Insuline basali a confronto

Edoardo Guastamacchia

Università degli Studi di Bari “A. Moro”
The Importance of Tight Glycemic Control—UKPDS

Intensive glycemic control was associated with reductions in the risk for T2DM-related complications.*

*Risk reduction for 0.9% decrease in HbA1c; HbA1c 7% in intensive control group vs 7.9% in conventional group

Despite Advances in Treatment, a Significant Proportion of Patients With T2DM Still Fail to Reach Target HbA1c Levels

GUIDANCE Study; 7,597 T2DM Patients
Gap exists between checking HbA1c and achieving target HbA1c <7%

L’insulina rappresenta il trattamento più efficace nel ridurre l’HbA1C
Effetti positivi dell’insulinizzazione tempestiva

**Effetti diretti sulla glicemia**

- **Effetti a breve termine**
  - Rapida riduzione della glucotossicità
  - Miglioramento della funzionalità beta-cellulare
  - Protezione beta-cellulare e preservazione della secrezione insulinica

- **Effetti a lungo termine**
  - Prolungato controllo glicemico
  - Remissione

**Effetti indiretti sulla glicemia**

- Migliora la sensitività all’insulina (riduce la resistenza insulinica)
- Riduce fattori di rischio cardiovascolari
- Riduce i marker dell’infiammazione e il profilo lipidico aterosclerotico

*omn G et al. Horm Metab Res 2009;41:116-122*
Insulin is Underused

Insulin treatment can be initiated at any point in the course of T2D. Early initiation of insulin and improved glycaemic control may help to preserve β-cell function, promote vascular endothelial health and minimise the risk of complications, although long-term clinical data are needed to clarify these potential associations. Nevertheless, rather than occurring early in treatment progression, initiation and intensification of insulin regimens in practice is often delayed in the face of poor or worsening glycaemic control.
Durata del diabete

INSULINA

Intervento!
Insulin is Underused

Insulin treatment can be initiated at any point in the course of T2D. Early initiation of insulin and improved glycaemic control may help to preserve β-cell function, promote vascular endothelial health and minimise the risk of complications, although long-term clinical data are needed to clarify these potential associations. Nevertheless, rather than occurring early in treatment progression, initiation and intensification of insulin regimens in practice is often delayed in the face of poor or worsening glycaemic control. 

Citation: European Endocrinology, 2014;10(2):124–30
Initiation of Insulin Therapy Is Often Delayed

- SOLVE™ study found that pre-insulin mean HbA1c ranged from 8.3% to 9.8%
- Insulin was started later than guidelines recommend in all countries
- Lack of support for patients and physicians is a key problem outside clinical trial settings
- Other reasons for delays include fear of hypoglycemia, weight gain, and needles

Patient Barriers to Earlier Glycemic Control

- Fear of hypoglycemia and weight gain
- Sense of personal failure and loss of control
- Perception that insulin is not effective or is actually harmful
- Lack of confidence in ability to manage insulin therapy
- Concerns of family, work, and friends

Patient barriers are often similar to those of physicians

Barriers to Insulin May Be More Prevalent Among Physicians Than Patients

Comparison of barriers cited by physicians and patients not treated with insulin

- Case-control study found that physicians' misconceptions of patient's fears contributed to existing barriers
- Important for physicians to discuss insulin with patients early in the course of T2DM
- Reassure patients that starting insulin does not mean they have failed

### Tabella 1

**Incidenza delle ipoglicemie sintomatiche nel DM1 e nel DM2: risultati dello studio HYPOS (numero di episodi per persona/anno).**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sintomatiche totali</td>
<td>5,57</td>
<td>9,5</td>
<td>10,76</td>
<td>14,55</td>
<td>18,36</td>
<td>53,3</td>
</tr>
<tr>
<td>Sintomatiche diurne</td>
<td>3,58</td>
<td>8,05</td>
<td>9,0</td>
<td>10,97</td>
<td>14,41</td>
<td>33,9</td>
</tr>
<tr>
<td>Sintomatiche notturne</td>
<td>1,16</td>
<td>1,06</td>
<td>1,9</td>
<td>3,75</td>
<td>4,42</td>
<td>13,5</td>
</tr>
</tbody>
</table>
Hypoglycemia Increases the Risk for CV Events and All-Cause Mortality

Retrospective cohort study of insulin-treated patients ≥30 years (10,422 with T2DM)

- Hypoglycemia increases the risk for adverse events
- Older patients and those with a long duration of T2DM are at higher risk for hypoglycemia

Figura 1. Studio Hypos-1: impatto delle ipoglicemie sul consumo di risorse sanitarie dirette. Rappresentazione a barra del tasso di incidenza per 100 anni-persona.
Figura 2. Studio Hypos-1: impatto delle ipoglicemie sul consumo di risorse sanitarie indirette. Rappresentazione a barra del tasso di incidenza per 100 anni-persona.
<table>
<thead>
<tr>
<th>Tabella 2</th>
<th>Fattori di rischio per l'ipoglicemia nel diabetico.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Dosi eccessive di insulina e/o di ipoglicemizzanti orali</td>
<td></td>
</tr>
<tr>
<td>- Assunzione concomitante di altri farmaci</td>
<td></td>
</tr>
<tr>
<td>- Ridotta assunzione di cibo (carboidrati)</td>
<td></td>
</tr>
<tr>
<td>- Per digiuno o pasto saltato</td>
<td></td>
</tr>
<tr>
<td>- Interventi chirurgici</td>
<td></td>
</tr>
<tr>
<td>- Consumo di alcolici</td>
<td></td>
</tr>
<tr>
<td>- Aumentato esercizio fisico</td>
<td></td>
</tr>
<tr>
<td>- Diminuzione del peso corporeo</td>
<td></td>
</tr>
<tr>
<td>- Insufficienza renale cronica</td>
<td></td>
</tr>
<tr>
<td>- Insufficienza renale acuta (uso di diuretici, disidratazione ecc.)</td>
<td></td>
</tr>
<tr>
<td>- Precedenti episodi di ipoglicemia grave o di ipoglicemia asintomatica</td>
<td></td>
</tr>
<tr>
<td>- Riscontro di basso valore di emoglobina glicata</td>
<td></td>
</tr>
<tr>
<td>- Obiettivo di mantenere basse le glicemie</td>
<td></td>
</tr>
<tr>
<td>- Presenza di neuropatia vegetativa</td>
<td></td>
</tr>
<tr>
<td>- Rifiuto della malattia</td>
<td></td>
</tr>
<tr>
<td>- Preparazione alla trasgressione alimentare</td>
<td></td>
</tr>
<tr>
<td>- Età avanzata</td>
<td></td>
</tr>
<tr>
<td>- Durata del diabete</td>
<td></td>
</tr>
<tr>
<td>- Carenze endocrine</td>
<td></td>
</tr>
<tr>
<td>- Presenza di altre malattie (per es: insufficienza del rene e del fegato)</td>
<td></td>
</tr>
<tr>
<td>- Ospedalizzazione recente</td>
<td></td>
</tr>
</tbody>
</table>
Strategies for Achieving Earlier Introduction of Insulin Therapy

- Educate the patient about T2DM and the benefits of insulin at the initial consultation
- Emphasize the fact that beta-cell dysfunction and insulin deficiency define the disease
- Explain that achieving effective glycemic control will improve outcomes for the patient
- Don't use insulin as a threat

Polonsky W. *Diabetes Educ.* 2007;33 (Suppl 7):241S-244S.
Quando iniziare la terapia insulinica?

Pazienti di nuova diagnosi o già in trattamento che, alla dose massimale di ipoglicemizzanti orali, non raggiungono rapidamente (sei mesi) gli obiettivi

- Glicemia a digiuno > 250 mg/dl
- Glicemia post-prandiale frequentemente > 300 mg/dl
- HbA1c > 10%
- Chetonuria
- Diabete sintomatico (perdita di peso, poliuria, polidipsia)
- Gravidanza
- Patologie acute che richiedono ospedalizzazione
- Precedente cardiopatia ischemica
Basal Insulin Analogues

- NPH
- Lente
- Ultralente
- Glargine
- Detemir

Once-daily basal insulin analogues have a flatter time-action profile, with reduced variability.

Basal Insulin Analogues: Less Peaked and Longer Duration of Action

Less Hypoglycemia With Basal Insulin Analogues

Reduction in nocturnal hypoglycemia is important as most basal insulins are dosed at bedtime.

Remaining unmet needs and challenges with basal insulin therapy

There is still a compromise between risk of hypoglycemia and target glycemic control\(^1,2\)

Patients compromise between fear of hypoglycemia and glycemic control, which may lead to poor patient adherence\(^3-6\)

- >70% physicians titrate less aggressively due to hypoglycemia concern\(^2\)
- 25–~75% patients modify insulin dose following an hypoglycemic event\(^4-6\)

Less than 50% of insulin-treated patients are at their glycemic target\(^7-9\)

Above HbA\(_{1c}\) level of 7%, 38% more macrovascular complications and 40% more microvascular complications per 1% HbA\(_{1c}\) increase\(^10\)

---

HbA\(_{1c}\), glycated hemoglobin A\(_{1c}\)

Desired Properties for A Basal Insulin Product Relative to Existing Therapy

- Clinical needs
  - Easier and safer dose titration without increasing risk of hypoglycemia
  - 1 injection per day
  - Flexibility in timing
- Glycemic control
  - Achieve treatment goals
  - Duration beyond 24 hours
- PK/PD Profile
  - Less variability
  - Consistent delivery of insulin
  - Flat, stable, and prolonged profile

Second-Generation Basal Insulin Analogues

- Introduced to the market or at an advanced stage of clinical testing
- Each has a unique mechanism of protraction:
  - **Degludec**—multihexamer chain (>5000 kDa)\[a\]
  - **Glargine U300**—3-fold concentrated insulin with a depot surface area half the size of glargine 100\[c\]
  - **LY2963016** (Insulin Glargine Biosimilar)

---

Novel Basal Insulins Reach Steady State After 3-4 Days

Insulin Glargine
300 (0.6 U/kg)[a]

Insulin Degludec
(0.4, 0.6, or 0.8 U/kg)[b]

Dosage should not be adjusted more than every 3-4 days after initiation.

PK/PD Evolution of Basal Insulin Preparations

Glucose Infusion Rate, mg/kg/min

Elapsed Time, h

Insulin detemir
Insulin glargine
NPH
Longer-acting basal

PD = pharmacodynamic; PK = pharmacokinetic.
Insulin degludec structure

LysB29(\(N\varepsilon\)-hexadecandioyl-\(\gamma\)-Glu) des(B30) human insulin

A chain

\[
\text{GIVEQCCCTSICSLYQLENYN} \]

B chain

\[
\text{FVNQHLCGSHLVEALYLVCGERGFYYTPK} \]

desB30 Insulin

Hexadecandioyl

Fatty diacid side chain

L-\(\gamma\)-Glu

Glutamic acid ‘spacer’

I Jonassen et al. Diabetes 59 (Suppl. 1): A11, 2010
Insulin Degludec from injection to absorption: multi-hexamer formation key to protraction mechanism

Injected formulation

S.c. depot formation

Absorption

In the injected formulation, insulin degludec di-hexamers undergo a series of transformations upon deposition in the subcutaneous depot.

1. Phenol is removed, leading to insulin degludec multi-hexamers.
2. Zn$^{2+}$ is removed, resulting in insulin degludec monomers.

These monomers are then absorbed into the bloodstream, completing the process.
Insulin degludec multi-hexamer formation at the injection site
Insulin degludec di-hexamer formation
As the zinc concentration decreases, insulin degludec multi-hexamers release monomers from the ends

Insulin Degludec PD Profile at Steady State

Glucose infusion rate (mg/[kg·min]) vs. Time since injection (hours)

**T1DM**

**T2DM**

PD, pharmacodynamic

---

1 Heise et al. Diabetologia 2011;54(Suppl. 1):S425; 2 Heise T et al., Diabetes Obesity and Metabolism 2012
Insulin Degludec Has a Two-fold Longer Half-life than Insulin Glargine

Heise T, Diabetes July 2011; vol 60 (Supplement 1): 37-LB
Lower Impact of Missed Dose With Basal Insulins

Once-Daily Dosing

Missed Dose

6-hour half-life

25-hour half-life

Day-to-day variability in glucose-lowering effect over 24 hours at steady state

Heise T, Diabetes July 2011; vol 60 (Supplement 1): 960-P
Insulin degludec results in lower rates of nocturnal hypoglycaemia and fasting plasma glucose vs. insulin glargine: A meta-analysis of seven clinical trials.

D. Russell-Jones a, M.A. Gali b, M. Niemeyer c, M. Diamant d, S. Del Prato e

*Nutrition, Metabolism & Cardiovascular Diseases (2015) 25, 898–905

Figure 2  Change from baseline in FPG and rate of nocturnal confirmed hypoglycaemia at the end of the trials.

FPG, fasting plasma glucose; IDeg, insulin degludec; IGlar, insulin glargine; PYE, patient years of exposure
*p<0.05 for IDeg versus IGlar. Error bars are SEM.
Benefits for Patients Who Need Higher Insulin Doses

Gla-300 has the same number of units of insulin as Gla-100 in 2/3 less volume\[^{a,b}\]

Depot surface area reduced by 1/2 leading to slower release and prolonged action profile\[^{a,b}\]

- Lower injection volume is beneficial to patients who need higher doses of insulin
- A concentrated form of degludec (U200) also available for patients who need higher doses\[^{c}\]

---

c. Korsatko S, et al. EASD, 2011; Abstract 2349-PO.
Double-blind, crossover euglycemic clamp study of Gla-300 vs Gla-100 in 30 patients with T1DM
Similar reductions in HbA$_{1c}$ vs Gla-100 in all T2DM trials

EDITION 1-2-3 T2DM Pooled Analysis

Improvement in HbA$_{1c}$ was not affected by gender, age, diabetes duration (<10 years and ≥10 years), HbA$_{1c}$ value at baseline (<8% or ≥8%) or baseline BMI

Modified intention-to-treat (mITT) population; LS, least squares


Gla-300: Reductions in confirmed or severe hypoglycemia and documented symptomatic hypoglycemia at any time (24 h) in T2DM

**EDITION 1-2-3 T2DM Pooled Analysis from Baseline to Month 6**

Percentage of participants with ≥1 hypoglycemic event

At any time (24 h)

- Confirmed (≤70 mg/dL [3.9 mmol/L]) or severe
  - Gla-300 %: 65.5
  - Gla-100 %: 72.0
  - Relative risk (95% CI): 0.91 (0.87-0.96)
- Documented symptomatic ≤70 mg/dL (3.9 mmol/L)
  - Gla-300 %: 49.6
  - Gla-100 %: 56.4
  - Relative risk (95% CI): 0.88 (0.82-0.94)
- Severe
  - Gla-300 %: 2.3
  - Gla-100 %: 2.6
  - Relative risk (95% CI): 0.85 (0.52-1.39)

Consistent results across the program

Relative risk (95% CI) for confirmed (≤70 mg/dL) or severe hypoglycemia at any time (24 h) from baseline to Month 6

- **EDITION 1**: 0.93 (0.88 to 0.99)
- **EDITION 2**: 0.90 (0.83 to 0.98)
- **EDITION 3**: 0.88 (0.77 to 1.01)

Safety population


Not for promotional use
Gla-300 reduced hypoglycemia even during the titration phase
Incidence/annualized rates of confirmed (≤70 mg/dL [3.9 mmol/L]) or severe hypoglycemia

<table>
<thead>
<tr>
<th>Annualized rates</th>
<th>% of participants</th>
<th>Annualized rates</th>
<th>% of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate ratio</td>
<td>95% CI</td>
<td>Relative risk</td>
<td>95% CI</td>
</tr>
<tr>
<td>BL to W8</td>
<td>0.77</td>
<td>0.68 to 0.89</td>
<td>0.83</td>
</tr>
<tr>
<td>W9 to M6</td>
<td>0.91</td>
<td>0.80 to 1.03</td>
<td>0.92</td>
</tr>
<tr>
<td>BL to M6</td>
<td>0.86</td>
<td>0.77 to 0.97</td>
<td>0.91</td>
</tr>
</tbody>
</table>

At any time (24 h)

<table>
<thead>
<tr>
<th>From baseline to Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized rate</td>
</tr>
<tr>
<td>-23% (0.68 to 0.89)</td>
</tr>
<tr>
<td>Incidence</td>
</tr>
<tr>
<td>-17% (0.77 to 0.89)</td>
</tr>
</tbody>
</table>

From baseline to Week 8
Annualized rate
-23% (0.68 to 0.89)
Incidence
-17% (0.77 to 0.89)

Nocturnal (00:00–05:59 h)

<table>
<thead>
<tr>
<th>Annualized rates</th>
<th>% of participants</th>
<th>Annualized rates</th>
<th>% of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate ratio</td>
<td>95% CI</td>
<td>Relative risk</td>
<td>95% CI</td>
</tr>
<tr>
<td>BL to W8</td>
<td>0.58</td>
<td>0.47 to 0.73</td>
<td>0.69</td>
</tr>
<tr>
<td>W9 to M6</td>
<td>0.75</td>
<td>0.60 to 0.94</td>
<td>0.80</td>
</tr>
<tr>
<td>BL to M6</td>
<td>0.69</td>
<td>0.57 to 0.84</td>
<td>0.75</td>
</tr>
</tbody>
</table>

From baseline to Week 8
Annualized rate
-42% (0.47 to 0.73)
Incidence
-31% (0.58 to 0.81)

BL, baseline; M6, Month 6; W8, Week 8; W9, Week 9
Adapted from Ritzel R et al. Diabetes Obes Metab. 2015 Apr 30. doi: 10.1111/dom.12485 [Epub ahead of print]
Gla-300: Reduction of confirmed or severe hypoglycemia beyond the predefined nocturnal period (00:00-05:59)

Rate of confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe events per participant-year

Nocturnal hypoglycemia

Clock time, hours

0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5

0 to 2 2 to 4 4 to 6 6 to 8 8 to 10 10 to 12 12 to 14 14 to 16 16 to 18 18 to 20 20 to 22 22 to 24

Gla-100
Gla-300

Safety population
Adapted from Ritzel R et al. Diabetes Obes Metab. 2015 Apr 30. doi: 10.1111/dom.12485 [Epub ahead of print]
### Glargine U-300 vs Glargine U-100 in Type 2 Diabetes Meta-Analysis

<table>
<thead>
<tr>
<th></th>
<th>Glargine U-300 (n=1247)</th>
<th>Glargine U-100 (n=1249)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA₁c (%) LS mean</td>
<td>-1.02</td>
<td>-1.02</td>
<td>Not specified</td>
</tr>
<tr>
<td>Weight (kg), LS mean</td>
<td>0.49</td>
<td>0.75</td>
<td><em>P = .058</em></td>
</tr>
<tr>
<td>Any hypoglycemia in 24 hr*</td>
<td>67.8</td>
<td>73.8</td>
<td>0.92 (0.87-0.96)</td>
</tr>
<tr>
<td>Any nocturnal hypoglycemia*</td>
<td>31.7</td>
<td>41.3</td>
<td>0.77 (0.69-0.85)</td>
</tr>
</tbody>
</table>

- Titrate dose every 3 days
- Higher daily dose may be needed

*Percent people with 1 or more events.
# Basal insulin dose at Month 6 in the overall EDITION program

<table>
<thead>
<tr>
<th>Mean basal daily insulin dose, U/kg</th>
<th>EDITION 1</th>
<th>EDITION 2</th>
<th>EDITION 3</th>
<th>EDITION 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gla-300</td>
<td>0.67</td>
<td>0.64</td>
<td>0.19</td>
<td>0.32</td>
</tr>
<tr>
<td>Gla-100</td>
<td>0.67</td>
<td>0.66</td>
<td>0.19</td>
<td>0.32</td>
</tr>
<tr>
<td>Gla-300</td>
<td>0.98</td>
<td>0.93</td>
<td>0.62</td>
<td>0.47</td>
</tr>
<tr>
<td>Gla-100</td>
<td>0.88</td>
<td>0.85</td>
<td>0.53</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>Relative difference for Gla-300 vs Gla-100, %</strong></td>
<td><strong>+11.55</strong></td>
<td><strong>+10.44</strong></td>
<td><strong>+16.58</strong></td>
<td><strong>+15.98</strong></td>
</tr>
</tbody>
</table>

- The higher final dose with Gla-300 compared to Gla-100 is consistent with the lower 24-h exposure of Gla-300 vs Gla-100 observed under steady-state conditions in PK and PD studies
  - This observation suggests a somewhat lower bioavailability of Gla-300 due to increased residence time in the subcutaneous depot, resulting in additional exposure to tissue peptidases
- This did not impact body weight as similar or less weight gain was observed with Gla-300 vs Gla-100
- Similarly, the higher Gla-300 dose was not associated with increased risk of adverse events (e.g. hypoglycemia) vs Gla-100

Gla-300 achieves glycemic control with a lower risk for nocturnal hypoglycemia and significantly less weight gain than Gla-100.
Safety profile overview of Gla-300 at Month 6 in the EDITION program

<table>
<thead>
<tr>
<th>Proportion of patients, %</th>
<th>T2DM</th>
<th>T1DM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EDITION 1</td>
<td>EDITION 2</td>
</tr>
<tr>
<td></td>
<td>BB</td>
<td>BOT switch</td>
</tr>
<tr>
<td>Gla-300</td>
<td>56.4</td>
<td>58.8</td>
</tr>
<tr>
<td>Gla-100</td>
<td>54.2</td>
<td>50.7</td>
</tr>
<tr>
<td>TEAEs</td>
<td>6.4</td>
<td>3.7</td>
</tr>
<tr>
<td>Serious TEAEs</td>
<td>5.2</td>
<td>3.7</td>
</tr>
<tr>
<td>TEAEs leading to discontinuation</td>
<td>1.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

- The safety profiles of Gla-300 and Gla-100 at Month 6 were similar

TEAEs, treatment-emergent adverse events
Safety population
Data on file, EDITION 1 CSR, pg 125; EDITION 2 CSR, pg 124; EDITION 3 CSR pg 139;
Generic vs. Biosimilar: Manufacturing Differences

**Generic**
- Not affected by slight changes in production process and environment\(^1\)
- Easy to purify and characterize using analytical methods\(^1\)
- Easy to detect and eliminate contamination\(^1\)
- Easy to establish reproducibility\(^1\)

**Biosimilar**
- Highly susceptible to slight changes in production process and environment; each step of the process can be a source of variation within the final product\(^1,2\)
- Complex purification process and difficult to characterize\(^1\)
- Difficult to detect or remove contamination\(^1\)
- Difficult to establish reproducibility\(^1\)

1. Sekhon BS and Saluja V. *Biosimilars* 2011;1:1-11
Regulatory Summary: Requirements for Biosimilarity\textsuperscript{1,2}

- Similarity demonstrated in preclinical in vitro and in vivo PD and toxicology studies
- Similarity demonstrated in clinical trials designed to assess PK and PD against standard acceptance limits
- No clinically meaningful differences in immunogenicity
- Head-to-head clinical trial(s) to detect relevant differences in efficacy or drug-related safety\textsuperscript{a}

\textsuperscript{a}Efficacy/safety trial needed unless biosimilarity convincingly demonstrated by nonclinical, pharmacology, and immunogenicity studies


PD=Pharmacodynamic; PK=Pharmacokinetic
Typical Production Process of Insulin

Gene sequence

Expression vector

Host cell (E. coli or yeast)

Final product (insulin)

Purification (downstream process)

Fermentation/Culture (upstream process)

LY IGlar Development Program

“The Totality of Evidence”

- Identical amino acid sequence and the same pharmaceutical form and strength as Lantus® insulin glargine (IGlar)
- Highly similar to IGlar based on principles of biosimilarity
- Comprehensive development program to demonstrate similarity at high standards

**Preclinical studies**

*Biochemical and physicochemical characterization*

**Phase 1 studies**

4–6

*PK / PD of LY IGlar versus IGlar*

**Phase 3 studies**

1–3

ELEMENT 1  T1DM

ELEMENT 2  T2DM


PD=pharmacodynamic; PK=pharmacokinetic; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus
On the Horizon: Biosimilar Insulins

First Biosimilar Insulin Glargine

- Biosimilar insulins are derived from living cells or organisms, most often using recombinant DNA technology
- Development, manufacturing, and approval of biosimilar products more complex than for generic versions of small molecules
- Biosimilar insulin MK-1293 demonstrated pharmacokinetic and pharmacodynamic equivalence vs glargine in single-dose euglycemic clamp study
- Biosimilar glargine approved for use by the EMA; US FDA has given this product tentative approval

ELEMENET 1: HbA$_{1c}$ Change from Baseline and over Time with LY IGlar and IGlar

- **24 Weeks LOCF**
  - IGlar (N=268): -0.46
  - LY IGlar (N=267): -0.35
  - Change: $\Delta = 0.108$
  - 95% CI: (-0.002, 0.219)
  - p = 0.055

- **52 Weeks LOCF**
  - IGlar (N=268): -0.28
  - LY IGlar (N=267): -0.26
  - Change: $\Delta = 0.020$
  - 95% CI: (-0.099, 0.140)
  - p = 0.737

Data are least squares mean ± standard error

*p = 0.03; no significant differences between treatment at any other time point

CI=confidence interval; HbA$_{1c}$=glycosylated hemoglobin; LOCF=last observation carried forward

Blevins et al., Diabetes Obes Metab. 2015 Aug;17(8):726-33
ELEMENT 1: Total, Nocturnal, and Severe Hypoglycemia

All p values >0.05

Blevins et al., Diabetes Obes Metab. 2015 Aug;17(8):726-33
ELEMENT 2: Total, Nocturnal, and Severe Hypoglycemia

- **Incidence**
  - **Total**: IGlar (N = 376), LY IGlar (N = 373)
  - **Nocturnal**: 78, 54
  - **Severe**: 79, 57

- **Event Rates**
  - **Total**: 22, 21
  - **Nocturnal**: 8, 7
  - **Severe**: <1, <1

All p values >0.05
SD=standard deviation

Rosenstock et al., Diabetes Obes Metab. 2015 Aug;17(8):734-41
Proportion of Patients with Detectable Antibodies: ELEMENT 1

<table>
<thead>
<tr>
<th></th>
<th>IGlar (N = 267)</th>
<th>LY IGlar (N = 265)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with detectable antibodies, n (%)</td>
<td>Overall 24 weeks 90 (34)</td>
<td>80 (30)</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>Overall 52 weeks 105 (39)</td>
<td>107 (40)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

LOCF=last observation carried forward

Ilag et al., Diabetes Obes Metab. 2015 Oct 5, doi: 10.1111/dom.12584
Proportion of Patients with Detectable Antibodies: ELEMENT 2

![Graph showing proportion of patients with detectable antibodies over time.](image)

- **IGlar (N = 365)**
- **LY IGlar (N = 365)**

<table>
<thead>
<tr>
<th>By week</th>
<th>IGlar</th>
<th>LY IGlar</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 (LOCF)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **p = 0.047**

<table>
<thead>
<tr>
<th>Patients with detectable antibodies, n (%)</th>
<th>Overall 24 weeks</th>
<th>LY IGlar</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with detectable antibodies, n (%)</td>
<td>40 (11)</td>
<td>56 (15)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

LOCF=last observation carried forward

Ilag et al., Diabetes Obes Metab. 2015 Oct 5, doi: 10.1111/dom.12584
Figure 2: Timeline for the development of short-acting, long-acting, and future rapid-acting analogues of insulin. NPH = neutral protamine hagedorn. PEG = polyethylene glycol. EDTA = edetic acid.
The First Recombinant, Fully Human, Monomeric Super-long-acting Basal Insulin

PE0139
A smart insulin patch

A microneedle-containing patch that is designed to sense elevated blood glucose levels and to respond by releasing insulin could offer people with diabetes a less-painful and more-reliable way to manage their condition.
Benefits of Newer Basal Insulins

- Ultra-long-acting insulin analogs
  - Duration up to 42 hours
- Flat, stable glucose-lowering profile
- Lower within patient day-to-day variability in glucose-lowering effect
- Similar glycemic control compared with available basal insulins
- Flexible timing of injection time, without compromising efficacy or safety
- Less nocturnal hypoglycemia
- Reduced weight gain
- Smaller doses with concentrated insulin
- More “forgiveness” if timing of injection changes or missed dose

Garber AJ. Diabetes Obes Metab. 2014;16:483-491.[15]
Nuove formulazioni insuliniche potranno portare ulteriori benefici in termini di efficacia e sicurezza, migliorando il controllo glicemico e la qualità di vita delle persone con diabete.

Tuttavia le attese della novità terapeutica non devono mai portare in secondo piano l’importanza dell’intervento educativo che rimane la vera chiave di successo del trattamento insulinico nella terapia del diabete.
Grazie...