Do We Really Need Ultra-Fast Acting Insulins?

Bruce W. Bode, MD, FACE
Atlanta Diabetes Associates
Atlanta, Georgia
Disclosures

• Consultant: Novo Nordisk, MannKind, Medtronic, Sanofi
• Speaker’s Bureau: Lilly, Novo Nordisk, Medtronic, Sanofi
• Grant and Research Support: Biodil, Lilly, MannKind, Medtronic, Sanofi
Do we need faster acting insulins than we have now?
**Better glycemic control**

- Faster, higher insulin concentrations and peak exposure (i.e., fast in) results in early glucose lowering effects and reduced post-meal hyperglycemia, which may lead to better A1C control

**Less hypoglycemia**

- Reduced late post-meal exposure (i.e., fast out) may result in fewer hypoglycemic events

**Less weight gain**

- Fewer hypoglycemic events and lower insulin doses could result in less self-medicating snacking
2005 Blinded CGM Study

- 101 people with diabetes were placed on a blinded CGM and were told to do 10 finger stick blood tests a day; they averaged 9 tests per day
  - < 30% of the day spent in normal glucose range (90-130 mg/dL)
  - 30% of day spent in high glucose range (>180 mg/dL)
  - two hours a day in hypoglycemic range (<60 mg/dL)
- New technology is needed to help patients get to goal

JDRF Study A1C Change in ≥ 7.0% Cohort with CGM Use ≥ 6 days/week in Month 12

Change in A1C (%)

Age ≥ 25
n = 34

Age 15-24
n = 6

Age 8-14
n = 15

0-26wks

0-52wks

JDRF CGM Study Group Diabetes Care 2009; 32:2047-2049
JDRF A1C < 7% Cohort: Change in the frequency of sensor glucose levels < 70 mg/dL

Median minutes/day

<table>
<thead>
<tr>
<th></th>
<th>RT-CGM</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>91</td>
<td>96</td>
</tr>
<tr>
<td>26 Wks</td>
<td>54</td>
<td>91</td>
</tr>
</tbody>
</table>

p = 0.002
p = 0.16
p = 0.43

JDRF CGM Study Group *Diabetes Care* 2009;32:1378-1383
Severe Hypoglycemia and A1C:
DCCT\textsuperscript{15} (1993), JDRF\textsuperscript{2} (2008), and STAR 3\textsuperscript{16} (2010) Studies

DCCT (intensive therapy):
62 per 100 pt-yrs,
A1C (6.5 yr): 9.0% → 7.2%

JDRF CGM (adults):
43.4 per 100 pt-yrs;
A1C (6 mo): 7.5% → 7.1%

Adapted from Figure 5B of: DCCT. *N Engl J Med.* 1993;329:977-986.
Severe Hypoglycemia and A1C: DCCT\textsuperscript{15} (1993), JDRF\textsuperscript{2} (2008), and STAR 3\textsuperscript{16} (2010) Studies

Adapted from Figure 5B of: DCCT. \textit{N Engl J Med.} 1993;329:977-986.


- **DCCT (intensive therapy):** 62 per 100 pt-yrs; A1C (6.5 yr): 9.0% $\rightarrow$ 7.2%

- **JDRF CGM (adults):** 20.0 per 100 pt-yrs; A1C (6 mo): 7.5% $\rightarrow$ 7.1%

- **STAR 3 MDI (all ages):** 13.5 per 100 pt-yrs; A1C (1 yr): 8.3% $\rightarrow$ 8.1%

- **STAR 3 SAP (all ages):** 13.3 per 100 pt-yrs; A1C (1 yr): 8.3% $\rightarrow$ 7.5%
Now on CGM and Pump
November 1 - 8, 2010
Example of Late Post-Meal Hypoglycemia

Breakfast (7) 6:00 AM - 10:00 AM
Avg Carbs: 46g
Avg Insulin: 3.8U (13g/U)

Lunch (8) 11:00 AM - 3:00 PM
Avg Carbs: 63g
Avg Insulin: 4.3U (12g/U)

Dinner (6) 4:00 PM - 10:00 PM
Avg Carbs: 47g
Avg Insulin: 3.7U (13g/U)
Even Current Insulins Work too Slowly and Last too Long for External Closed-Loop Systems
Why Do We Need Faster Insulins for Fully Automated External CL Systems?

- **Unlike the β-cell:** insulin is injected under the skin, not secreted into the portal vein.
- **Unlike Open-Loop Insulin Delivery:**
  - Meal-stimulated insulin delivery is not initiated until after food is ingested and interstitial glucose concentrations begin to rise
  - The meal bolus is stretched over >2 hours rather than being administered over a few minutes
Metabolic Consequences

- Exaggerated post-meal excursions, especially after breakfast
  
  &

- Vulnerability to late post-meal hypoglycemia, especially after dinner.
Artificial External Insulin Pump

Steil G et al, Diabetes 53:A3, 2004
Closed-loop vs. hybrid control

![Graph showing glucose levels over time for closed-loop and hybrid closed-loop control systems. The graph includes setpoints, meals, and nocturnal peak PP values for both control methods.]

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Nocturnal</th>
<th>Peak PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Closed Loop</td>
<td>156 (149-163)</td>
<td>109 (87-131)</td>
<td>232 (208-256)</td>
</tr>
<tr>
<td>Hybrid Closed Loop</td>
<td>135 (129-141)</td>
<td>114 (98-131)</td>
<td>191 (168-215)</td>
</tr>
</tbody>
</table>

Weinzimer SA, et al., Diabetes Care 2008; 31: 934-939
Approaches to Accelerate the Time Action Profiles of Fast-Acting Insulins

• Faster insulins
  – Linjeta-Biodel
  – Novo Nordisk

• Warming the infusion site
  – InsuLine

• Co-formulate with hyaluronidase
  – Halozyme

• Alternate Routes
  – Intra-dermal: Micro-needle infusion sets-BD
  – Inhaled Insulin: Afrezza-MannKind
  – Intra-peritoneal: DiaPort-Roche
Linjeta™ (AKA ViaJet): Mechanism of Ultra-Rapid Absorption

EDTA chelates zinc, de-stabilizing the insulin hexamer

Citric acid prevents reaggregation and facilitates absorption
Linjeta Preparations

- VJ25 formulation: pH 4, 25 U/ml
  - Used in Phase 3 studies

- VJ7 formulation: neutral pH, 100 U/ml
Characterization of PK and PD of VJ7

• Study aims:
  – Comparison of pharmacokinetic and pharmacodynamic characteristics of VJ7 and insulin lispro

• Study drug dose = 12 U
Linjeta vs. Lispro PD Profiles

The graph shows the glucose infusion rates (GIR) in mg/kg/min over time in minutes, comparing Linjeta and Lispro. The red line represents VIAject 7, and the green line represents Lispro. The inset graph provides a closer view of the initial response during the first 60 minutes.
Linjeta™: Current Status

- Phase 3 Trial failed to meet criteria for non-inferiority versus comparator
- Increased incidence of complaints of “stinging” or “burning” following subcutaneous injections.
- BIOD-105 and BIOD-107 are revised formulations designed to reduce injection site discomfort are being tested
The InsuPatch™ applies controlled heat around the insulin infusion site.
Effect of the InsuPatch on the time action profile of a 0.2U/kg bolus of aspart insulin
Effect of InsuPatch on $T_{\text{early} 50\% \text{ GIR}}$

- **No IP**
  $T_{\text{early} 50\% \text{ GIR}} = 58 \pm 20\text{ min}$

- **With IP**
  $T_{\text{early} 50\% \text{ GIR}} = 39 \pm 13\text{ min}$

$p = 0.02$
Effect of InsuPatch on $T_{\text{max}}$ GIR

Unanswered Questions:
- Optimal temperature
- Timing and duration of warming period
- Effect of infusion set age

$p=0.0001$

Time (min)

No IP

126 ± 28min

with IP

90 ± 21min
rHuPH20 * Is the First and Only Recombinant Human Hyaluronidase Enzyme

- Hyaluronidase acts *transiently* and *locally* to temporarily disrupt the intestinal matrix, allowing rapid spread of injected materials.
- There is no systemic exposure to rHuPH20.

*Halozyme Therapeutics*
Enhancement of Drug Delivery with Recombinant Human Hyaluronidase (rHuPH20)

- Recombinant Human Hyaluronidase (rHuPH20) increases the absorption and dispersion of injected drugs
The three marketed rapid acting analog insulins have similar time exposure profiles.

Morrow et al. ADA oral presentation 2010
PK Results

- Faster in after 1 hour With rHuPH20 $P < 0.0001$
- Faster Out after 2 hours (all $P < 0.0001$)

Morrow et al. ADA oral presentation 2010
rHuPH20 PD Results

Morrow et al. ADA oral presentation 2010
rHuPH20 PD Results

Morrow et al. ADA oral presentation 2010
Effect of Infusion Site Age on Insulin PD/PK: Day 1 vs Day 4

Pharmacodynamics

Pharmacokinetics

All Subjects: 12 hrs vs. 84 hrs of site insertion

GIR (mg/kg/min)

0 25 50 75 100 125 150 175 200 225 250 275 300

0 1 2 3 4

12 hrs
84 hrs

TIME (MIN)

All subjects - 12 vs. 84 hrs of site insertion

Insulin levels (uU/mL)

0 30 60 90 120 150 180 210 240 270 300

0 10 20 30 40 50 60 70 80 90 100 110 120

12 hrs
84 hrs

TIME (MIN)
rHuPH20 Reduces effect of infusion set age on insulin absorption

1st Clamp performed at 12 hours after infusion set change
2nd Clamp performed at 60 hours

Morrow et al., ADA Poster 27-LB (2011)
Comparable Glycemic Profiles by SMBG at the End of Each Treatment Period

8-point Glucose Profile

Buse, Garg and Skyler, ADA, 2011
## Safety Evaluation: Adverse Events

~9,500 injections of each study drug

Buse, Garg and Skyler, ADA, 2011

### Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>RHI+rHuPH20</th>
<th>Lispro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any Treatment-Emergent Adverse Event</td>
<td>24 of 45 (53%)</td>
<td>24 of 43 (56%)</td>
</tr>
<tr>
<td>Study Drug related</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Maximum severity: Mild</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Maximum severity: Moderate</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Maximum severity: Severe</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Patient discontinued due to Adverse Event (not study drug related)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Patients with Serious Adverse Events (none reported as related)</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

### Local Tolerability

<table>
<thead>
<tr>
<th>Tolerability</th>
<th>RHI+rHuPH20</th>
<th>Lispro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site bruise/hemorrhage</td>
<td>3 episodes in 2 patients</td>
<td>1 episode in the same patient reporting 2 episodes for RHI+rHuPH20</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Pump Study Design with PH 20

- Study Population: 18 T1DM pumpers
- Data from 1st 13 completers available
- Procedure:
  - Admit to clinical research center 17:00 Hrs Day 1
    - New infusion set at admission
    - Adjust basal to target FBS = 110 mg/dL (adjust with IV insulin between 05:00 and 06:30 as needed)
  - Perform euglycemic glucose clamp at 07:00 Hrs on Day 2
    - Administer bolus (0.15 U/kg) of either Aspart-PH20 or Aspart alone
  - Assess Safety and Tolerability for 72 hours CSII
  - Readmit to CRC 5-14 days later for repeat procedure

Muchmore et al, AACE Late Breaking Oral 2011
Accelerated Insulin Absorption with PH20

Similar PK results in pump study in T1DM as compared to previous MDI study in healthy volunteers

T1DM CSII, 0.15 U/kg

Volunteers MDI, 0.15 U/kg

- Faster In (pump study):
  - With PH20 insulin aspart exposure in the 1st hour was 164% of control ($P < 0.0001$)

- Faster Out (pump study):
  - Insulin aspart exposure after 2 hours decreased by 42% for PH20 coinjection ($P = 0.0003$)

Muchmore et al, AACE Late Breaking Oral 2011
Accelerated Insulin Action with PH20

T1DM CSII, 0.15 U/kg

Volunteers MDII, 0.15 U/kg

- Faster In:
  - With PH20 insulin aspart action in the first 2 hours was 120% of control ($P = 0.047$)

- Faster Out:
  - Insulin aspart exposure after 4 hours decreased by 37% for PH20 coinjection ($P = 0.008$)
Aspart-PH20 Well Tolerated by CSII

<table>
<thead>
<tr>
<th>Category</th>
<th>Aspart-PH20 (N=13)</th>
<th>Aspart alone (N=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects w/ an AE</td>
<td>7 (54%)</td>
<td>9 (69%)</td>
</tr>
<tr>
<td>Procedure Related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(IV Infusion Site Reactions, etc.)</td>
<td>5 (38%)</td>
<td>6 (46%)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>0 (0%)</td>
<td>4 (31%)</td>
</tr>
<tr>
<td>(Headache, Dizziness)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Nausea, Abdominal Pain, Diarrhea)</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>CSII Site Reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Erythema, Pruritus)</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Neck Pain)</td>
<td>0 (0%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Respiratory/Thoracic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Cough, Nasal congestion)</td>
<td>0 (0%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Ecchymosis, not at CSII site)</td>
<td>1 (8%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

- Except for 1 moderate headache (Aspart alone), all AEs were mild.
Summary and Conclusions with Hyaluronidase

- Addition of recombinant human hyaluronidase to rapid acting analog insulin confers an “ultrafast” profile
- This profile has been shown to improve glycemic control in test meal settings
- Treatment studies are underway to assess clinically relevant outcomes
  - A1C
  - Glycemic excursions
  - Hypoglycemia rates
  - Safety and Tolerability
- The pump study results show that the PK and PD findings previously demonstrated with SC injection are also observed with CSII
- Clinical studies of pump use in the take-home treatment setting are planned
Alternate Routes of Insulin Delivery

- Intra-dermal: Micro-needle infusion sets-BD
- Inhaled Insulin: Afrezza-MannKind
- Intra-peritoneal: DiaPort-Roche
BD’s stainless steel micro-cannula provide reliable ID delivery, without breakage.

1mm, 34 G Steel Microneedle Cannula

Single Microneedle cannula in swine dermis

hair follicles

microneedle
Insulin levels after ID & SC dosing of insulin lispro

Afrezza – MannKind Corp.  
*An inhaled ultra-rapid acting insulin*

Technosphere Insulin given by inhalation

- Very early peak and short duration
- Questions of pulmonary safety and other issues related to new device and pulmonary route of insulin delivery

MKC-TI-117: More Appropriately Timed Prandial Insulin Titration

**117: 2-Hr PPG**

- **GIR** = glucose infusion rate; **RAA** = rapid-acting insulin analogue

**Pivotals: Pre-next meal**

![Graph showing corrected GIR (mg/kg-min) over time (min) for 1 x 30 U of TI and 10 U of sc RAA.](image)
MKC-TI-117 Study Design

Visit 1: Screening (2 weeks prior to beginning of Run-in Phase)

Visit 2, 3, 4: Run-in Phase Transfer to Lantus® (includes 3 telephone contacts)

Visit 5: Randomization (3 weeks after the start of the Run-in Phase, V2)

Visits 5A-14: Treatment Phase (16 weeks from Randomization, V5; includes 9 telephone contacts)

Visit 15: Follow-up (4 weeks after end of Treatment Phase, V14)

Note: At trial completion, subjects may be invited to participate in a clinical trial extension
## Baseline Demographics
### Safety Population

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>Category/Statistic</th>
<th>Afreza (n = 65)</th>
<th>Humalog (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td>Male</td>
<td>40 (61.5)</td>
<td>33 (50.8)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>25 (38.5)</td>
<td>32 (49.2)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>Caucasian</td>
<td>56 (86.2)</td>
<td>59 (90.8)</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>3 (4.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>5 (7.7)</td>
<td>5 (7.7)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>1 (1.5)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>N</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Mean (± SD)</td>
<td>38.6 (11.82)</td>
<td>39.4 (11.46)</td>
</tr>
<tr>
<td><strong>Age group (y)</strong></td>
<td>18-30</td>
<td>20 (30.8)</td>
<td>18 (27.7)</td>
</tr>
<tr>
<td></td>
<td>31-49</td>
<td>31 (47.7)</td>
<td>33 (50.8)</td>
</tr>
<tr>
<td></td>
<td>50-64</td>
<td>13 (20.0)</td>
<td>13 (20.0)</td>
</tr>
<tr>
<td></td>
<td>65+</td>
<td>1 (1.5)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td><strong>Duration of diabetes (y)</strong></td>
<td>N</td>
<td>61</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Mean (± SD)</td>
<td>16.8 (11.54)</td>
<td>17.6 (10.37)</td>
</tr>
</tbody>
</table>
## Baseline Characteristics
### Safety Population

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>Category/Statistic</th>
<th>Afrezza (n = 65)</th>
<th>Humalog (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>N</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>74.49 (13.270)</td>
<td>74.18 (13.894)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>N</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>172.22 (9.238)</td>
<td>169.61 (9.807)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>N</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>25.07 (3.744)</td>
<td>25.63 (3.141)</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>N</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>7.76 (0.550)</td>
<td>7.62 (0.602)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>N</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>86.26 (10.445)</td>
<td>87.31 (10.669)</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>N</td>
<td>64</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>178.06 (76.916)</td>
<td>176.20 (67.268)</td>
</tr>
</tbody>
</table>
### Afrezza Is Noninferior to Humalog in A1c Reduction: ITT with LOCF

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Statistics</th>
<th>Afrezza (n = 61)</th>
<th>Humalog (n = 65)</th>
<th>Afrezza – Humalog</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>N</td>
<td>61</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Mean (± SD)</td>
<td>7.75 (0.553)</td>
<td>7.62 (0.602)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Week 16</strong></td>
<td>N</td>
<td>61</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Mean (± SD)</td>
<td>7.69 (0.800)</td>
<td>7.61 (0.720)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Change from Baseline to Week 16</strong></td>
<td>N</td>
<td>61</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>LS Mean (± SE)</td>
<td>-0.09 (0.079)</td>
<td>-0.05 (0.076)</td>
<td>-0.04 (0.108)</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>(-0.24,0.07)</td>
<td>(-0.20,0.10)</td>
<td>(-0.25,0.18)</td>
<td></td>
</tr>
</tbody>
</table>

ANCOVA models include baseline HbA1c value, country, and treatment as the covariates.
A1c Responder Rates: Significantly More Patients ≤ 6.5%

<table>
<thead>
<tr>
<th>Responder Category</th>
<th>Afrezza (n = 52)</th>
<th>Humalog (n = 58)</th>
<th>Afrezza versus Humalog$^a$</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c ≤ 6.5 %</td>
<td>5 (9.62)</td>
<td>2 (3.45)</td>
<td></td>
<td>13.825</td>
<td>(1.334, 143.3)</td>
<td>0.0277</td>
</tr>
<tr>
<td>HbA1c ≤ 7.0 %</td>
<td>9 (17.31)</td>
<td>14 (24.14)</td>
<td></td>
<td>1.121</td>
<td>(0.378, 3.324)</td>
<td>0.8367</td>
</tr>
<tr>
<td>HbA1c ≤ 7.0 % without experiencing severe hypoglycemia</td>
<td>2 (3.85)</td>
<td>5 (8.62)</td>
<td></td>
<td>0.766</td>
<td>(0.125, 4.691)</td>
<td>0.7736</td>
</tr>
</tbody>
</table>

The odds ratio, 95% CI of the odds ratio, and p values were derived from logistic regression analysis with the treatment, country, and baseline HbA1c in the model. Percentages were based on the number of subjects who had valid measurements at specific visits.
Better Improvements in FBG with Afrezza with Same Lantus Dose

FBG (mg/dL) Change from Baseline to Week 16

-60 -50 -40 -30 -20 -10 0

Afrezza (n = 52)
HUMALOG (n = 58)
Afrezza – HUMALOG
Afrezza Improves Postmeal Glucose Control in Type 1 Diabetes

Mean Postprandial Glucose Levels: Meal Challenge Results Week 16 (MKC-TI-117)

- Afrezza (n1) vs. Humalog (n2)
No Difference in 7-Point BG Levels Except @ Pre Dinner: Week 16
Effective Control with Lower Rate of Hypoglycemia than Injected Insulins in Type 1 Diabetes

In Study MKC-TI-117, Afrezza had significantly lower rates of Total and Mild/Moderate hypoglycemia in patients with type 1 diabetes using Afrezza when compared to subcutaneous insulin analog Humalog.

<table>
<thead>
<tr>
<th>Hypoglycemia</th>
<th>Afrezza n = 65</th>
<th>Humalog n = 65</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild/Moderate</td>
<td>5.97</td>
<td>8.01</td>
<td>0.0269</td>
</tr>
<tr>
<td>Severe</td>
<td>0.19</td>
<td>0.18</td>
<td>0.9070</td>
</tr>
<tr>
<td>Total</td>
<td>6.17</td>
<td>8.19</td>
<td>0.0345</td>
</tr>
</tbody>
</table>
No Difference in Weight Over 16 Weeks
DiaPort: Intraperitoneal Insulin Infusion via a Percutaneous Port System

- Preliminary efficacy studies:
  - less severe hypoglycemia vs CSII
  - mean HbA1c were not different
- Safety Concerns: local site infection or inflammation
  0.47 event per pt year and catheter obstruction 0.14 events per pt year
Each of these approaches looks promising based on PK and PD studies. Each has its own issues regarding safety and/or practicality. None have been shown to have enhanced clinical efficacy for open-loop therapy except for MannKind insulin. None have been tested in closed-loop systems.
For a copy of these slides:

Email me at bbode001@aol.com

Thank you for your attention