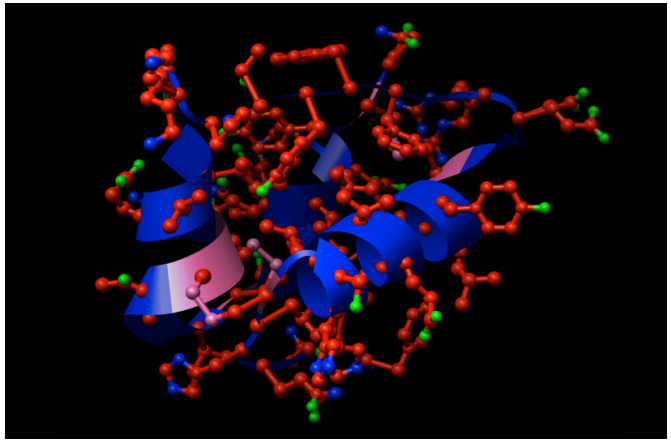
Congresso
AMD-SID
Emilia-Romagna

L'ASSISTENZA DIABETOLOGICA
IN EMILIA-ROMAGNA:
UN IMPEGNO PER TUTTI

9 e 10 ottobre 2015

Nuove insuline e biosimilari

Giulio Marchesini
SSD Malattie del Metabolismo e Dietetica Clinica
"Alma Mater Studiorum"
Università di Bologna



Baggiovara (MO)
UNA Hotel Modena
Via Luigi Settembrini, 10

Disclosures

Giulio Marchesini

- **Advisory Board**: Sanofi
- **Honoraria**: Sanofi, Merck Sharp & Dome, Novartis
- **Clinical Studies**: Boehringer Ingelheim, Sanofi, Lilly, Novo Nordisk, GILEAD, GENFIT, Janssen

Insulina basale … sempre più basale

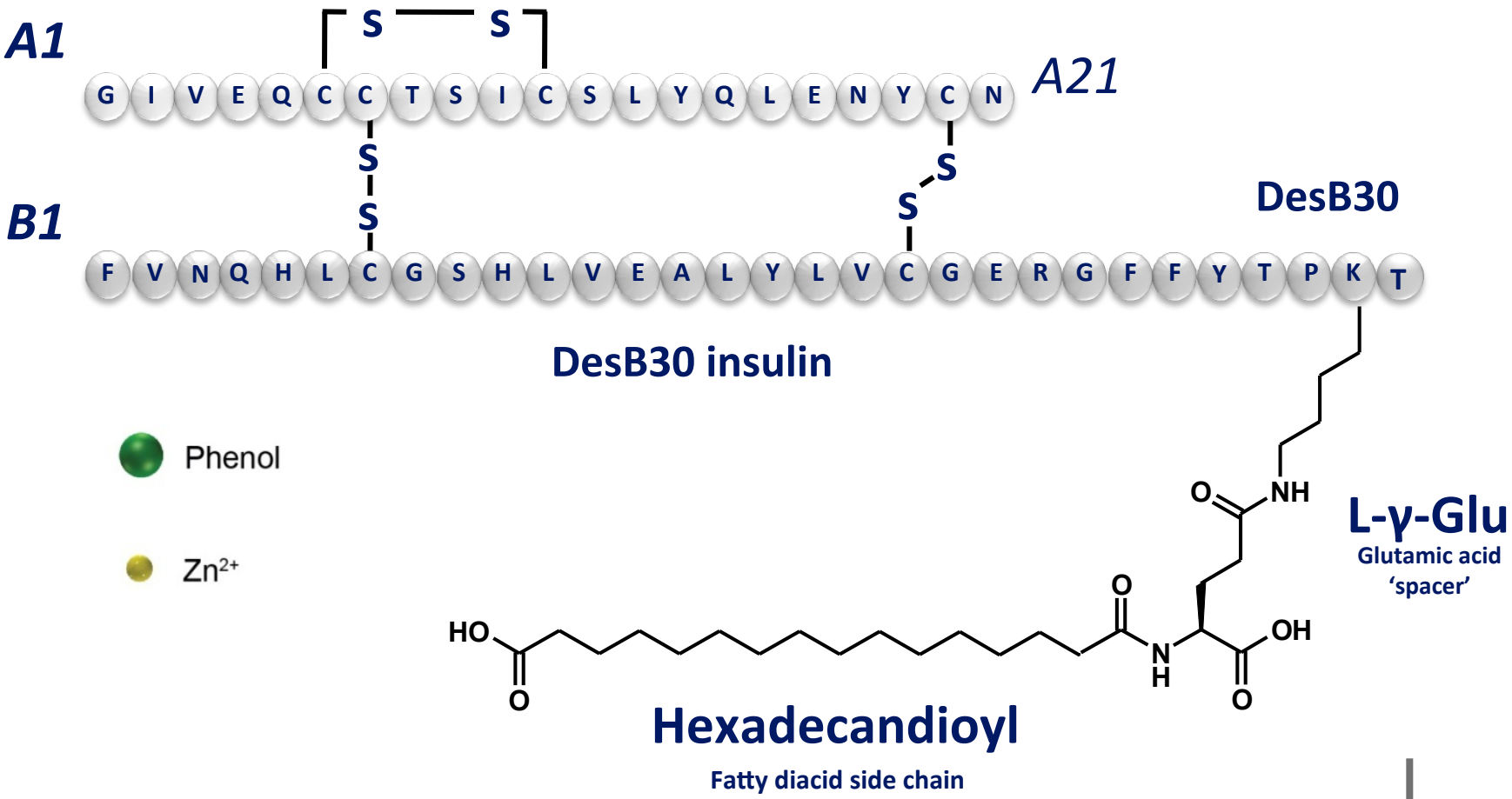
- Degludec
- Glargine U-300
- Insulina Pegilata

…. (LL, IdegL)

- Biosimilari

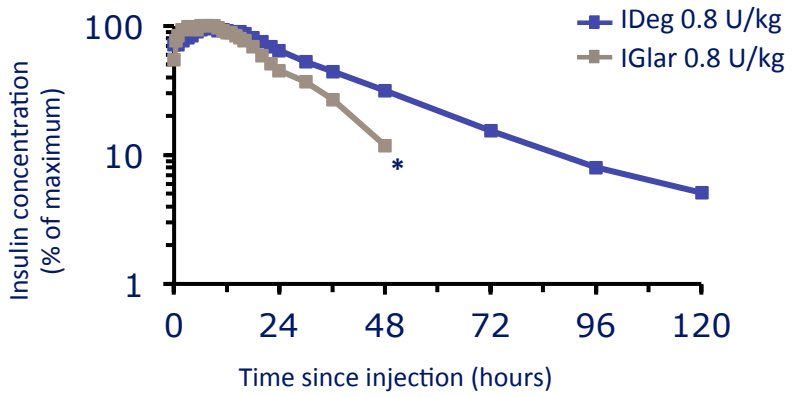
Insulin degludec: rationally designed, beyond sequence modification

Des(B30) LysB29(γ-Glu Nε-hexadecandioyl) human insulin

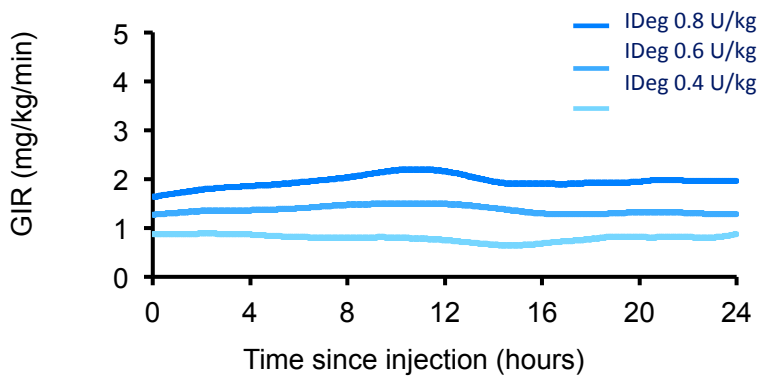


Glucose-lowering profile and day-to-day variability

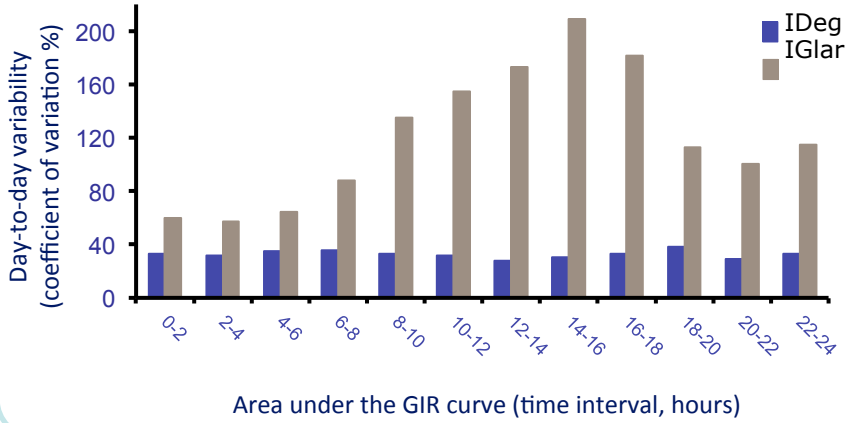
Half-life



IDeg glucose-lowering profile



Variability in glucose-lowering effect over 24 hours at steady state



IDeg half-life (25.4 hours) is twice that of IGlar (12.5 hours)

IDeg variability is four-fold lower than IGlar

*Insulin glargine was undectable after 48 hours.

CV, coefficient of variation; GIR, glucose infusion rate; IDeg, insulin degludec; IGlar, insulin glargine; T1D, type 1 diabetes

Heise *et al. Diabetes Obes Metab* 2012;14:944–50; Heise *et al. Diabetologia* 2011;54(Suppl. 1):S425; Heise *et al. Diabetes Obes Metab* 2012;14:859–64

Background: Pre-specified meta-analysis

- Meta-analysis was prospectively planned
- Statistical analysis plan was reviewed by the FDA
- Review included:
  - Which trials to include and how to analyse the data

Insulin degludec phase 3a study program: Meta-analysis

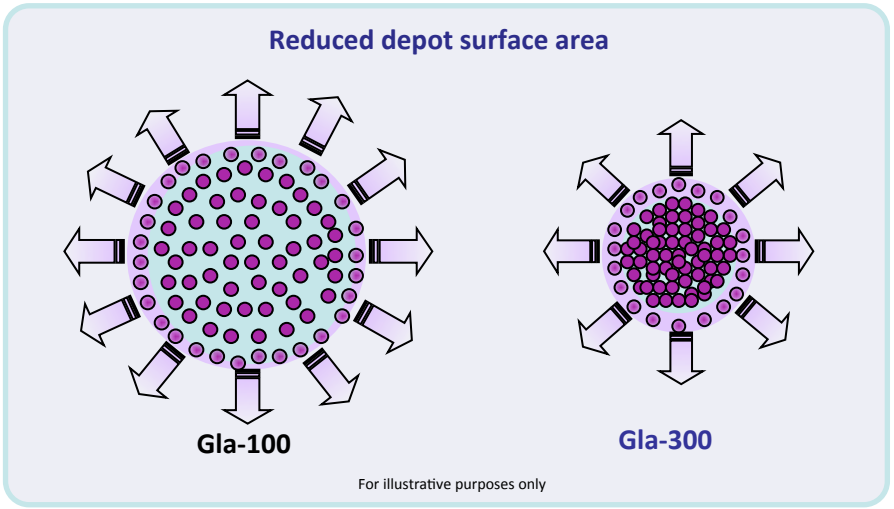
	Full trial Overall	Maintenance Overall
Pooled insulin-naïve	**–17%***	**–28%***
Pooled T2D	**–17%***	**–25%***
Pooled T1D	**+10%**	**+2%**
Pooled T2D/T1D	**–9%***	**–16%***
	Nocturnal	**Nocturnal**
Pooled insulin-naïve	**–36%***	**–49%***
Pooled T2D	**–32%***	**–38%***
Pooled T1D	**–17%**	**–25%***
Pooled T2D/T1D	**–26%***	**–32%***

*Statistically significant, $p<0.05$

Ratner *et al. Diabetes Obes Metab* 2013;15:175–84

Gla-300: A novel insulin glargine formulation

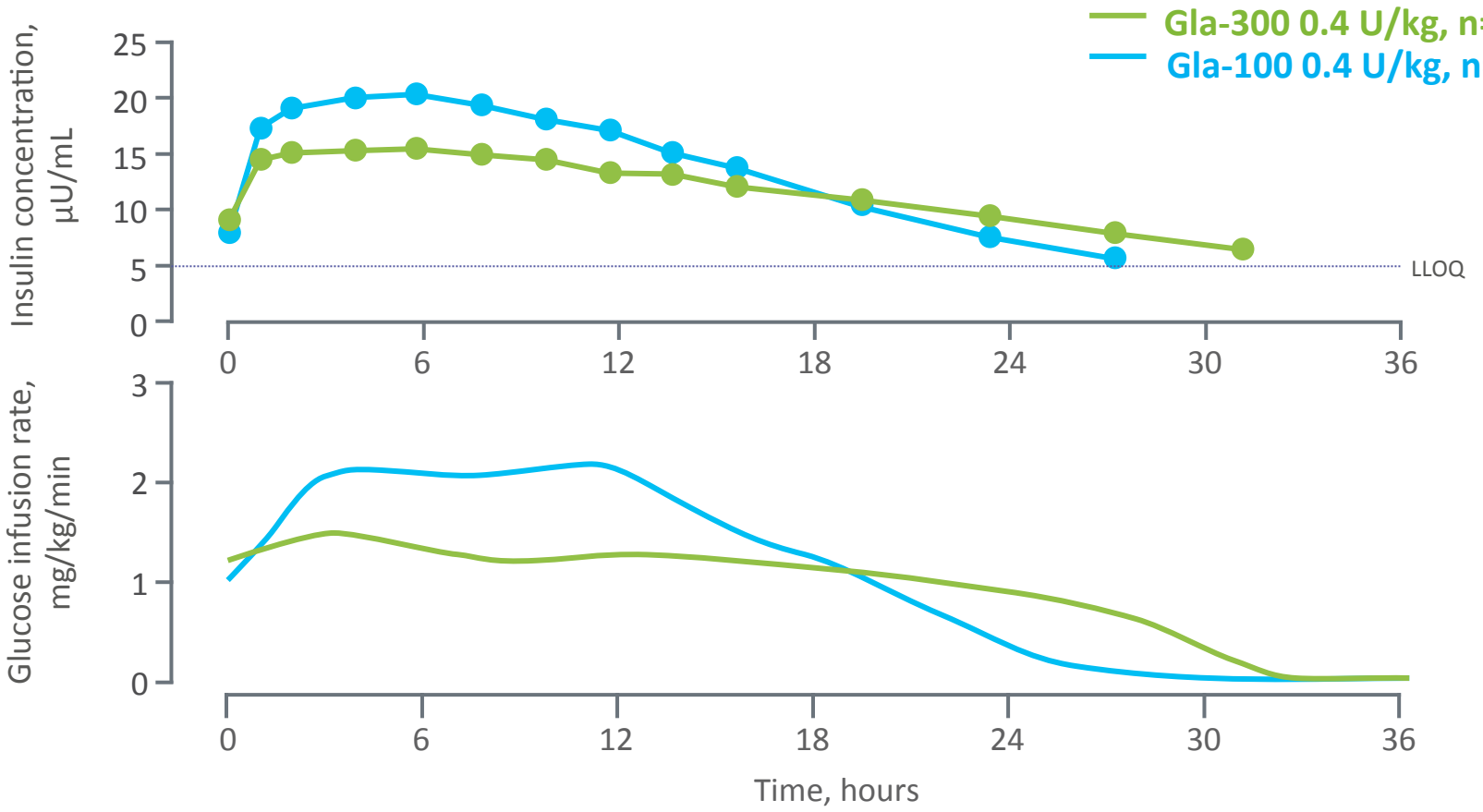
- Gla-300 is a new insulin glargine formulation, which is not bioequivalent to Gla-100 (insulin glargine 100 U/mL) and not interchangeable
- Gla-300 has the same mode of protraction (forming microprecipitates) as Gla-100 but with a smaller depot surface area
- Gla-300 contains 3-times the amount of insulin glargine per mL as Gla-100
  - the same unit amount in one third the volume



The more sustained release of insulin glargine from the Gla-300 precipitate compared to Gla-100 is attributable to the reduction of the injection volume by two thirds that results in a smaller precipitate surface area

- Gla-300 has the same metabolism (main circulating moiety is M1) as for Gla-100

More stable and prolonged (beyond 24 hours) PK/PD profile with Gla-300 vs Gla-100



- Double-blind, crossover euglycemic clamp study of Gla-300 vs Gla-100 in 30 patients with T1DM

LLOQ, lower limit of quantification; PD, pharmacodynamic; PK, pharmacokinetic; T1DM, type 1 diabetes mellitus

Characteristics of the T2DM patients randomized in EDITION 1-2-3

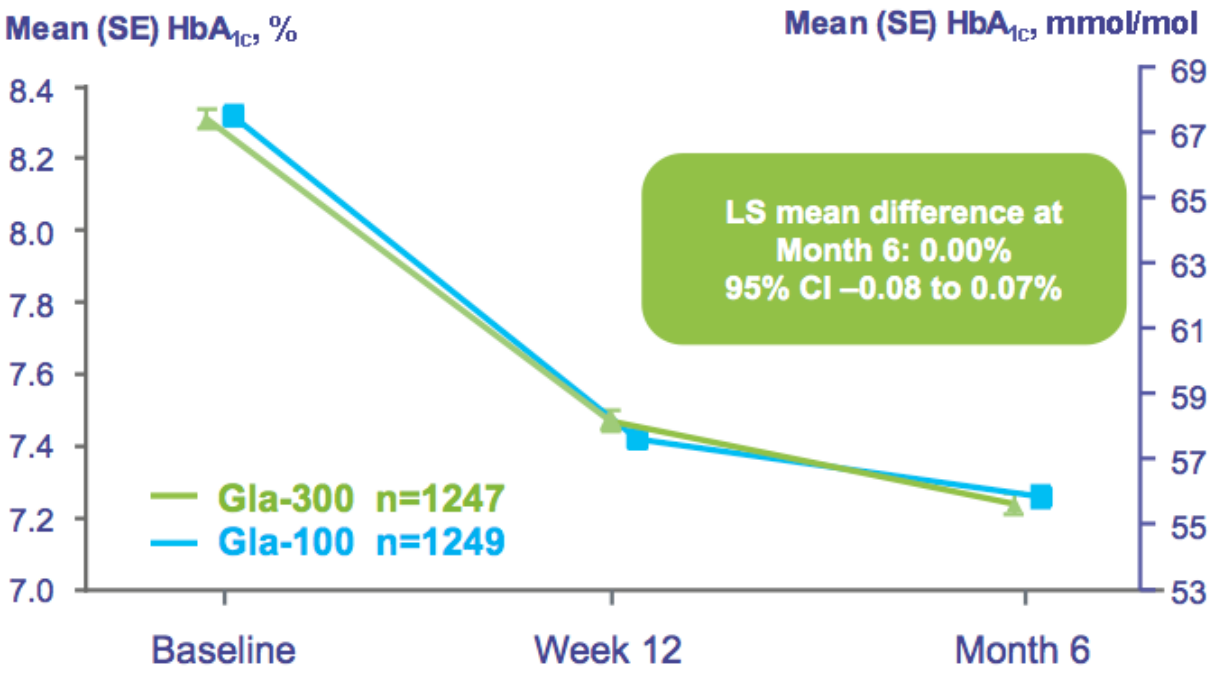
- 2496 patients with different background therapies: BB, BOT and insulin naive

	EDITION 1		EDITION 2		EDITION 3		POOLED ANALYSIS	
Trial description and treatment	Gla-300 vs Gla-100 (+mealtime insulin+Met)		Gla-300 vs Gla-100 (+Met+OADs*)		Gla-300 vs Gla-100 (+Met+OADs†)		N/A	
Number of participants								
Gla-300	404		404		439		1247	
Gla-100	403		407		439		1249	
Glucose-lowering therapy at screening	Basal + mealtime insulin + OADs		Basal insulin + OADs		Insulin naive + OADs		N/A	
Inclusion criteria								
Insulin dose	≥42 U		≥42 U					
HbA_{1c}	7–10%		7–10%		7–11%		N/A	
Age, y	≥18		≥18		≥18			
Mean at baseline	**Gla-300**	**Gla-100**	**Gla-300**	**Gla-100**	**Gla-300**	**Gla-100**	**Gla-300**	**Gla-100**
BMI, kg/m²	36.6	36.6	34.8	34.8	32.8	33.2	34.7	34.8
Age, y	60.1	59.8	57.9	58.5	58.2	57.2	58.7	58.5
Duration of diabetes, y	15.6	16.1	12.7	12.5	10.1	9.6	12.7	12.6
HbA_{1c}, %	8.15	8.16	8.26	8.22	8.51	8.57	8.31	8.32

*Use of SUs were prohibited within 2 months prior to screening and during the study
†Except SUs, glinides and other OADs not approved for use with insulin
BMI, body mass index; Met, metformin; N/A, not applicable

Similar reductions in HbA_{1c} vs. Gla-100 in all T2DM trials

EDITION 1-2-3 T2DM Pooled Analysis



Individual EDITION study data:

EDITION 1
Difference: 0.00%
95% CI –0.11 to 0.11%

EDITION 2
Difference: –0.01%
95% CI –0.14 to 0.12%

EDITION 3
Difference: 0.04%
95% CI –0.09 to 0.17%

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

Ritzel R et al. Diabetes Obes Metab. 2015 Apr 30. doi: 10.1111/dom.12485 [Epub ahead of print]; Riddle MC et al. Diabetes Care. 2014;37:2755-62; Yki-Järvinen H et al. Diabetes Care. 2014;37:3235-43; Bolli GB et al. Diabetes Obes Metab. 2015;17:386-94;

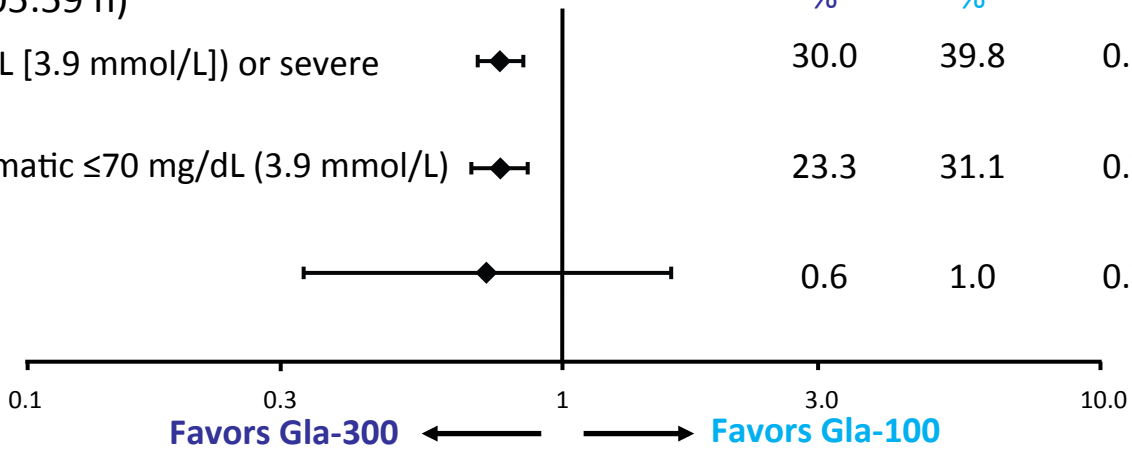
Gla-300: Reductions in nocturnal confirmed or severe hypos and documented symptomatic hypos in T2DM

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

Percentage of participants with ≥1 hypoglycemic event

Nocturnal (00:00–05:59 h)

	Gla-300 %	Gla-100 %	Relative risk (95% CI)
Confirmed (≤70 mg/dL [3.9 mmol/L]) or severe	30.0	39.8	0.75 (0.68-0.83)
Documented symptomatic ≤70 mg/dL (3.9 mmol/L)	23.3	31.1	0.75 (0.66-0.85)
Severe	0.6	1.0	0.71 (0.32-1.59)



Consistent results across the program

Relative risk (95% CI) for confirmed (≤70 mg/dL) or severe nocturnal hypoglycemia

EDITION 1	0.78 (0.68 to 0.89)
EDITION 2	0.71 (0.58 to 0.86)
EDITION 3	0.76 (0.59 to 0.99)

Main secondary endpoint

EDITION 1	0.79 (0.67 to 0.93)
EDITION 2	0.77 (0.61 to 0.99)
EDITION 3	0.89 (0.66 to 1.20)

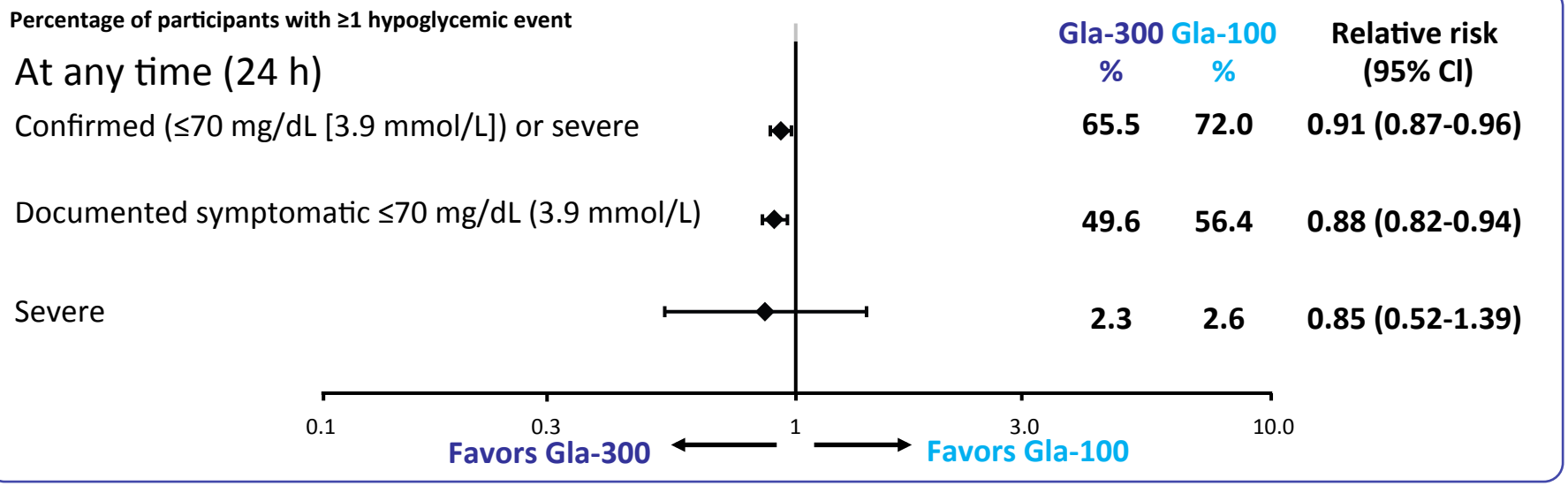
mITT population for main secondary endpoint; safety population for other data

Ritzel R et al. Diabetes Obes Metab. 2015 Apr 30. doi: 10.1111/dom.12485 [Epub ahead of print];
Data on file, Meta-analysis T2DM_pack_2014-05-28.doc, pg 10; Riddle MC et al. Diabetes Care. 2014;37:2755-62;
Yki-Järvinen H et al. Diabetes Care. 2014;37:3235-43; Bolli GB et al. Diabetes Obes Metab. 2015;17:386-94

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

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

Percentage of participants with ≥1 hypoglycemic event



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

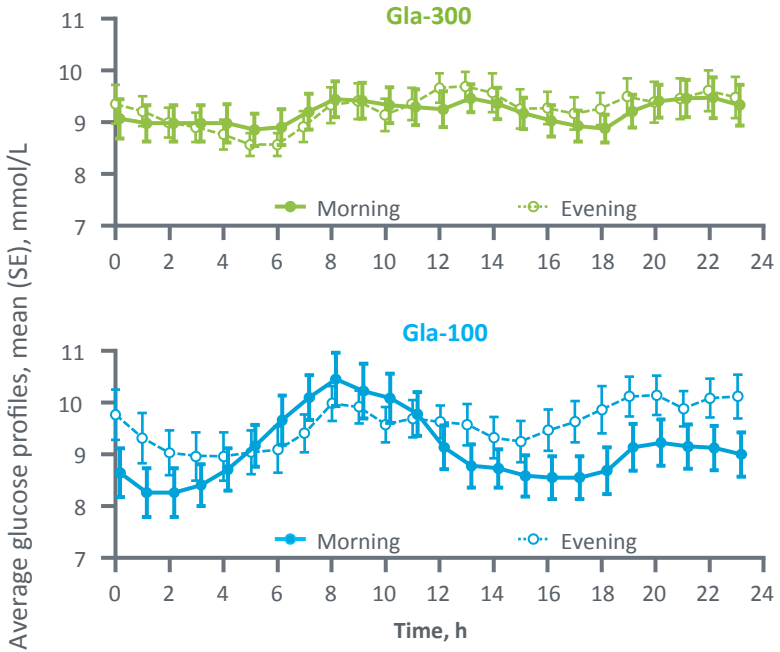
EDITION 1	0.93 (0.88 to 0.99)
EDITION 2	0.90 (0.83 to 0.98)
EDITION 3	0.88 (0.77 to 1.01)

Safety population

Riddle MC et al. Diabetes Care. 2014;37:2755-62; Yki-Järvinen H et al. Diabetes Care. 2014;37:3235-43;
Bolli GB et al. Diabetes Obes Metab. 2015;17:386-94; Ritzel R et al. Diabetes Obes Metab. 2015 Apr 30. doi: 10.1111/dom.12485 [Epub ahead of print]

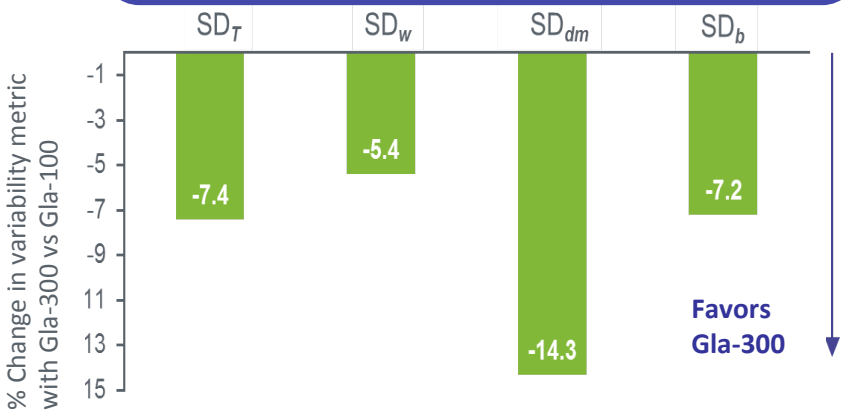
Glucose profile with Gla-300 vs Gla-100
Continuous glucose monitoring (CGM) study in T1DM (PDY 12777)

More constant glucose profiles with Gla-300 compared with Gla-100, independent of the time of injection (morning or evening)



Average 24-h glucose profiles during the last 2 weeks of each treatment period (continuous glucose monitoring population; pooled data period A + B)

All metrics for intra-subject within- and between-day glucose variability were numerically lower for participants receiving Gla-300 vs Gla-100

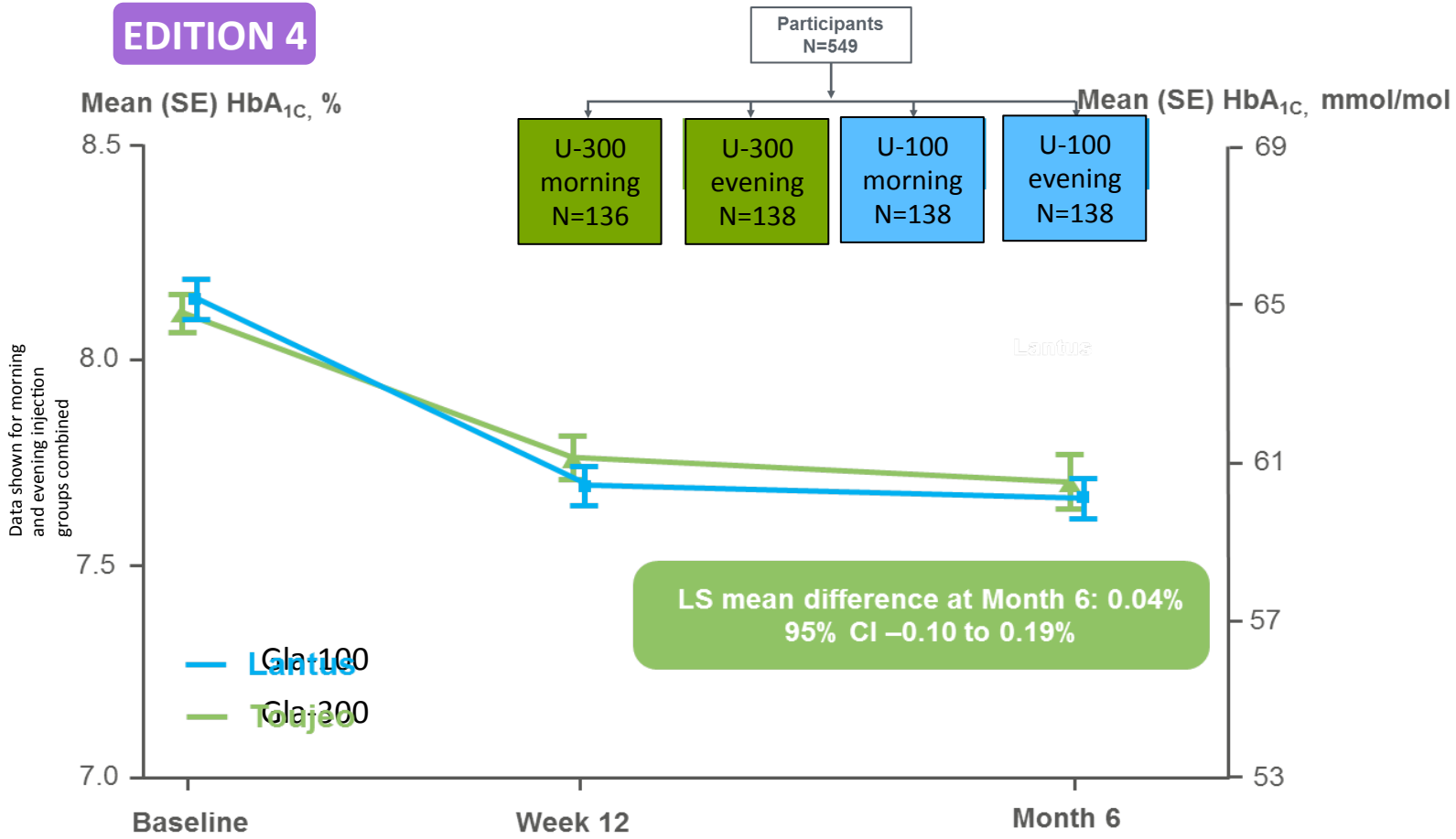


Absolute values; mean (SE) (mg/dL)	SD_T Total standard deviation variability	SD_w Within-day variability	SD_{dm} Variability between daily means	SD_b Variability between daily means
Gla-100	76.1 (2.7)	61.4 (1.8)	41.4 (2.5)	71.3 (2.9)
Gla-300	70.5 (2.4)	58.1 (2.1)	35.5 (1.7)	66.2 (2.3)
P-value	0.1259	0.2286	0.052	0.1568

- Phase 2, parallel group, crossover CGM study of Gla-300 vs Gla-100 injected either in the morning or evening in 59 patients with T1DM

Bergenstal RM et al. Oral presentation at ATTD 2015. Diabetes Tech Ther. 2015;17(Suppl 1):A16-17 (abstract no. 39);
Bergenstal RM et al. Poster presentation at EASD 2014; Abstract 949

Gla-300: Similar efficacy as Gla-100 for HbA_{1c} reduction in T1DM



- Comparable HbA_{1c} reductions were observed independent of injection time (morning or evening)

mITT population for primary endpoint (Gla-300: n=273; Gla-100: n=273)
Once-daily insulin dose titrated to FPG 80–130 mg/dL (4.4–7.2 mmol/L)

Home PD et al. Diabetes Care. 2015 Jun 17. pii: dc150249. [Epub ahead of print]

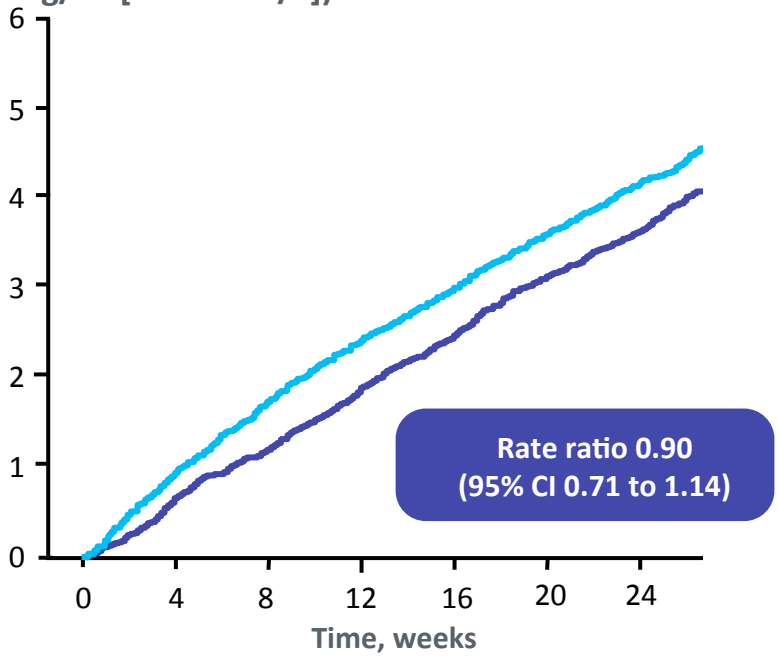
Gla-300: Incidence of confirmed or severe hypos vs Gla-100; Lower nocturnal hypos with Gla-300 during the first 8 weeks

EDITION 4

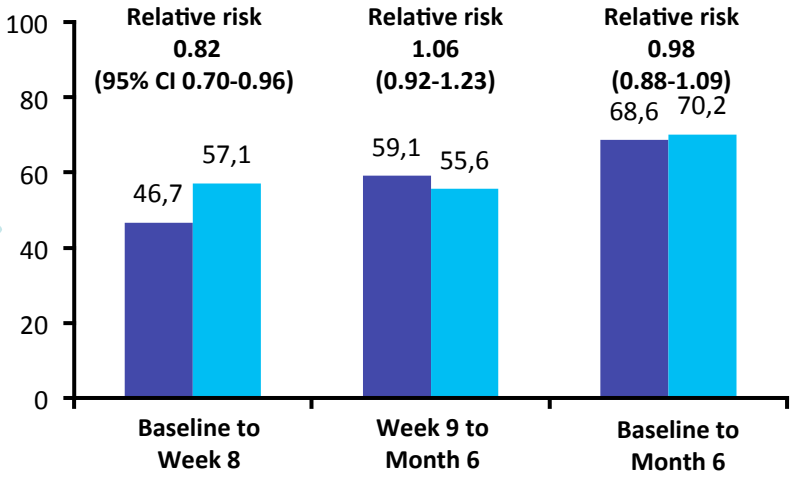
Nocturnal hypoglycemia (00:00–05:59 h)

Gla-300 Gla-100

Cumulative mean number of confirmed (≤70 mg/dL [3.9 mmol/L]) or severe events



Participants with ≥1 confirmed (≤70 mg/dL [3.9 mmol/L]) or severe events (%)



Lower risk of nocturnal hypoglycemia during the first 8 weeks and similar effect from baseline to Month 6

EDITION 4 was not designed and powered to test the difference in hypoglycemia risk between Gla-300 and Gla-100 as a pre-specified endpoint
Data for morning and evening injection groups combined
Safety population

Home PD et al. Diabetes Care. 2015 Jun 17. pii: dc150249. [Epub ahead of print]

Basal insulin dose at Month 6 in the overall EDITION program

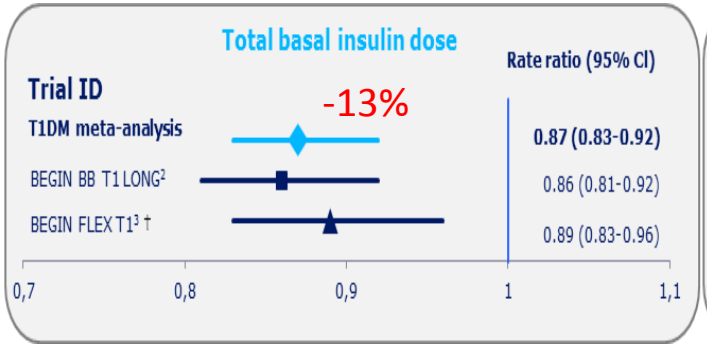
Mean basal daily insulin dose, U/kg	EDITION 1		EDITION 2		EDITION 3		EDITION 4	
	Gla-300	Gla-100	Gla-300	Gla-100	Gla-300	Gla-100	Gla-300	Gla-100
At baseline	0.67	0.67	0.64	0.66	0.19	0.19	0.32	0.32
At Month 6	0.98	0.88	0.93	0.85	0.62	0.53	0.47	0.40
Relative difference for Gla-300 vs Gla-100, %	+11.55		+10.44		+16.58		+15.98	

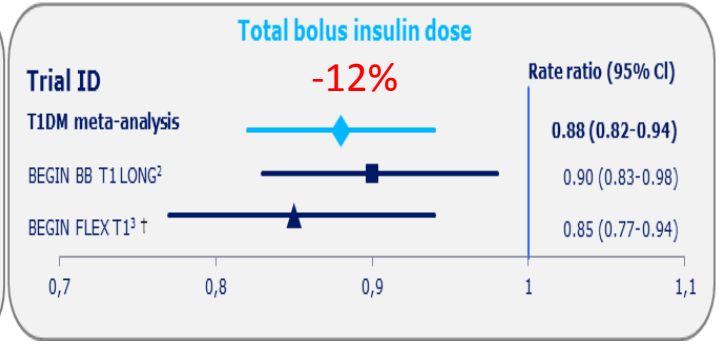
- The higher final dose with Gla-300 compared to Gla-100 is consistent with the lower 24-h exposure of Gla-300 vs Gla-100 observed under steady-state conditions in PK and PD studies
  - This observation suggests a somewhat lower bioavailability of Gla-300 due to increased residence time in the subcutaneous 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

Data on file, E19_Insulin dose_Absolute and Relative differences_M12_2014-09-03.doc, pg 6, 12, 14, 22; Becker RH et al. Diabetes Care. 2015;38:637-43; Yki-Järvinen H et al. Diabetes Care. 2014;37:3235-43; Riddle MC et al. Diabetes Care. 2014;37:2755-62; Bolli GB et al. Diabetes Obes Metab. 2015;17:386-94; Home PD et al. Diabetes Care. 2015 Jun 17. pii: dc150249. [Epub ahead of print]

Insulin degludec: meta-analysis of dosages

- For T1DM patients, the total daily dose of IDeg was significantly 12% lower than IGlar ($p<0.0001$)[1]
- When analysed separately, significantly 13% lower daily basal and 12% lower bolus doses were observed with IDeg compared with insulin glargine[1]

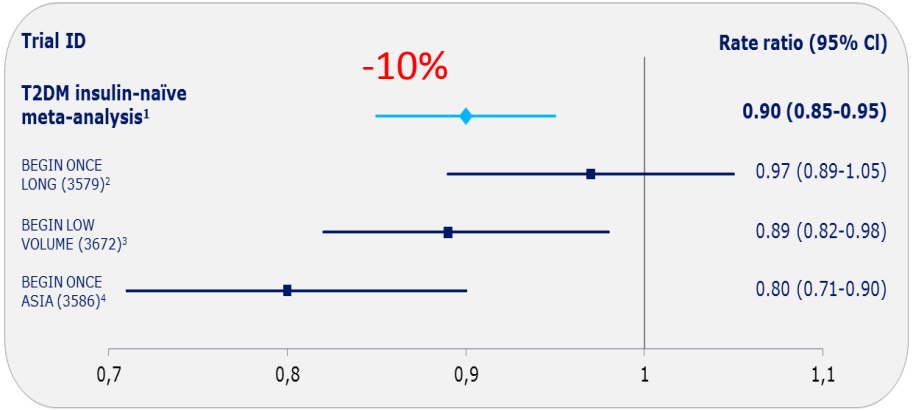




1. Data on file, DOF-MA-IDeg-24APR2013-001, Novo Nordisk A/S.
2. Heller et. al. *Lancet* 2012; 379:1489-97.
3. Mathieu et.al. *J Clin Endocrinol Metab* 2013;98(3):1154-62

†Ratios deviate from those in the reference Table 2 as the publication analyses all IDeg patients together (incl. forced flexible dosing arm); ratios here are IDeg standard dosing arm only.

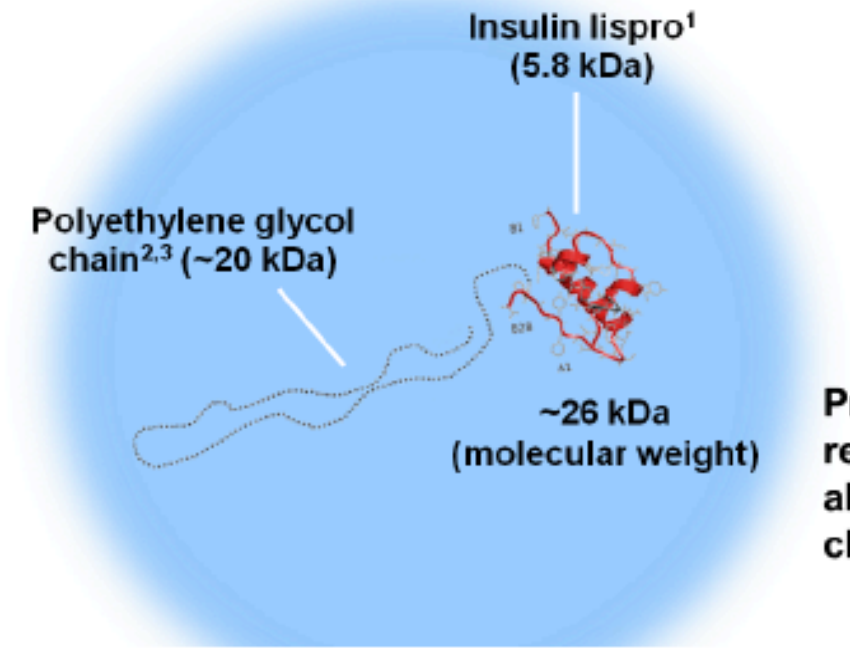
- For insulin-naïve T2DM patients, the total daily dose was 10% lower with IDeg than IGlar ($p=0.0004$)[1]



1. Data on file, DOF-MA-IDeg-24APR2013-001, Novo Nordisk A/S.
2. Zinman et al. *Diabetes Care*. 2012; 35(12):2464-71 (+ supplementary online data).
3. Gough et.al., *Diabetes Care* 2013; May 28. [Epub ahead of print].
4. Onishi et.al. *Journal of Diabetes Investigation* 2013; DOI: 10.1111/jdi.12102 [Epub ahead of print] (+ supplementary online information).

Basal Insulin Peglispro (BIL)

Basal Insulin Peglispro (BIL)



T ½ = 2-3 days[5]

Hepato-preferential action due to reduced peripheral effect[7-9]

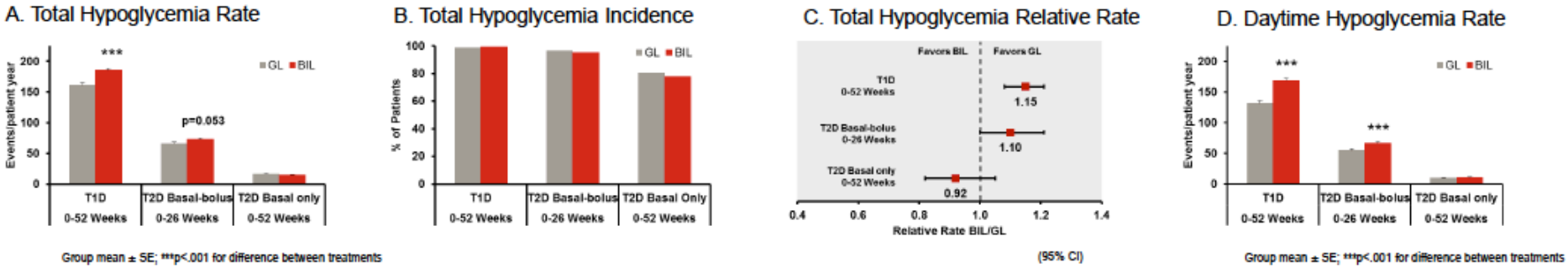
Prolonged activity related to delayed absorption and reduced clearance[5,6]

Hydrodynamic size of BIL: 71-98 kDa [2,3]

For perspective, the hydrodynamic size of BIL is ≥ albumin[4]

Nocturnal hypos with BIL vs. Insulin Glargine: Pooled Analyses of 5 RCTs

Figure 2. Total Hypoglycemia

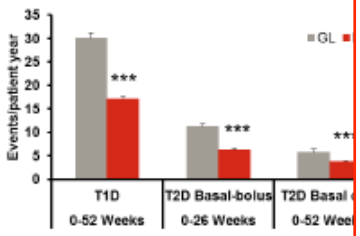


Group mean ± SE; ***p<.001 for difference between treatments

- Total hypoglycemia rate was higher with T2D
- Total hypoglycemia incidence was n
- The individual study results were co

Figure 3. Nocturnal Hy

A. Nocturnal Hypoglycemia Rat



Group mean ± SE; ***p<.001 for difference be

- In each study, BIL treatment met the rate (with multiplicity adjustment)
- The individual study results were co

Table 1. Severe Hypoglycemia

	Rate (events/100 patient years)					Incidence				
	GL		BIL		p-value	GL		BIL		p-value
Study	N	Rate†	N	Rate†		N	n (%)	N	n (%)	
Integrated T1D	608	18.7	955	22.1	.347	608	63 (10)	955	110 (12)	.472
IMAGINE 1 (OL)	159	9.1	293	28.3	.006	159	9 (6)	293	40 (14)	.011
IMAGINE 3 (DB)	449	22.5	662	19.7	.520	449	54 (12)	662	70 (11)	.451
T2D Basal-bolus	676	4.7	689	5.31	.814	676	10 (1.5)	689	16 (2.3)	.259
Integrated T2D - Basal only	694	0.80	1305	0.34	.203	694	5 (0.7)	1305	4 (0.3)	.188

†Aggregated rate; OL, open label; DB, double-blind

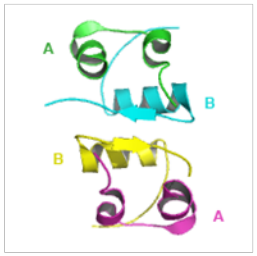
- In studies in T1D, the rate and incidence of severe hypoglycemia were higher with BIL compared to GL in the open label IMAGINE 1 study and were not significantly different between treatment groups in the double-blind IMAGINE 3 study
- There were no significant differences in the rate or incidence of severe hypoglycemia between treatments in the T1D or T2D integrated analyses

Rosenstock et al, Abstract EASD-Wien 2015

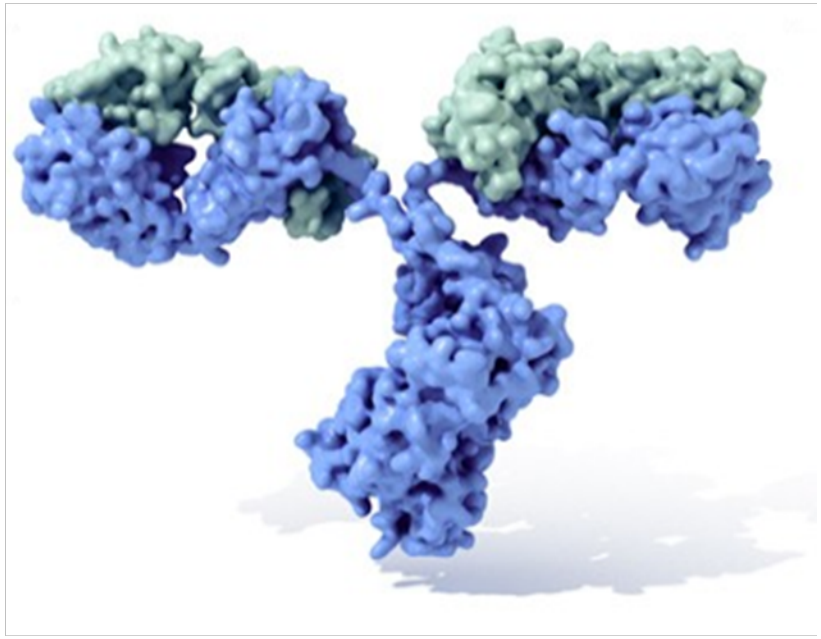
Glargine biosimilare

Aspirin

Insulin



Monoclonal Antibody



Small Chemical Molecule	Simple Biologic	Complex Biologic
MW = 180 Da 0 amino acids	MW = ~5800 Da 51 amino acids	MW = ~150,000 Da >1000 amino acids

Generic vs. Biosimilar

Generic

- Copies of small molecule medicinal products derived from chemical manufacturing processes[1]
- Identical chemical structures to those of already marketed products[1]

Biosimilar

- Similar versions of biological medicinal products derived from biotechnological manufacturing processes[1]
- Amino acid sequence should be identical to the reference product[2]
- Differences in biotechnological manufacturing processes between companies mean that biosimilar products cannot be described as identical[1,3]

1. Sekhon BS and Saluja V.*Biosimilars* 2011;1:1-11
2. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/05/WC500127960.pdf
3. Owens DR et al. *Diabetes Technol Ther* 2012;14:989-96

Generic vs. Biosimilar: Key Differences

Generic

- Low molecular weight[1]
- Known structure[1]
- Stable at room temperature[1,2]
- Administered through different routes of administration[2]
- Organic/chemical synthesis[1,2]

- Homogeneous product with high purity with established standards[2]
- Rarely immunogenic[1,2]

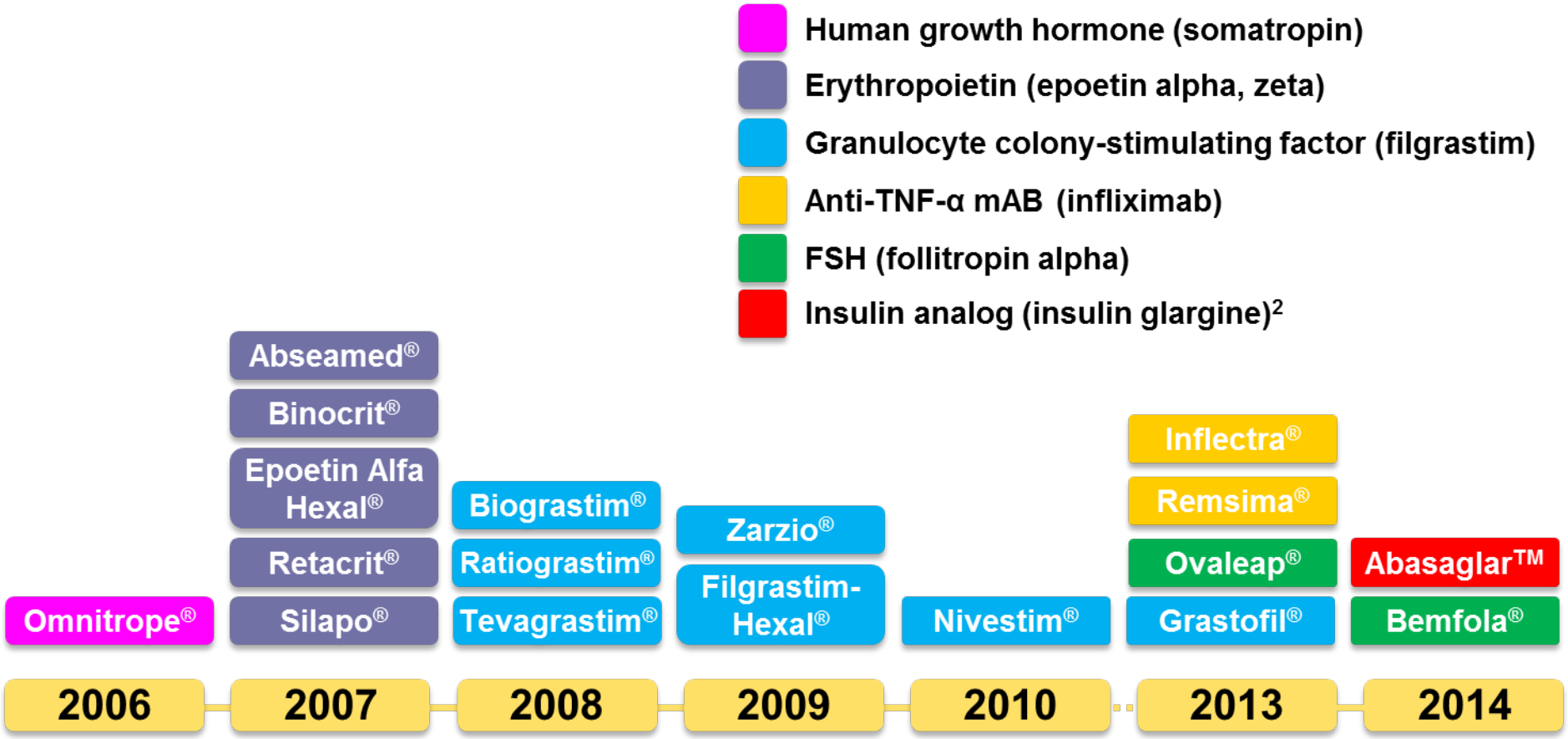
Biosimilar

- Higher molecular weight[1]
- Complex, heterogeneous structure[1]
- Unstable, sensitive to heat and shear[1,2]
- Mostly parenteral administration[2]

- Produced from living cells or organisms using biotechnology[1,2]
- Heterogeneous product that is difficult to standardize[2]
- Higher immunogenic risk[1,2]

1. Declerck PJ. *GaBI J* 2012;1:13-6
2. Sekhon BS and Saluja V. *Biosimilars* 2011;1:1-11

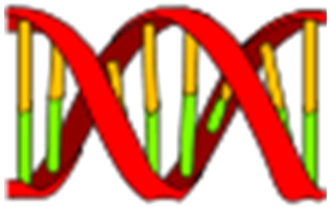
Overview of Approved Biosimilars in the EU[1]



1. http://goo.gl/x8LP6Z
2. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002835/smops/Positive/human_smop_000706.jsp&mid=WC0b01ac058001d127

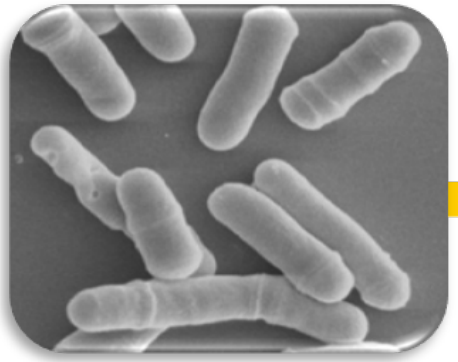
Typical Production Process of Insulin

Gene sequence



Expression vector

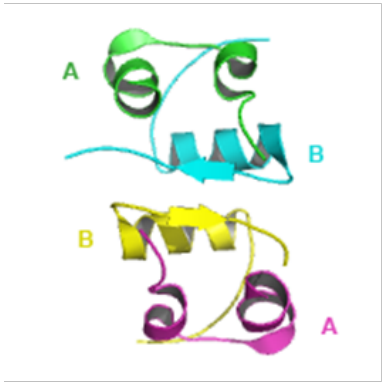
Host cell
(E. coli or yeast)



Fermentation/Culture
(upstream process)

Purification
(downstream process)

Final product
(*insulin*)



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
2. Mellstedt H et al. *Ann Oncol* 2008;19:411-9

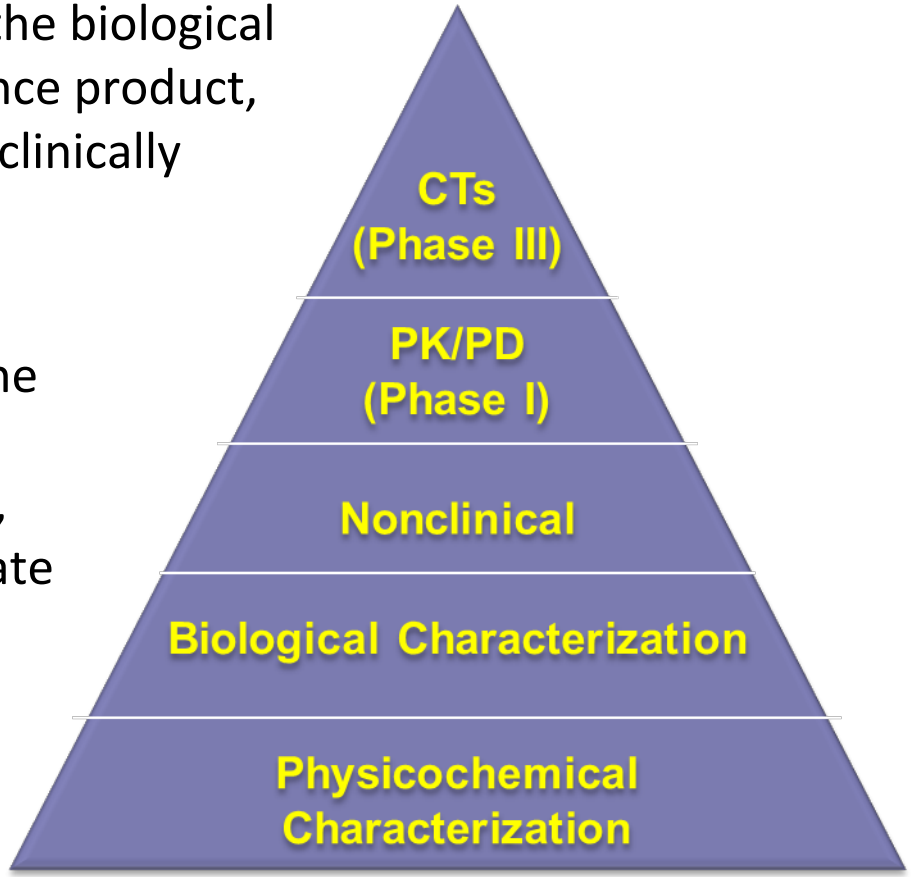
Biosimilars approved in the US and EU

- No biosimilars are currently approved in the US[1]
- Biosimilars were first introduced in Europe in 2006[2]
- The biosimilars currently approved in Europe belong to 6 product types[2,3]
  - Growth hormone (somatropin)
  - Erythropoietin (epoetin alfa, zeta)
  - Granulocyte colony-stimulating factor (filgrastim)
  - Monoclonal antibody (infliximab)
  - Follicle-stimulating hormone (follitropin alfa)
  - Long-acting insulin analog (insulin glargine)[3]

1. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241718.htm
2. http://goo.gl/x8LP6Z
3. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002835/smops/Positive/human_smop_000706.jsp&mid=WC0b01ac058001d127

Biosimilars Development Program[1,2]

- Analytical studies: Demonstrate that the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components
- Animal studies (eg, toxicology)
- A clinical study or studies (including the assessment of immunogenicity and PK or PD): Demonstrate safety, purity, and potency in one or more appropriate conditions of use for which reference product is licensed/intended to be used, for which licensure is sought for the biological product



1. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291134.pdf
2. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500144124.pdf

Regulatory Summary: Requirements for Biosimilarity[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[a]	✓

[a]Efficacy/safety trial needed unless biosimilarity convincingly demonstrated by nonclinical, pharmacology, and immunogenicity studies

1. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf
2. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500144124.pdf

LY2963016 immunogenicity and PK-PD

1. Evaluation of Immunogenicity of **LY2963016** Insulin Glargine Compared with Lantus® Insulin Glargine in Patients with Type 1 Diabetes Mellitus or Type 2 Diabetes Mellitus.

   Ilag LL, Deeg MA, Costigan T, Hollander P, Blevins TC, Edelman SV, Konrad RJ, Ortmann RA, Pollom RK, Huster WJ, Zielonka JS, Prince MJ.

   Diabetes Obes Metab. 2015 Oct 5. doi: 10.1111/dom.12584. [Epub ahead of print]

   PMID: 26434665

   Similar articles

2. Comparison of the Pharmacokinetics and Pharmacodynamics of **LY2963016** Insulin Glargine and European Union- and U.S.-Approved Versions of Lantus Insulin Glargine in Healthy Subjects: Three Randomized Euglycemic Clamp Studies.

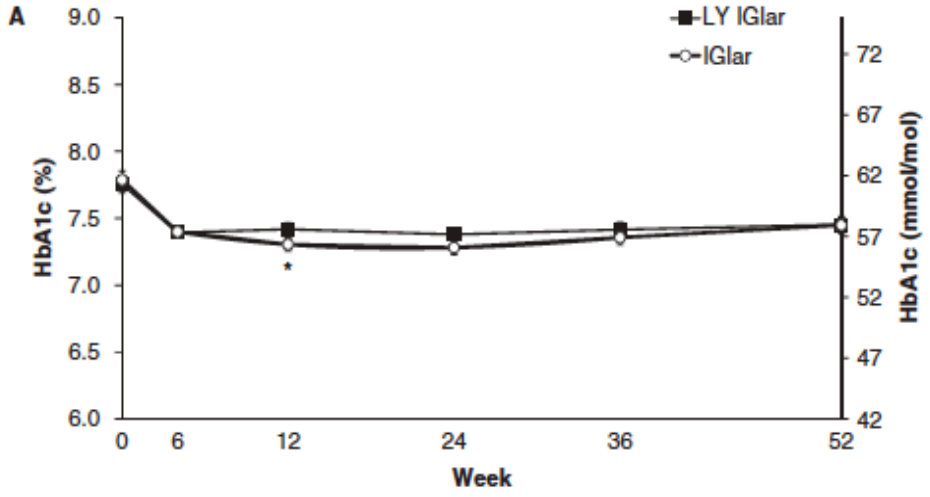
   Linnebjerg H, Lam EC, Seger ME, Coutant D, Chua L, Chong CL, Ferreira MM, Soon D, Zhang X.

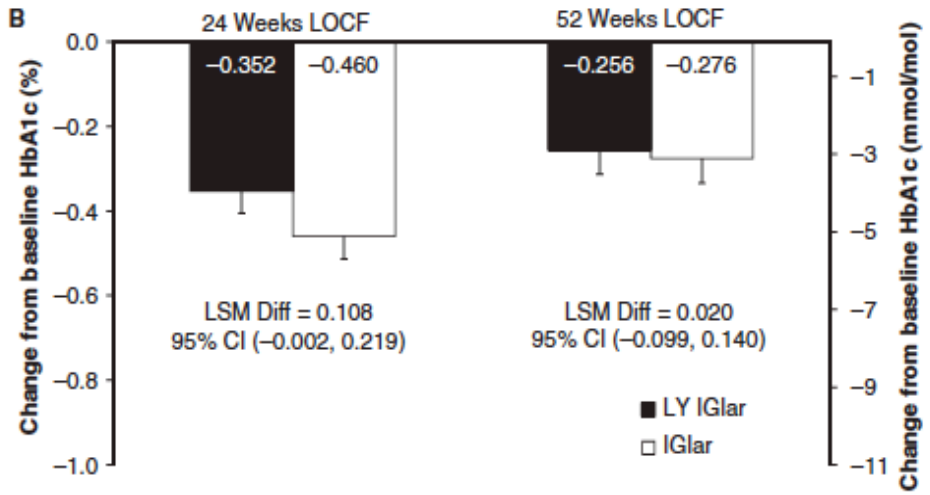
   Diabetes Care. 2015 Aug 25. pii: dc142623. [Epub ahead of print]

   PMID: 26307603

   Similar articles

Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus®) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study

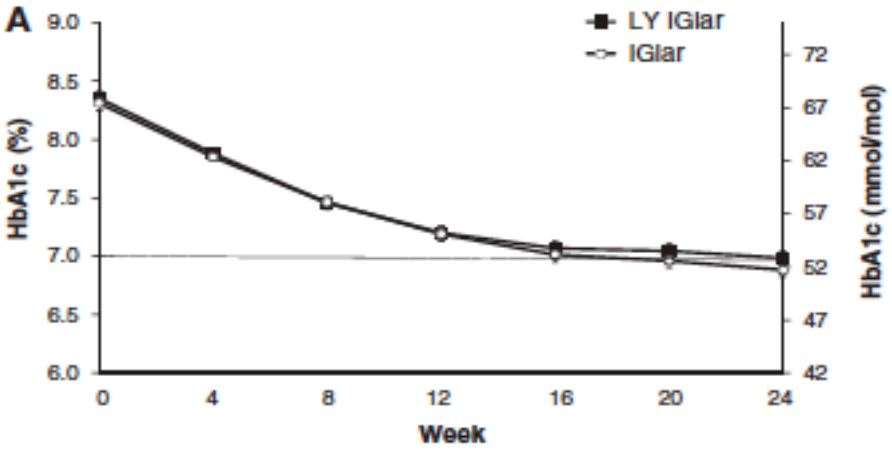


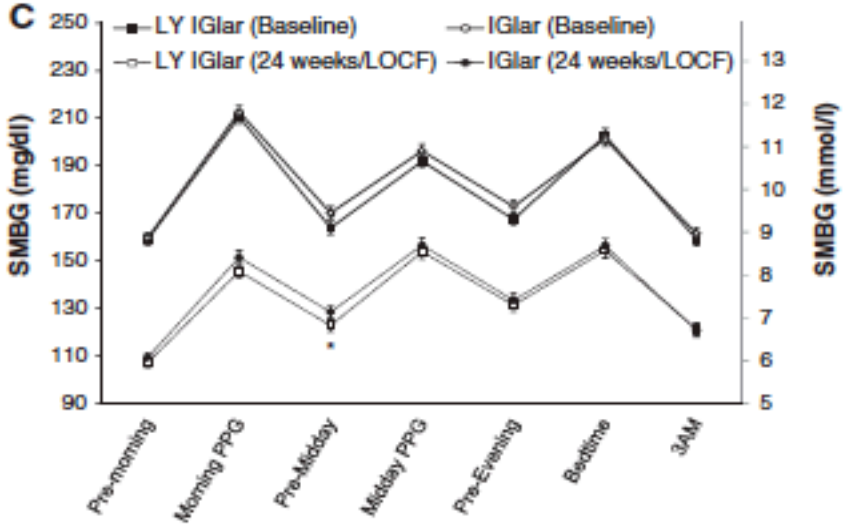


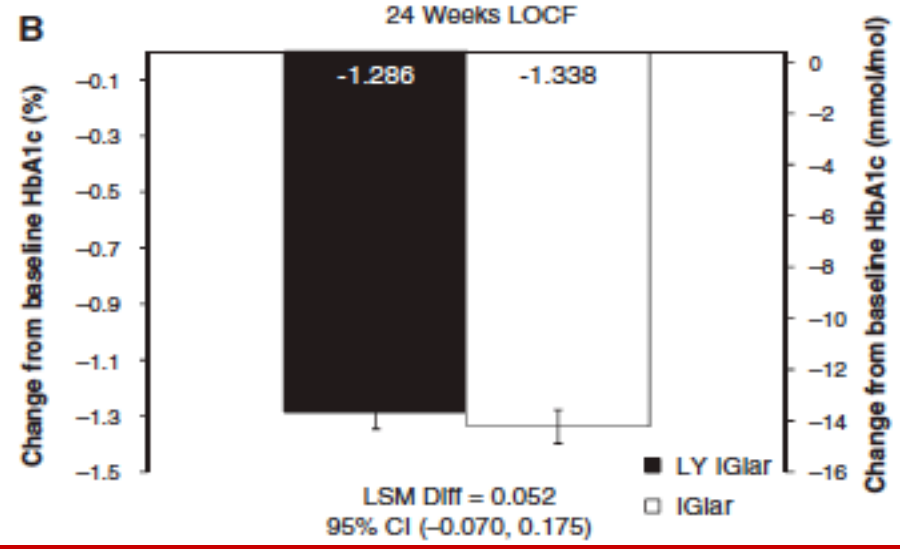
AEs*	LY IGlar	IGlar
Deaths	0 (0)	1 (<1)
SAEs	20 (8)	24 (9)
Discontinuations due to an AE	2 (1)	6 (2)
Injection site AE	7 (3)	3 (1)
AEs	167 (62)	166 (62)
AE possibly related to study drug	17 (6)	14 (5)
AE possibly related to study procedure	2 (1)	2 (1)
AE possibly related to study disease state (diabetes)	21 (8)	16 (6)
Special topic assessment of allergic reactions	20 (8)	11 (4)
Pruritus, rash, dermatitis, other†	7 (3)	4 (2)
Arthralgia, arthritis	4 (2)	5 (2)
Injection site (reaction, induration, nodule, swelling)	6 (2)	2 (1)
Drug hypersensitivity and hypersensitivity	1 (<1)	1 (<1)
Allergic respiratory symptom, asthma	2 (1)	0 (0)
Injection site reaction (patient questionnaires)	7 (3)	3 (1)
Pain	6 (2)	2 (1)
Pruritus	2 (1)	1 (<1)
Rash	2 (1)	1 (<1)

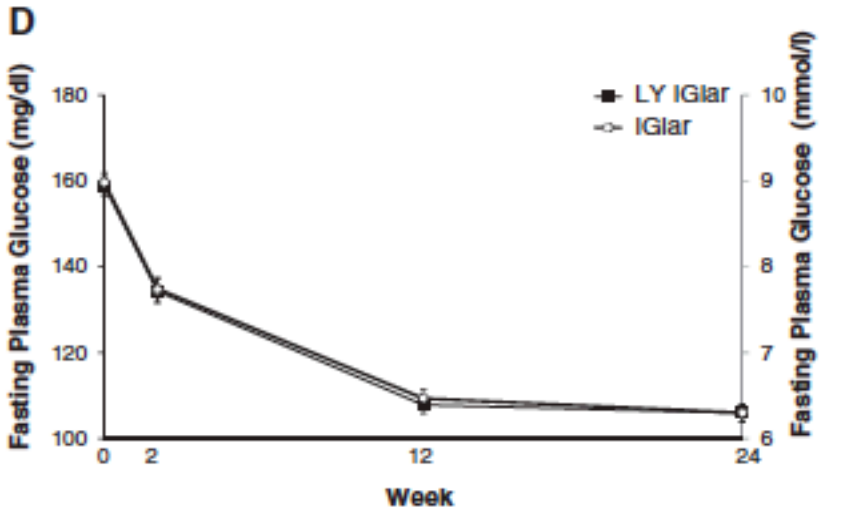
Blevins, DOM 2015

Similar efficacy and safety of LY2963016 insulin glargine and insulin glargine (Lantus®) in patients with type 2 diabetes who were insulin-naïve or previously treated with insulin glargine: a randomized, double-blind controlled trial (the ELEMENT 2 study)









Efficacy and safety in T2DM

	Insu LY I N =
HbA1c, %	
Endpoint HbA1c	6.86
Change from baseline	−1.4
LS mean difference (95% CI)	0.06
HbA1c, mmol/mol	
Endpoint HbA1c	51 ±
Change from baseline	−16
LS mean difference (95% CI)	0.7 (
Target HbA1c, n (%)	
<7% (<53 mmol/mol)	117
≤6.5% (≤48 mmol/mol)	65 (3
FPG†(change from baseline)	
mg/dl	−57
mmol/l	−3.1
Insulin dose, U/kg/day	0.42
Hypoglycaemia rate overall‡, mean ± s.d.	
Total	21.6
Nocturnal§	6.7 ±
Severe	(n =
Weight change, kg	2.0 ±

AEs*	LY IGlar N = 376†	IGlar N = 380†
Deaths	1 (<1)	1 (<1)
SAEs	15 (4)	18 (5)
Discontinuations due to an AE	6 (2)	11 (3)
Injection site AE	13 (4)	11 (3)
AEs	196 (52)	184 (48)
AE possibly related to study drug	26 (7)	23 (6)
AE possibly related to study procedure	6 (2)	8 (2)
AE possibly related to study disease state (diabetes)	19 (5)	18 (5)
Special topic assessment of allergic reactions	21 (6)	27 (7)
Pruritus, rash, dermatitis, other‡	8 (2)	12 (3)
Arthraglia, periarthritis	7 (2)	9 (2)
Injection site (reaction, pruritis, induration)	5 (1)	4 (1)
Asthma, nasal oedema	3 (1)	5 (1)
Injection site reaction (patient questionnaires)	13 (4)	11 (3)
Pain	10 (3)	5 (1)
Pruritus	4 (1)	4 (1)
Rash	3 (1)	3 (1)

Rosenstock, DOM 2015

Biosimilar: Conclusions (1 of 2)

- Biosimilars
  - Are therapeutic protein molecules that should have an identical amino acid sequence to that of a previously marketed product, with no clinically meaningful difference in safety or efficacy
  - Are not generics; they are similar but not the same
  - Provide valuable options that create choice for prescribers and patients
- Biosimilar manufacturing quality matters
  - Manufacturing processes that may influence quality and/or immunogenicity of biological products include protein production, purification, formulation, and storage and handling

Biosimilar: Conclusions (2 of 2)

- To comply with regulatory guidelines, in comparison to the reference product, a biosimilar medicine must demonstrate
  - In vitro and in vivo nonclinical characteristics similar to the reference product
  - Similar PK and PD within predefined regulatory acceptance limits
  - No clinically meaningful difference in efficacy (eg, based on noninferiority studies)
  - No clinically meaningful differences in drug-related AEs and immunogenicity
- Currently, there are 18 biosimilar products available in the EU;however, no biosimilar products are approved so far in the US
- Biosimilar pricing may affect patient acceptance directly (out of pocket expense) and indirectly (via preferred prescription formulary status)
- Insulin glargine biosimilar complies with the regulatory demands of EMA and may be safely and effectively used in patients with DM


«Io ne ho viste cose che voi umani non potreste immaginarvi: navi da combattimento in fiamme al largo dei bastioni di Orione, e ho visto i raggi B balenare nel buio vicino alle porte di Tannhäuser.
E tutti quei momenti andranno perduti nel tempo, come lacrime nella pioggia.
È tempo di morire. »
s@ffidoc