New Basal and Prandial Insulins

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New Subcutaneous Insulins and Those in Development

- Basal (Ultra-long-acting)
  - Degludec
    - Approved in the European Union, Mexico, and Japan
  - LY2605541

- Bolus (Ultra-rapid-acting)
  - Bio-238 and -250
  - Analogs plus Hyaluronidase
  - FIAsp
Insulin Degludec

- A new, ultra-long-acting basal insulin
- Forms soluble multihexamers after SQ injection
- Gradual release of insulin monomers into the circulation
- 25 hour half-life
- > 42 hour duration of action
- Similar HbA1c lowering when dosed either at a fixed time or at intervals of 8-40 hours*

* Meneghini L et al. Diabetes care 2013 Apr;36(4):858-64
Structure of Insulin Degludec

A chain

B chain

DesB30

L-γ-Glu

Glutamic acid 'spacer'

C16 Fatty di-acid

Hexadecanedioic acid
Mean 24-hour Insulin Concentrations in 33 Subjects with Type 1 Diabetes
Mean HbA1c (%) by Treatment Week – Degludec T1DM Trials

- Trial 3583
  T1DM BB 12m

- Trial 3585
  T1DM BB 6m

- Trial 3770
  T1DM BB 6m Flex
Summary of Insulin Degludec vs Glargine Effects in Type 1 Patients over 104 Weeks

- Nocturnal hypoglycemia reduced by 25%
- Similar HbA1c lowering
- Similar fasting and 9-point self-measured plasma glucose
- At study end lower insulin requirements
  - 12% less basal insulin
  - 9% less total daily insulin
  - 6% less bolus insulin

Bode BW et al. Diabetic Medicine Published online: 17 JUN 2013
Glycemic Control in Insulin-naive Patients with Type 2 Diabetes: Insulin Degludec versus Insulin Glargine

Overall Confirmed Hypoglycemia in Insulin-naive Patients with Type 2 Diabetes: Insulin Degludec versus Insulin Glargine

Nocturnal Confirmed Hypoglycemia in Insulin-naive Patients with Type 2 Diabetes: Insulin Degludec versus Insulin Glargine

Zinman B et. al; Diabetes Care. 2012 Dec;35(12):2464-71
Nocturnal Confirmed Hypoglycemia – Degludec Phase 3 Trials with Insulin Comparators

- **T2DM Basal-only Therapy**
  - Trial 3579 vs lGlar
  - Trial 3672 vs lGlar
  - Trial 3586 vs lGlar
  - Trial 3668 Flex vs lGlar

- **T2DM Basal-bolus Therapy**
  - Trial 3582 vs lGlar

- **T1DM Basal-bolus Therapy**
  - Trial 3583 vs lGlar
  - Trial 3585 vs lDet
  - Trial 3770 Flex vs lGlar

Estimates and 95% Confidence Intervals:

- **3579 vs lGlar**
  - Estimate: 0.64* [0.42; 0.98]

- **3672 vs lGlar**
  - Estimate: 0.64 [0.30; 1.37]

- **3586 vs lGlar**
  - Estimate: 0.62 [0.38; 1.04]

- **3668 Flex vs lGlar**
  - Estimate: 0.77 [0.44; 1.35]

- **3582 vs lGlar**
  - Estimate: 0.75* [0.58; 0.99]

- **3583 vs lGlar**
  - Estimate: 0.75* [0.59; 0.96]

- **3585 vs lDet**
  - Estimate: 0.66* [0.49; 0.88]

- **3770 Flex vs lGlar**
  - Estimate: 0.60* [0.44; 0.82]
In November 2012, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted 8 to 4 in favor of licensing degludec but stipulated that the company conduct a rigorous postmarketing study to evaluate cardiovascular safety.

No clinically relevant differences between IDeg and comparator in other cardiovascular assessments, namely blood pressure, pulse, lipids, or ECG.

In Feb, 2013 degludec FDA submission not approved.

FDA requested additional CV data from a dedicated CV outcomes trial.

Cardiovascular outcomes trials in US planned.
Basal Insulin LY2605541

- Insulin lispro modified with a 20-kDa polyethylene glycol (PEG) moiety
- Larger size delays absorption and slows clearance
- Preferential hepatic uptake and greater lipolysis observed in a dog model
  - Hypothesized potential for less lipogenesis, increased lipid oxidation and weight loss

Rosenstock J et al. Poster #1026-P 2012 Scientific Sessions of the ADA
Glycemic Control after 8 weeks of LY2605541 Compared with Once Daily Glargine in Type 1 Diabetes

LEFT:
- □ Baseline for both
- ■ insulin GL
- □ LY2605541

RIGHT:
- △ Baseline for both
- ○ insulin GL
- □ LY2605541
  - * $P < 0.01$

N=137

Rosenstock J. et al, Diabetes Care 2013;36(3): 522-528
### Basal Insulin LY2605541 compared to Insulin Glargine in Type 1 Diabetes


<table>
<thead>
<tr>
<th>Hypoglycemia Type</th>
<th>Baseline</th>
<th>LY</th>
<th>GL</th>
<th>Relative Risk LY/GL (90% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Hypoglycemia Rates</td>
<td>4.05±4.09</td>
<td>9.18±7.91</td>
<td>8.11±7.02</td>
<td>1.10 (1.01–1.21)</td>
<td>.074</td>
</tr>
<tr>
<td>Nocturnal Hypoglycemia Rates</td>
<td>0.50±1.20</td>
<td>0.92±1.22</td>
<td>1.24±1.47</td>
<td>0.73 (0.60–0.88)</td>
<td>.007</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- BG = blood glucose
- CI = confidence interval
- GL = insulin glargine
- LY = LY2605541
- SD = standard deviation

*Values are mean±SD unless otherwise indicated.

*Signs/symptoms of hypoglycemia and/or a measured BG concentration of ≤70 mg/dL.

*Hypoglycemia occurring between bedtime and waking.

**Figure 6. Hypoglycemia Rate per Time of Day**
Total and Nocturnal Hypoglycemia: LY2605541 Compared with Glargine for 12 Weeks in Patients with Type 2 Diabetes

Bergenstal R M et al. Diabetes Care 2012;35:2140-2147
Mean Change in Body Weight with LY2605541 versus Insulin Glargine for 12 weeks in Type 2 Diabetes

Bergenstal R M et al. Diabetes Care 2012;35:2140-2147
Five ongoing Phase 3 IMAGINE trials in patients with type 1 and type 2 diabetes, when compared with currently available basal insulin analogs.
Concentrated Insulins on the Horizon

- Degludec U200
  - Contains 2 units in each 0.01 ml (or 1 unit mark on an insulin syringe)

- Glargine U300
  - Contains 3 units in each 0.01 ml (or 1 unit mark on an insulin syringe)
## U300 vs U100 Glargine in Type 2 Diabetes (EDITION I)

<table>
<thead>
<tr>
<th></th>
<th>Glargine U300</th>
<th>Glargine U100</th>
<th>RR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔA1C at 6 months</td>
<td>-0.83%</td>
<td>-0.83%</td>
<td></td>
<td>-0.11-0.11</td>
</tr>
<tr>
<td>Any hypoglycemia</td>
<td>83.4%</td>
<td>88.6%</td>
<td>0.94</td>
<td>0.89-0.99</td>
</tr>
<tr>
<td>Any nocturnal hypoglycemia</td>
<td>45.3%</td>
<td>59.7%</td>
<td>0.76</td>
<td>0.66-0.87</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>5.0%</td>
<td>5.7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Riddle MC et al. ADA June 21–25 2013; Chicago, IL, USA (Abstract 43-LB)*
Increasing Absorption of Lispro Formulations: Biodel Approach

Krasner A, et al. 73rd Scientific Sessions Late Breaking Poster #44, 2013
Formulations BIOD-238 and BIOD-250 in Type 1 Diabetes

Krasner A, et al. 73rd Scientific Sessions Late Breaking Poster #44, 2013
Lispro Formulations BIOD-238 and BIOD-250 in Type 1 Diabetes

Krasner A, et al. 73rd Scientific Sessions Late Breaking Poster #44, 2013
Rapid-acting Insulin Analogs in combination with Hyaluronidase

- Hyaluronidases increase the dispersion and absorption of subcutaneously administered drugs
- Accelerates the absorption and action of co-injected regular human insulin and the rapid-acting insulin analog lispro
- No increased injection site pain, erythema or induration, and no other increased adverse effects

Hompesch M et al. Diabetes Care 2011 Mar;34(3):666-8
Accelerated Insulin Pharmacokinetics and Improved Postprandial Glycemic Control in Patients With Type 1 Diabetes After Coadministration of Prandial Insulins With Hyaluronidase

Cumulative exposure and action of insulins glulisine, lispro, and aspart after subcutaneous injection with and without Hyaluronidase (rHuPH20)

- Time to 50% exposure decreased from about 2 hours for the analogs alone to 75 min when injected with rHuPH20
- Early (first-hour) exposure was doubled with rHuPH20 and halved beyond 2 h (all \( P < 0.0001 \))

Aspart insulin with excipients

- Nicotinamide
  - Postulated to help speed absorption
- Arginine
  - Stabilizes insulin
Future for FIAsp

- Large Phase 3 clinical trials planned to start in 2013 and 2014 in patients with type 1 and type 2 diabetes
**Alternative Methods of Insulin Delivery**

- Transdermal (613 Citations)
- Nasal Insulin (643 Citations)
- Sublingual Insulin (75 Citations)
- Buccal Insulin (128 Citations)
- Oral Insulin (23, 557 Citations)
- Inhaled Insulin (963 Citations)
- Intraperitoneal Insulin (2511 Citations)
Oral-lyn formulation

Human rDNA insulin (regular), dissolved in a buffer at neutral pH, identical to insulin injection USP; aerosolized, aqueous insulin formulation

With addition of: Absorption enhancers, Stabilizers, Non-CFC propellant (HFA-134a); approved by FDA and GRAS listed

RapidMist™ Device
Current Status?

• Efficacy and Safety provided in review for US FDA in December 2011. Approval Denied

• Medical acceptability and commercial success requires formulation modification to achieve ideal insulin dose with only 2 to 4 sprays.

• Effective dosing will require device (valve and canister) modification.

• Completing definitive study in India for approval there.
Oral Insulin Delivery

- **Biocon IN-105**
  
  "Biocon announces that it has entered into an option agreement with Bristol-Myers Squibb for Biocon’s IN-105, an Oral insulin candidate”  
  
  November 16, 2012

- **Oramed ORMD 0801**
  
  “Oramed Receives Clearance to Initiate Oral Insulin Trials in the U.S.”  
  
  May 17, 2013

- **Capsulin**
  
  Preparing for Phase IIb Under IND
  
  Development, marketing and distribution license to leading oral diabetes company in India for India

- **NovoNordisk**
  
  “Novo Nordisk’s Oral Insulin Successfully Completes Early Study”  
  
  March 20, 2013
  
  - NNC0148-0000-0362: Phase 1 (Completed)
  - NNC0148-0000-0287: Phase 1 (Recruiting)
  - NNC0123-0000-0338: Phase 1 (Completed)
  - NNC0123-0000-0338 in Subjects With Type 2 Diabetes
Technosphere® Insulin

Recombinant Human Insulin Adsorbed on to fumaryl diketopiperazine

pH < 6
as TI Inhalation Powder

pH > 6 in the lungs
Technosphere® Insulin

MKC-TI-176: Dose/absorption Proportionality

New Insulins: Are They Better?

- **Ultra-long-acting Basal insulins**
  - Evidence of reduced nocturnal hypoglycemia and decreased weight gain at comparable A1c lowering when compared with glargine
  - Larger phase 3 clinical trials needed to confirm hepatic and cardiovascular safety

- **Ultra-rapid-acting Bolus insulins**
  - Evidence for reduced postprandial hyperglycemia, and potential for more convenient dosing
  - Larger phase 2 + 3 trials underway to confirm efficacy, site tolerability and cardiovascular safety

- **Non-injectible insulins**
  - Pulmonary: Affinity 1 and 2 Trials to report in August with FDA submission in September or October
  - Oral: Phase 1 and 2 studies planned or ongoing