table>
<thead>
<tr>
<th>Type of Hypoglycemia</th>
<th>Afrezza</th>
<th>Aspart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>18.4%</td>
<td>29.2%</td>
</tr>
<tr>
<td>All</td>
<td>96.0%</td>
<td>99.4%</td>
</tr>
</tbody>
</table>

Consistent with the finding that Afrezza was less effective than comparator
Hypoglycemia

Type 2 Diabetes Trial 175, Afrezza vs. Placebo

<table>
<thead>
<tr>
<th>Type of Hypoglycemia</th>
<th>Afrezza</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>5.1%</td>
<td>1.7%</td>
</tr>
<tr>
<td>All</td>
<td>67.8%</td>
<td>30.7%</td>
</tr>
</tbody>
</table>

Greater hypoglycemia risk of insulin vs. placebo is expected
No clear, consistent evidence of hypoglycemia advantage of Afrezza
Summary of Non-Pulmonary Safety Evaluation

• Issues to consider
  – Lung cancer
    • 4 to 0 imbalance not favoring Afrezza
  – DKA (Diabetic ketoacidosis)
    • Imbalance in DKA events not favoring Afrezza
  – Hypoglycemia
    • Consistent with the observed efficacy of Afrezza and results from the original NDA
Acknowledgements

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• Ali Mohamadi
• Karen M. Mahoney
• Rich Whitehead
Epidemiology and Post-Market Surveillance

April 1, 2014

Patricia Bright, PhD
Division of Epidemiology 1
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Objectives

- Provide background on Exubera experience (another inhaled insulin) to help inform decisions about Afrezza
- Share information presented by Pfizer at the International Conference on Pharmacoepidemiology (ICPE) in August 2012, covering:
  - Follow-Up Study of the Exubera clinical trial population (FUSE) for: lung cancer incidence, lung cancer mortality, and all-cause mortality
- Discuss the limitations of postmarketing strategies to evaluate a possible lung cancer risk with Afrezza
Background

Exubera

• An orally inhaled insulin from Pfizer

• Approved by the FDA in January 2006 for the treatment of adults with types 1 & 2 diabetes mellitus in US

  – contraindicated in smokers and in those who had discontinued smoking less than 6 months
**Background**

**Exubera**

- Identified risk: Small, non-progressive and reversible decrease in pulmonary function
- Hypothetical risk: Serious pulmonary events & lung cancer
- Product labeling changed in September 2008 to reflect lung cancer cases with Exubera use
- Withdrawn by the sponsor in September 2008 due to lower than expected sales
Background

Nationally estimated number of dispensed prescriptions and patients receiving Exubera from U.S. outpatient retail pharmacies, 1Q2006-1Q2010

Source: IMS Health, Vector One®: National (VONA) and Total Patient Tracker. Data Extracted June 2011

Oct 2007: Pfizer publically announced it would stop selling Exubera

Sept 2008: Labeling change
Background

Slides copied and adapted for this presentation:

**Source:**
Follow-up Study of the Exubera (FUSE) Clinical Trial Population

• Known imbalance of lung cancer cases at NDA filing

• By 2008: 5 in Exubera exposed: 1 in non-exposed
  – Crude hazard ratio = 5.1 (95% CI: 0.71 - 121.4)

• All cases among former smokers

• Possible detection bias of lung cancer
  – Most patients randomized in open-label (unblinded) trials
  – Mild pulmonary symptoms associated with Exubera use (e.g., cough)
  – Novel route of insulin administration
AIM of FUSE Study

To evaluate whether Exubera exposed patients experienced primary lung cancer mortality at a higher rate than unexposed patients
Endpoints

• **Primary endpoint:** Primary lung cancer mortality

• **Secondary endpoints:**
  – Primary lung cancer mortality among former smokers
  – Primary lung cancer incidence
  – All-cause mortality

• Lung cancers and lung cancer deaths reported by study investigators

• Adjudicated by external expert committee (blinded to randomized group)
  – Lung cancer classified as “highly likely” or “likely”
Study Design

All data = FUSE

Clinical Trials

1\textsuperscript{st} trial visit

n = 7,439

Last trial visit

n = 4,347

Prospective Baseline

Interim

Updated data from sites participating in prospective follow-up

Prospective Data

Year 1:
Vital status

n = 2,631

Year 2:
Vital status
“In-study” vs. “Continuous”

The 2012 ICPE presentation included results for:

- **“In-study”:** no interim data
  - Clinical trials → Prospective
  - Clinical trials → Interim → Prospective

- **“Continuous”:** with interim data
  - Clinical trials → Prospective

We present the “Continuous” data.
Baseline Results: Study Population

Patients at eligible sites: 7,439 (52% Exubera, 48% Comp.)

Site participates: 4,347 patients

Site does not participate: n = 3,092 patients

Patient does not participate: n = 1,716 patients

Patient participates: 2,631

Patient discontinues: n = 95 patients

Patient completes FUSE: 2,536 (34% of original patients)
Baseline Results: Covariates Balanced

• Potential confounders measured at original trial baseline: (Age, gender, race, smoking, pack-years, BMI, HbA$_{1c}$, lung function tests, type 1/type 2 DM, history of: cancer, asthma, COPD)

• Balanced across:
  – All Exubera and comparator subjects
  – Exubera and comparator subjects who participated in prospective follow-up
  – Prospective participants and non-participants

• Additional covariates measured at FUSE baseline:
  – Balanced across Exubera and comparator subjects
Baseline Clinical and Demographic Characteristics: Prospective Subjects Only

<table>
<thead>
<tr>
<th>At Trial Baseline</th>
<th>Exubera (n = 1,356)</th>
<th>Comparator (n = 1,271)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking History (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>56</td>
<td>57</td>
</tr>
<tr>
<td>Ever</td>
<td>44</td>
<td>43</td>
</tr>
<tr>
<td>Mean pack-years</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Median pack-years</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Pack-years of Smoking (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>56</td>
<td>57</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Available</td>
<td>41</td>
<td>40</td>
</tr>
<tr>
<td>Q1 (0-5)</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>Q2 (&gt;5-15)</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Q3 (&gt;15-32)</td>
<td>22</td>
<td>28</td>
</tr>
<tr>
<td>Q4 (&gt;32-180)</td>
<td>27</td>
<td>23</td>
</tr>
</tbody>
</table>
## Endpoint Summary*: Smokers

<table>
<thead>
<tr>
<th>End Point</th>
<th>Randomized Group</th>
<th>Reported</th>
<th>“Highly likely” or “likely”</th>
<th>Adjudicated as: “Highly likely” or “likely” among former smokers**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Lung Cancer Incidence</td>
<td>Exubera</td>
<td>15</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Comparator</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Primary Lung Cancer Mortality</td>
<td>Exubera</td>
<td>6</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Comparator</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>All-Cause Mortality***</td>
<td>Exubera</td>
<td>76</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Comparator</td>
<td>87</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*FUSE “continuous” data (trial, interim, prospective)

** Mean pack-years: Exubera = 50 (3 unknown), Comparator = 51.4 (1 unknown)

***For all-cause mortality all reported endpoints are included
# Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Randomized Group</th>
<th>n</th>
<th>Person years (PY) follow-up</th>
<th>No. with event (%)</th>
<th>Rate per 1,000 PY</th>
<th>Incidence density ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer incidence**</td>
<td>Exubera</td>
<td>3,875</td>
<td>12,606</td>
<td>12 (0.3%)</td>
<td>1.07</td>
<td>3.75 (1.01 – 20.68)</td>
</tr>
<tr>
<td></td>
<td>Comparator</td>
<td>3,564</td>
<td>11,803</td>
<td>3 (0.1%)</td>
<td>0.29</td>
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</tr>
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<td>Lung cancer mortality**</td>
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<td>0.17</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Exubera</td>
<td>3,875</td>
<td>12,606</td>
<td>76 (2.0%)</td>
<td>6.0</td>
<td>HR*** = 0.81 (0.60 – 1.10)</td>
</tr>
<tr>
<td></td>
<td>Comparator</td>
<td>3,564</td>
<td>11,803</td>
<td>87 (2.4%)</td>
<td>7.4</td>
<td></td>
</tr>
</tbody>
</table>

*FUSE “continuous” data (trial, interim, prospective)

** Events adjudicated as “highly likely” or “likely”

***HR = Hazard Ratio
Timing of Lung Cancer Diagnosis

1st trial visit

↓

n = 3 Exubera, 1 Comparator

4 During clinical trials

↓

8 interim

Last trial visit

Prospective baseline

↓

Year 1: vital status

↓

n = 2 Exubera, 1 Comparator

3 During prospective follow-up

Year 2: vital status

↓

n = 7* Exubera, 1 comparator

TOTAL = 12 Exubera, 3 Comparator

*6 of 7 diagnosed <365 days after the last trial visit
## Timing of Lung Cancer Diagnosis

<table>
<thead>
<tr>
<th>Retrospective plus interim</th>
<th>Prospective follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exubera exposed: 9,876.5 PY</td>
<td>Exubera exposed: 2,729.4 PY</td>
</tr>
<tr>
<td>Comparator: 9,232.2 PY</td>
<td>Comparator: 2,570.3 PY</td>
</tr>
</tbody>
</table>

\[ n = 3 \text{ Exubera, 1 Comparator} \]

\[ n = 2 \text{ Exubera, 1 Comparator} \]

4 During clinical trials

3 During prospective follow-up

8 interim

\textbf{TOTAL} = 12 \text{ Exubera, 3 Comparator}
Study Strengths

- Large source population, with baseline trial data available for all patients. Allowed comparison of baseline trial data among:
  - Participants and non-participants
  - Exubera and comparator prospective FUSE participants
- Geographically and ethnically diverse study population
- Balance in all measured potential confounders at baseline
Study Limitations

- **FUSE**: Low participation of sites and patients (34% of original trial participants)
- Potential for detection and reporting biases in endpoints for Exubera exposed
- Possible changes over time in covariates
- Small numbers leading to insufficient power to draw clear conclusions
Pfizer Summary

• Data indicative of a potential increased lung cancer risk, but inconclusive

• Trend toward increased risk may be explained by:
  – Reporting/detection bias associated with preferential screening and reporting of cases for subjects exposed to Exubera in the original studies
  – Promotional effect of Exubera among smokers
  – Combination of both

• No increased risk in all-cause mortality
Postmarketing Assessment of Afrezza
Postmarketing Assessment of Afrezza

**Exubera**: an orally inhaled insulin with a potential risk of increased lung cancer, but inconclusive data

• How do we evaluate for an increased lung cancer risk with Afrezza?

• Strategies for postmarketing assessment of lung cancer risk
  – Three approaches
  – Multiple challenges
Challenges of Planning Study of Afrezza and Lung Cancer

• Comparison groups may not be similar
  – Users of standard insulin may differ from users of inhaled insulin

• Small expected number of outcomes

• Long follow-up time needed for latency period

• Drug uptake unknown

• Mean length of exposure to Afrezza unknown

• Detection bias in Afrezza exposed

• Smoking a strong confounder for lung cancer
#1: Sponsor Proposed Approach
Sponsor Proposed Approach

A prospective, observational, voluntary, product exposure registry without an internal comparator

- **Exposure**: Afrezza use
- **Primary Outcome**: Incidence of primary pulmonary malignancies in patients taking Afrezza
- **Secondary Outcomes**: All other malignancies (except non-melanoma skin cancers), serious pulmonary, allergic, & hypoglycemic events requiring medical intervention
- **External Comparator**: Incidence rate in U.S. population (age-adjusted SEER data)
Sponsor Proposed Approach

- 200 sites, patients with type 1 or type 2 diabetes
- In U.S. with other countries added
- Age ≥ 18 years starting Afrezza, providing informed consent
- Non-interventional, usual care visits (minimum every 6 months)
- 1,800 patients enrolled and followed for 5 - 7 years
- Compare lung cancer incidence rate in registry to incidence rate in the U.S. population (age-adjusted SEER data)
- If the lower limit of the 95% confidence interval is above 64.6 per 100,000, then exposure to Afrezza deemed a significant risk for pulmonary malignancies
Sponsor Proposed Approach

**Strength**: Quickest (?)

**Limitations:**

- Voluntary – unknown enrollment
- Detection bias will increase rate in registry even if Afrezza does not increase risk
- Inhaled insulin users differ from general population
- Unmeasured smoking in SEER population -- confounding
- Limited covariate collection in SEER data -- may lead to more unmeasured confounding
## Estimates for Incident Rate of Pulmonary Malignancies

<table>
<thead>
<tr>
<th>Source</th>
<th>per 100,000 person-years (PY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEER General U.S. Population age-adjusted, based on 2006-2010 cases</td>
<td>61.4/100,000 PY</td>
</tr>
<tr>
<td>Exubera trials plus FUSE follow-up</td>
<td>107/100,000 PY</td>
</tr>
<tr>
<td>Afrezza trials Based on 2 cases in the drug development program</td>
<td>73/100,000 PY (plus 2 spontaneous reports)</td>
</tr>
</tbody>
</table>

Lung cancer incidence strongly driven by smoking history in population
#2 Registry with Internal Comparator
Registry with Internal Comparator

• Similar to sponsor registry:
  – 200 sites, patients with type 1 or type 2 diabetes
  – In U.S. with other countries added
  – Age ≥ 18 years starting Afrezza, providing informed consent

• Comparison groups defined by exposure duration

• Exposure: categorical, short vs. longer Afrezza duration

• Outcomes: Incidence of lung cancer, lung cancer mortality, and all-cause mortality at 3, 5, and 10 years by Afrezza use

• Careful documentation of confounders and adjustment for pack-years of smoking
Registry with Internal Comparison

**Strength**: Increased similarity between comparison groups

**Limitations:**

- Voluntary – unknown enrollment
- Those stopping Afrezza could be different from those continuing (side effects, adherence differences)
- Detection bias – coughing from Afrezza in group continuing Afrezza
- May require larger sample size and take longer time to accumulate needed registry participants
  - Cut points for shorter use versus longer use?
#3 Randomized Clinical Trial
Randomized Clinical Trial

- **Exposure**: Randomized to Afrezza use vs. standard of care insulin

- **Outcomes**: Incidence of lung cancer, lung cancer mortality, and all-cause mortality, adjusting for pack-years of smoking if unbalanced (others?)
  - 200 sites, patients with type 1 or type 2 diabetes
  - In U.S. with other countries added
  - Age ≥ 18 years starting Afrezza, providing informed consent
Randomized Clinical Trial

**Strength**: Randomization would reduce bias due to unmeasured confounding

**Limitations:**

- Patients may refuse enrollment (needle phobia)
- Detection bias – higher rate likely in Afrezza
- Requires large sample size and long time
  - Significance level 0.05, power 0.8, two treatment groups 1:1, Fisher’s exact test: To detect a relative risk of 2 or more, the sample size would need to be 62,152 total (31,076 per group) if the baseline lung cancer incidence rate in the diabetic population is 80/100,000 PY
Summary

• Evaluating lung cancer risk with inhaled insulin use in the postmarketing setting is challenging.

• Several approaches may be needed to assess risk.

• Each has advantages and disadvantages.

• Smoking data are critical in assessing lung cancer risk.
Back-Up Slides
Identifying Outcomes

**Retrospective:** All subjects in prior included clinical trials

**Interim:** Same as above, but only at sites participating in prospective FUSE follow-up:
- Alive & contacted by study investigators: person-time through screening in retrospective analysis (regardless of consent for prospective FUSE)
- Died between trial and start of prospective FUSE: person-time through death in retrospective analysis (obtained: death certificate, hospital, medical records, charts needed for adjudication)

**Prospective:** Collected from the patient interview and medical records at prospective FUSE baseline
- Year 1 & 2: The investigator/designee recorded patient’s vital status and current smoking, reported lung cancer diagnosis
Timing of Lung Cancer Diagnoses & Deaths

Exubera cases

Comparator

Start of original trial  End of original trial  Interim  Start of FUSE follow-up  End of FUSE follow-up

Diagnosis = darker
Death = lighter

4 Exubera cases enrolled in FUSE

2 comparator cases in FUSE
Time Between Date of Randomization and Diagnoses

Each bar is a case adjudicated as "highly likely or "likely"
Cases from the Comparator: Smoking Intensity and Histology

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Smoking History (Pack-Years)</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator</td>
<td>84</td>
<td>Squamous Cell Carcinoma, Tx N2 M0 is the imputed stage based on reported treatment algorithm + mediastinal nodes</td>
</tr>
<tr>
<td>Comparator</td>
<td>18.75</td>
<td>T4 N3 M0, Extensive Small Cell with Malignant Pleural Effusion</td>
</tr>
<tr>
<td>Comparator</td>
<td>Unknown</td>
<td>Small Cell Lung Cancer, Limited stage</td>
</tr>
</tbody>
</table>
### Exubera Exposed: Smoking and Histology

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Smoking History (Pack-Years)</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exubera</td>
<td>Unknown</td>
<td>Tx Nx M1, Metastatic Bronchial Carcinoma</td>
</tr>
<tr>
<td>Exubera</td>
<td>Unknown</td>
<td>T1 N0 M0</td>
</tr>
<tr>
<td>Exubera</td>
<td>0</td>
<td>Primary Squamous Cell Lung Cancer</td>
</tr>
<tr>
<td>Exubera</td>
<td>10</td>
<td>Adenocarcinoma, T1 N2 M0</td>
</tr>
<tr>
<td>Exubera</td>
<td>92</td>
<td>T2 N2 M0</td>
</tr>
<tr>
<td>Exubera</td>
<td>88</td>
<td>Small Cell Lung Cancer</td>
</tr>
<tr>
<td>Exubera</td>
<td>22</td>
<td>Small Cell</td>
</tr>
<tr>
<td>Exubera</td>
<td>46</td>
<td>Lung Adenocarcinoma Metastatic</td>
</tr>
<tr>
<td>Exubera</td>
<td>72</td>
<td>IIIB</td>
</tr>
<tr>
<td>Exubera</td>
<td>84</td>
<td>Tx Nx Mx, Lung cancer</td>
</tr>
<tr>
<td>Exubera</td>
<td>35</td>
<td>Squamous Cell Carcinoma, T4 N2 M0</td>
</tr>
<tr>
<td>Exubera</td>
<td>0.25</td>
<td>Tx Nx Mx</td>
</tr>
</tbody>
</table>
Methods

- Hazard ratios derived from Cox proportional hazards model
- When number of events was small (i.e. <10 events in any treatment group), incidence density ratios derived from Poisson regression using exact method
- Anticipated approximately 80% power to detect 3-fold+ rate of primary lung cancer mortality
Primary Endpoint: Primary Lung Cancer Mortality

<table>
<thead>
<tr>
<th>Analysis</th>
<th>n</th>
<th>PY of follow-up</th>
<th>No. with event (%)</th>
<th>Rate per 1,000 PY</th>
<th>Incidence density ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-study a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exubera</td>
<td>3,875</td>
<td>11,191</td>
<td>1 (0.0%)</td>
<td>0.09</td>
<td>0.94 (0.01 – 73.46)</td>
</tr>
<tr>
<td>Comparator</td>
<td>3,564</td>
<td>10,473</td>
<td>1 (0.0%)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Continuous b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exubera</td>
<td>3,875</td>
<td>12,606</td>
<td>6 (0.2%)</td>
<td>0.48</td>
<td>2.81 (0.50 – 28.46)</td>
</tr>
<tr>
<td>Comparator</td>
<td>3,564</td>
<td>11,803</td>
<td>2 (0.1%)</td>
<td>0.17</td>
<td></td>
</tr>
</tbody>
</table>

- Excludes events in which death occurred after the original trial, but before the start of prospective FUSE follow-up
- Includes all events from the start of original trial to end of FUSE follow-up

Note: No change to rates in sensitivity analyses that add events adjudicated as “insufficient” or “unlikely”
### Secondary Endpoint: Primary Lung Cancer Mortality in Former Smokers

<table>
<thead>
<tr>
<th>Analysis</th>
<th>n</th>
<th>PY of follow-up</th>
<th>No. with event (%)</th>
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<th>Incidence density ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In-study</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exubera</td>
<td>1,681</td>
<td>4,761</td>
<td>1 (0.1%)</td>
<td>0.21</td>
<td>0.91 (0.01 – 71.80)</td>
</tr>
<tr>
<td>Comparator</td>
<td>1,533</td>
<td>4,355</td>
<td>1 (0.1%)</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td><strong>Continuous</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exubera</td>
<td>1,681</td>
<td>5,341</td>
<td>5 (0.3%)</td>
<td>0.94</td>
<td>2.29 (0.37 – 24.01)</td>
</tr>
<tr>
<td>Comparator</td>
<td>1,533</td>
<td>4,886</td>
<td>2 (0.1%)</td>
<td>0.41</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Excludes events in which death occurred after the original trial, but before the start of prospective FUSE follow-up

<sup>b</sup> Includes all events from the start of original trial to end of FUSE follow-up

Note: No change to rates in sensitivity analyses that add events adjudicated as “insufficient” or unlikely
Secondary Endpoint: Incident Primary Lung Cancer

<table>
<thead>
<tr>
<th>Analysis</th>
<th>n</th>
<th>PY of follow-up</th>
<th>No. with event (%)</th>
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<td>In-study a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exubera</td>
<td>3,875</td>
<td>11,178</td>
<td>4 (0.1%)</td>
<td>0.36</td>
<td>1.87 (0.27 – 20.69)</td>
</tr>
<tr>
<td>Comparator</td>
<td>3,564</td>
<td>10,458</td>
<td>2 (0.1%)</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Continuous b</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>Comparator</td>
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<td>10,468</td>
<td>3 (0.1%)</td>
<td>0.29</td>
<td></td>
</tr>
</tbody>
</table>

a Excludes events in which diagnosis occurred after the original trial, but before the start of prospective FUSE follow-up

b Includes all events from the start of original trial to end of FUSE follow-up
## Secondary Endpoint: All Cause Mortality

<table>
<thead>
<tr>
<th>Analysis</th>
<th>n</th>
<th>PY of follow-up</th>
<th>No. with event (%)</th>
<th>Rate per 1,000 PY</th>
<th>Incidence density ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In-study a</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exubera</td>
<td>3,875</td>
<td>11,191</td>
<td>38 (1.0%)</td>
<td>3.4</td>
<td>0.83 (0.53 – 1.28)</td>
</tr>
<tr>
<td>Comparator</td>
<td>3,564</td>
<td>10,473</td>
<td>42 (1.2%)</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td><strong>Continuous b</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
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<tr>
<td>Comparator</td>
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<td>11,803</td>
<td>87 (2.4%)</td>
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<td></td>
</tr>
</tbody>
</table>


*a* Excludes events in which death occurred after the original trial, but before the start of prospective FUSE follow-up

*b* Includes all events from the start of original trial to end of FUSE follow-up