Basal Insulin: Efficacy and Safety

SPED Mayo 28, 2017

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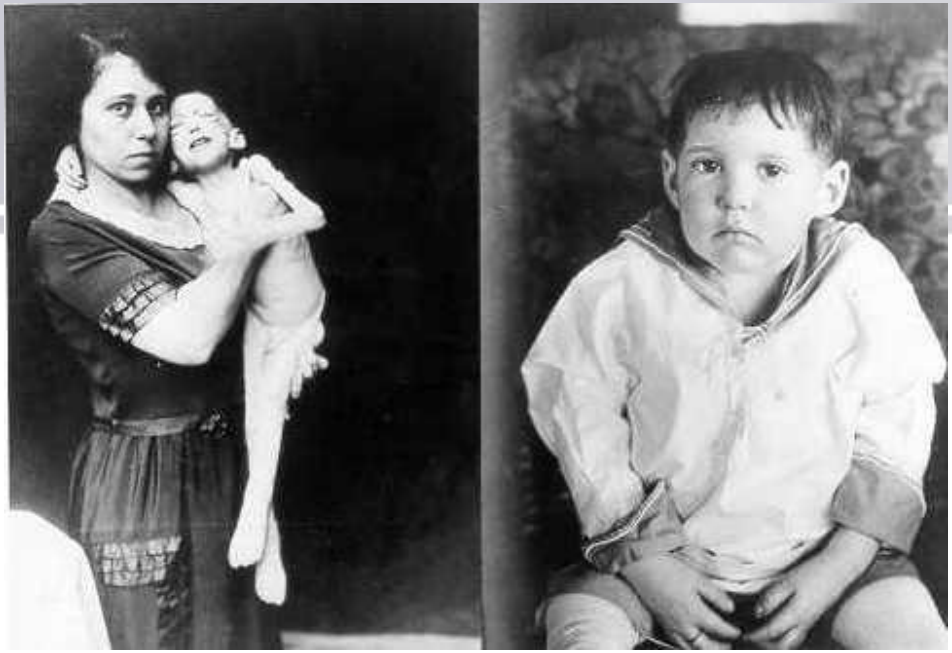
NO FINANCIAL DISCLOSURES TO REPORT

Learning Objectives:

- Apply Key, clinically relevant data derived from pivotal trials of new and emerging basal insulin products.
- Identify the potential place in therapy for new basal insulins
- Identify how these indication compare to those of the previously available basal insulins.

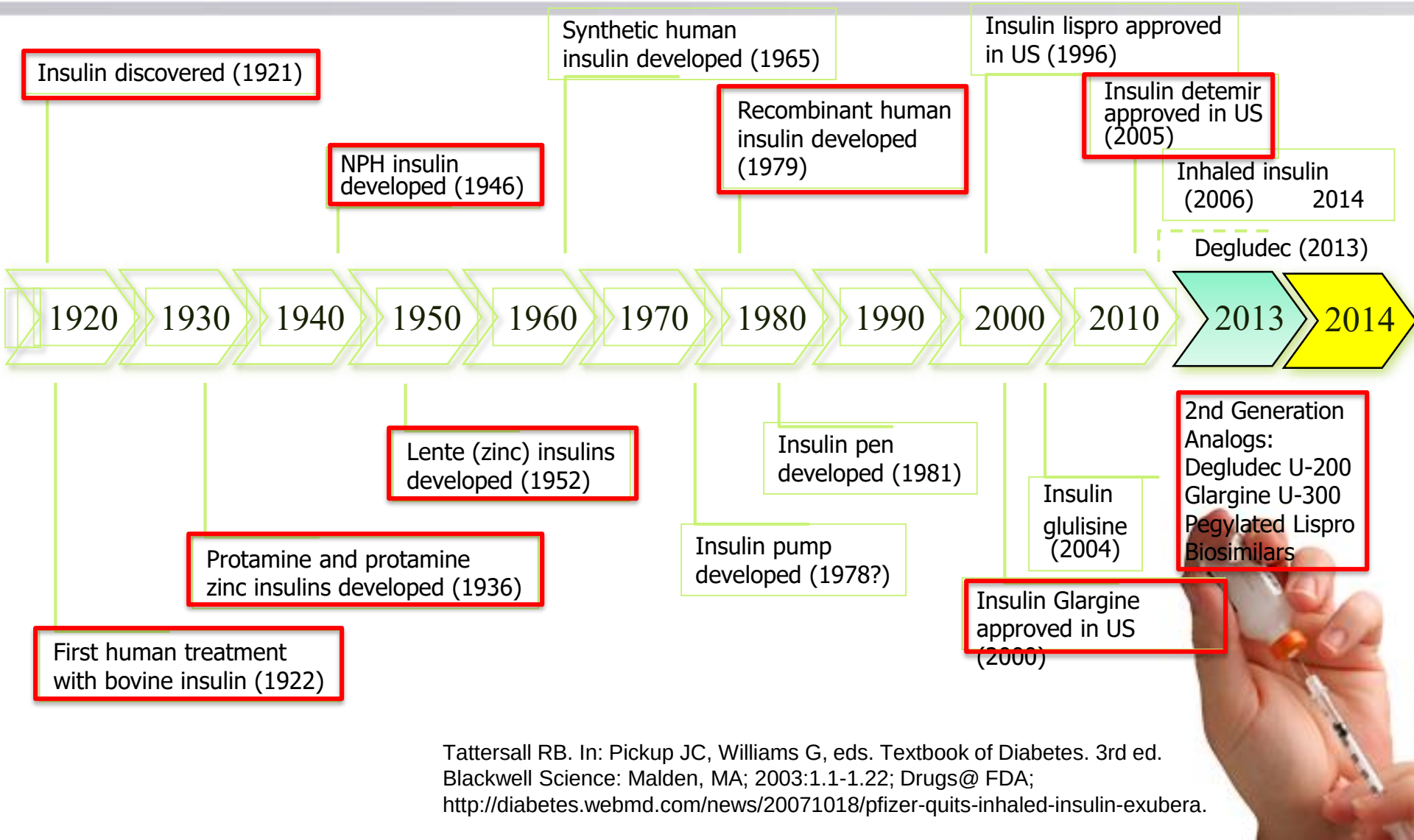
Before Insulin



JL Before Insulin and 2 months later

- Before insulin was discovered in 1921, everyone with type 1 diabetes died within weeks to years of its onset.
- Remains the most effective treatment controlling blood glucose levels in type 1 diabetes but also in type 2.

Milestones in Insulin Development



Tattersall RB. In: Pickup JC, Williams G, eds. Textbook of Diabetes. 3rd ed. Blackwell Science: Malden, MA; 2003:1.1-1.22; Drugs@ FDA; http://diabetes.webmd.com/news/20071018/pfizer-quits-inhaled-insulin-exubera.

Many Challenges with use of Basal Insulin

Provider

- Knowledge of new & old basal insulins
- Selection of the appropriate basal insulin
- Balancing control vs risk of hypoglycemia
- Time to address patient issues or fears with insulin use
- Prescribing / dispensing errors

Patient

- Fears of Injections, fears of hypoglycemia and fears to insulin
- Appropriate administration techniques
- Complexity of the regiment
- Cost
- Ability to problem solves issues with their regimen

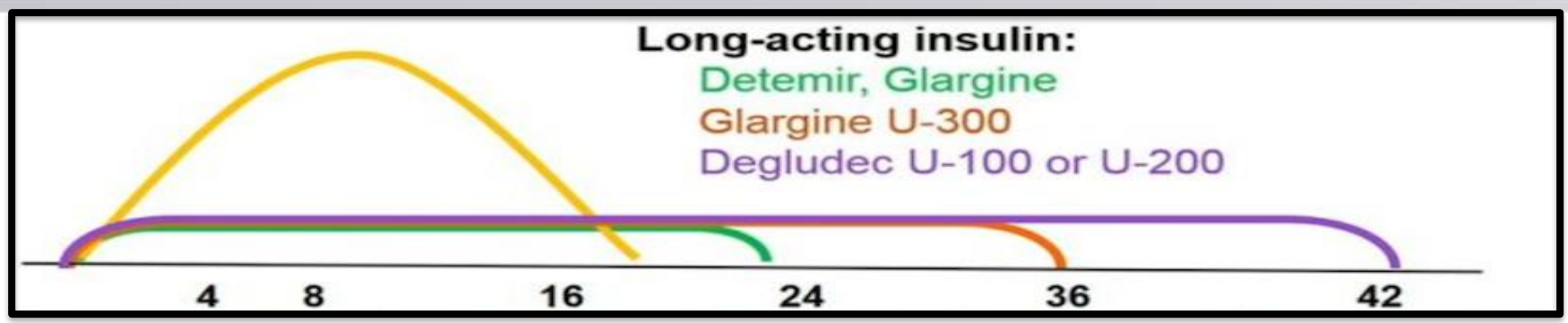
Desired Characteristics of Replacement Basal Insulin

- Mimics natural pancreatic basal insulin secretory pattern
- No distinct peak effect
- Continued effect over 24 hours
- Minimizes risk of nocturnal hypoglycemia
- Administered once daily for optimal patient adherence
- Reliable absorption pattern

Ultra – Long Basal Insulin: Place in Therapy

- Patients who need a better basal insulin, often include people with:
  - Nocturnal hypoglycemia or overall hypoglycemia
  - Shift workers
  - Complaints of variability of glucose levels
  - Patients with adherence issues
  - Split Basal Insulin user (~ 10 to 20% of patients)
  - Large Basal user (>50 units / day), Small Basal user (< 10 units / day)

Basal Insulins

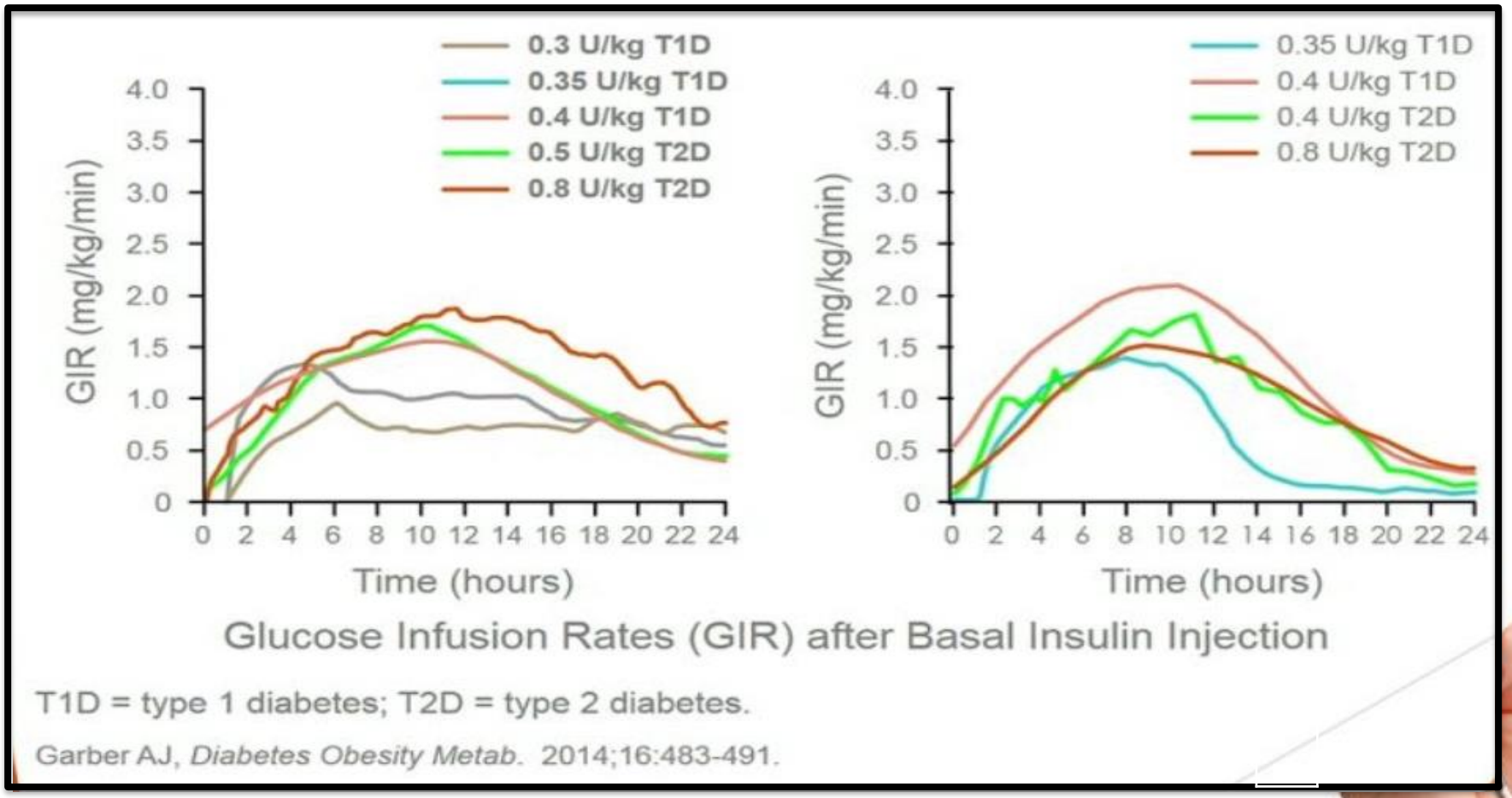


Insulin Type	Product	Onset	Peak	Duration
Human NPH	Humulin N Novolin N	1.5 to 4 hrs	4 -12 hrs	Up to 24 hrs
Detemir Glargine	Levemir Lantus/ Basaglar	45 min to 4hrs	Minimal peak depending on the Dose	Up to 22 hrs
Glargine U – 300	Tougeo	- 6hrs		Up to 36 hrs
Degludec U-100 or U-200	Tresiba	1 hr		Up to 42 hrs

Pharmacodynamics Profiles of Basal Insulin Analogs Glargine U – 100 & Detemir

Glargine

Detemir



Glucose Infusion Rates (GIR) after Basal Insulin Injection

T1D = type 1 diabetes; T2D = type 2 diabetes

Garber AJ, Diabetes Obesity Metab, 2014; 16:483-491

Variability of Effect

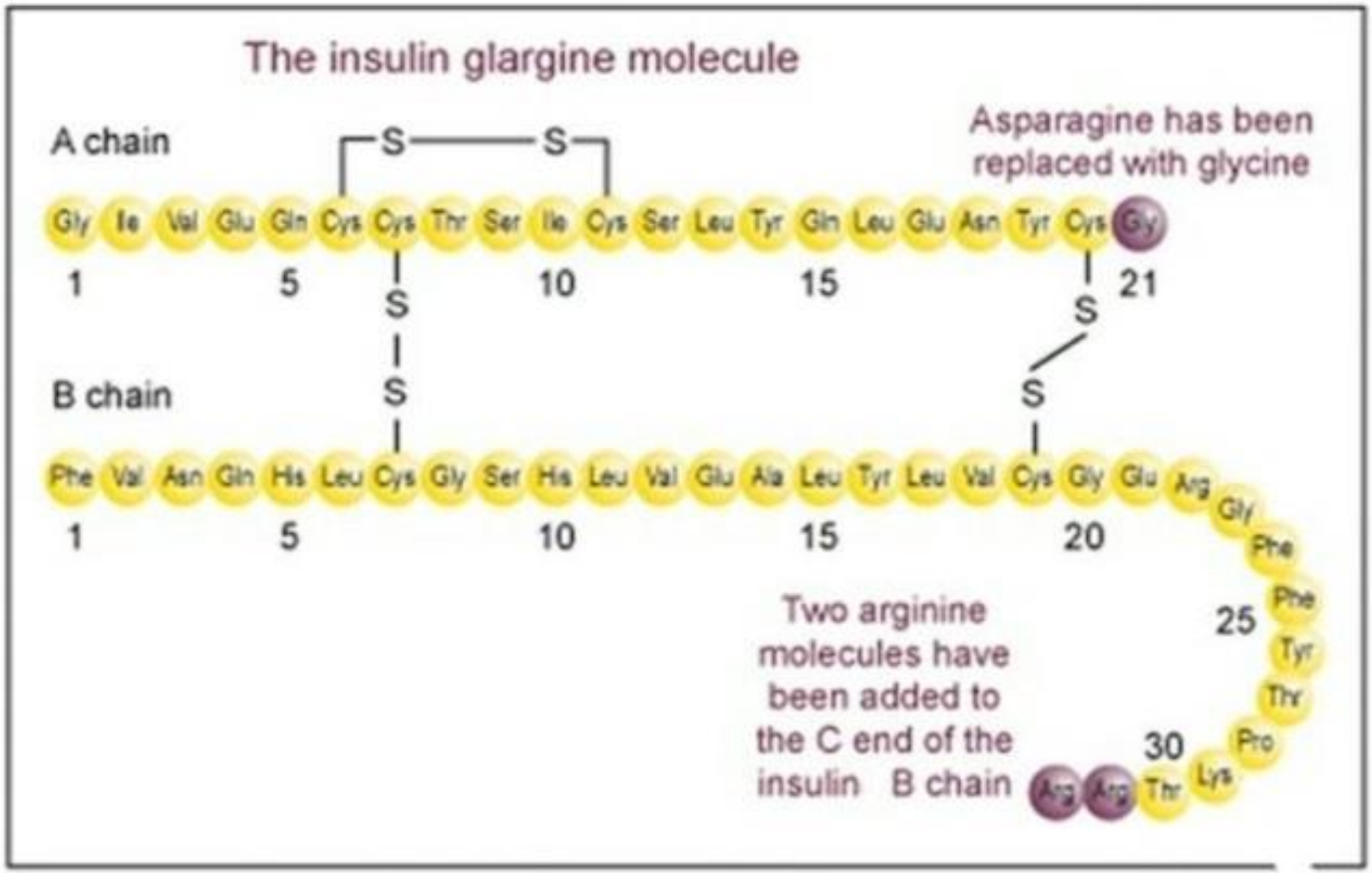
- Variability in effects of an insulin can cause unexplainable variations in glucose control from day to day

Insulin	Within Subject Variability (CV% of AUC GIR)
NPH	68
Glargine U-100	48-99
Detemir	27
Glargine U-300	34.8
Degludec	20

Adapted from: Rossetti P, et al. Diabetes Obes Metab, 2014: 16:695-706;Becker RHA, et al. Diabetes Obes Metab, 2015: 17:261-7

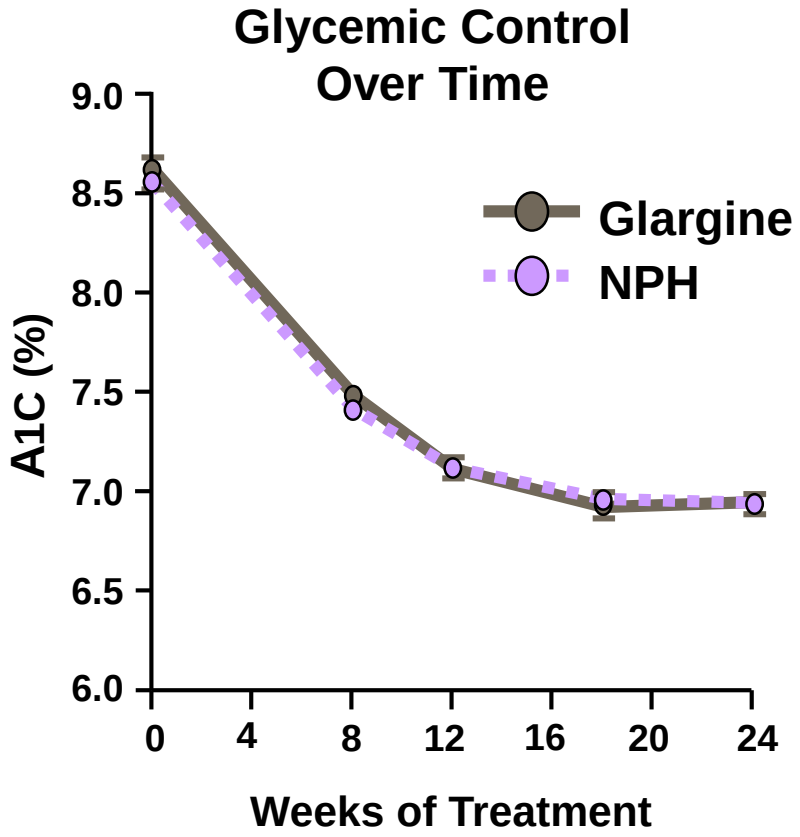
Glargine Molecule

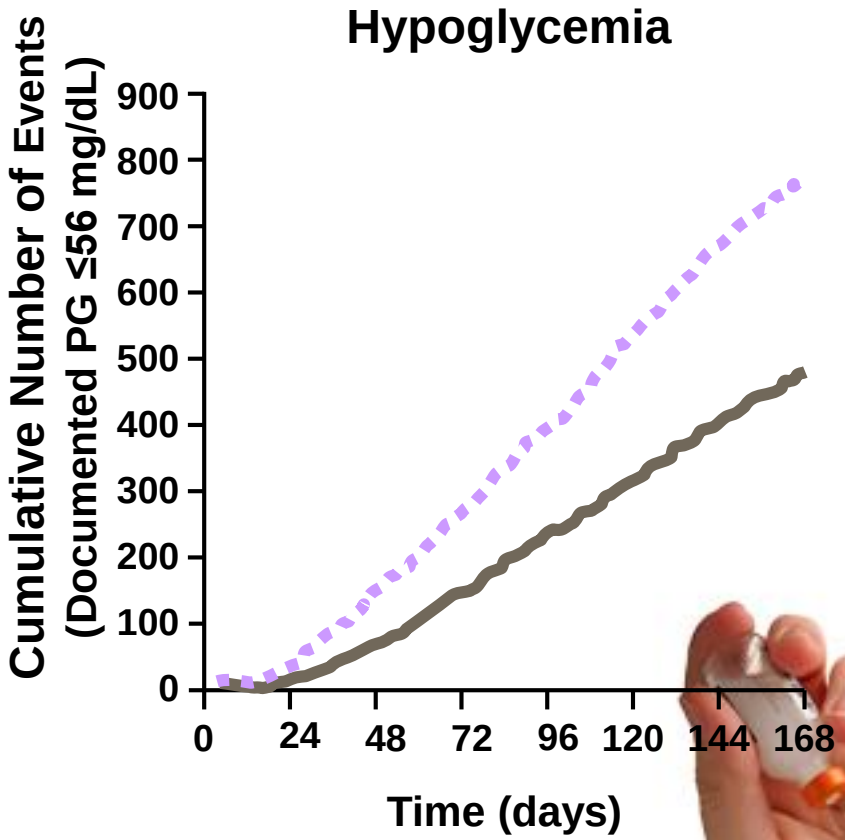
- **Soluble at pH = 4.0 in vial or pen**
- **Forms precipitate at ph = 7.4**



Addition of Basal Insulin to Oral Therapy
Treat-to-Target Trial

756 Patients with Type 2 Diabetes on 1 or 2 Oral Agents

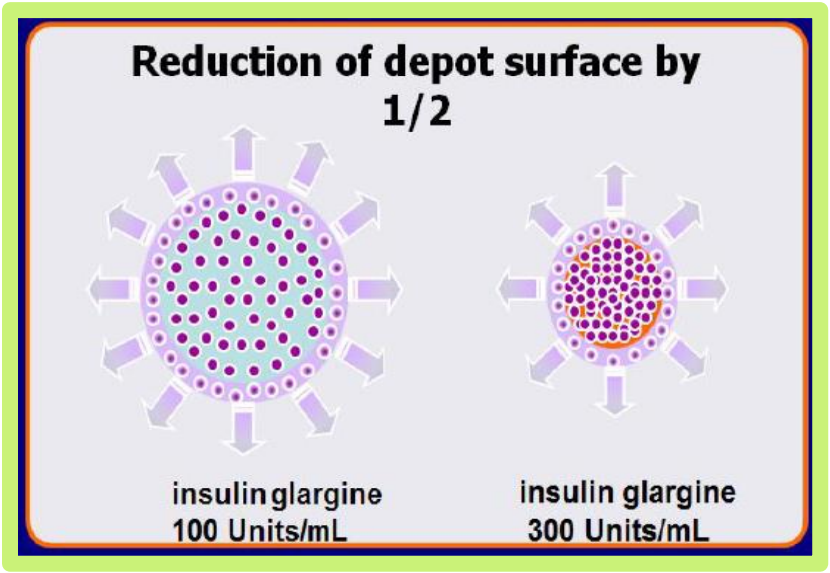


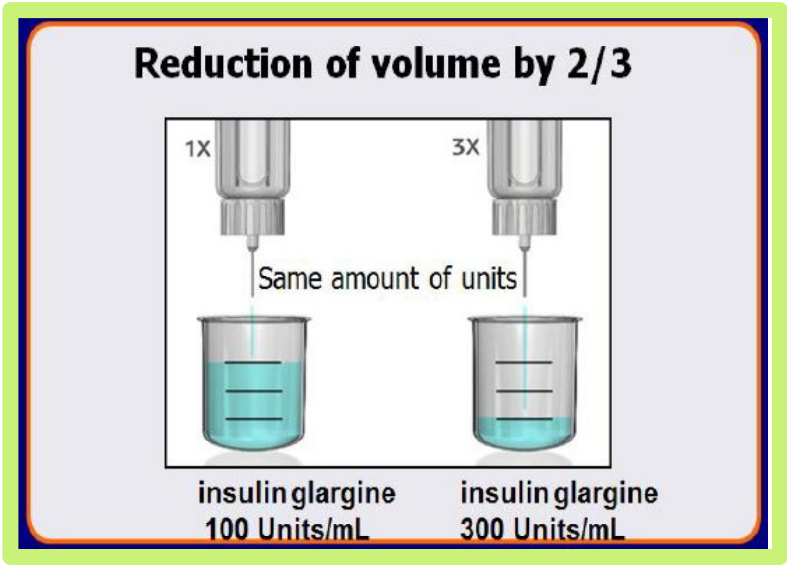


Abbreviations: NPH, neutral protamine Hagedorn; PG, plasma glucose.

With permission from Riddle MC, et al. *Diabetes Care*. 2003;26:3080-3086.

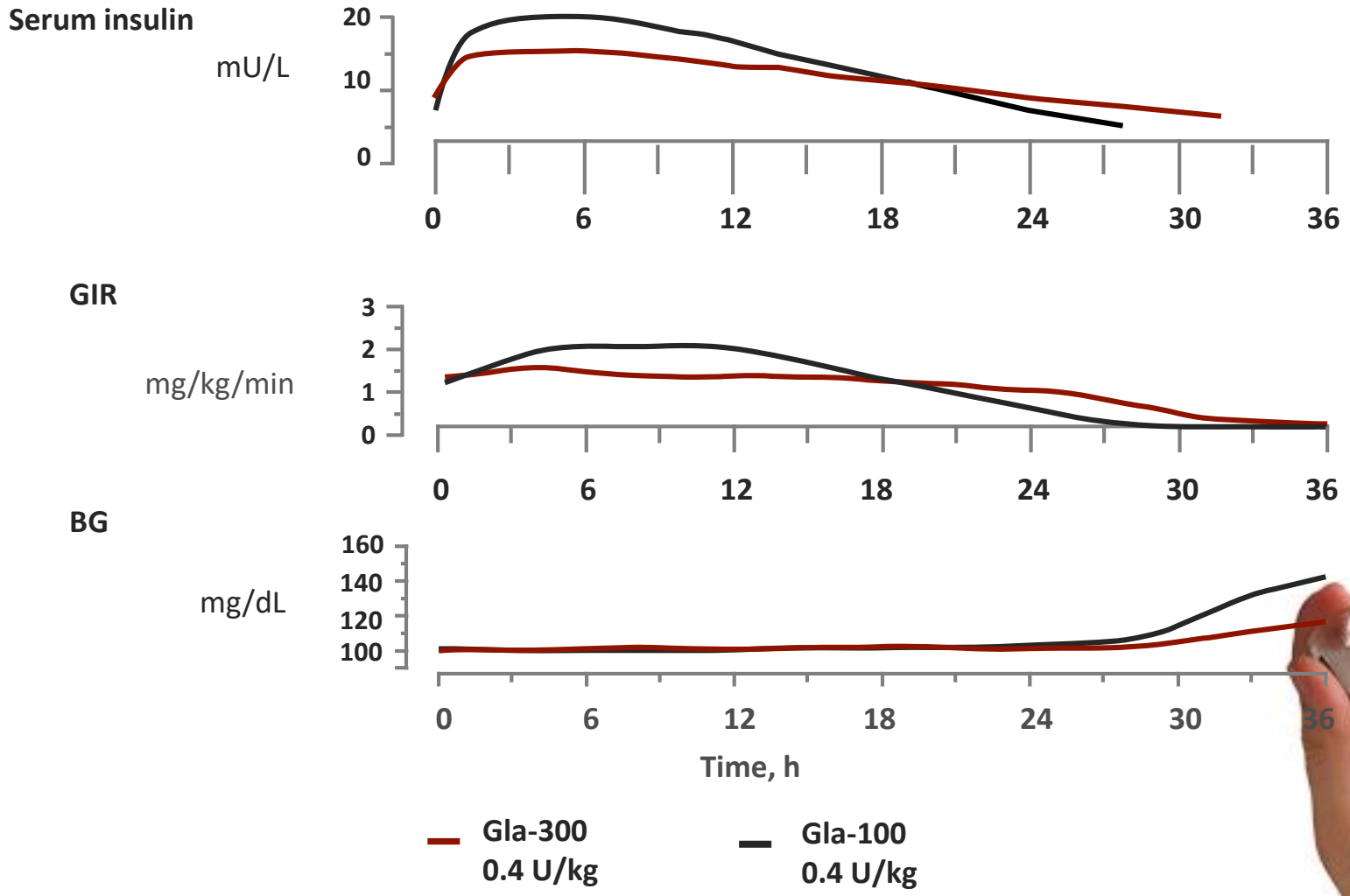
U – 300 Glargine has 2/3 less Volume than U – 100 Glargine





- Three – fold more concentrated formulation of glargine
- Reduced volume (1/3) and reduced surface area (1/2) of subcutaneous depot
- Slower and more constant rate of absorption

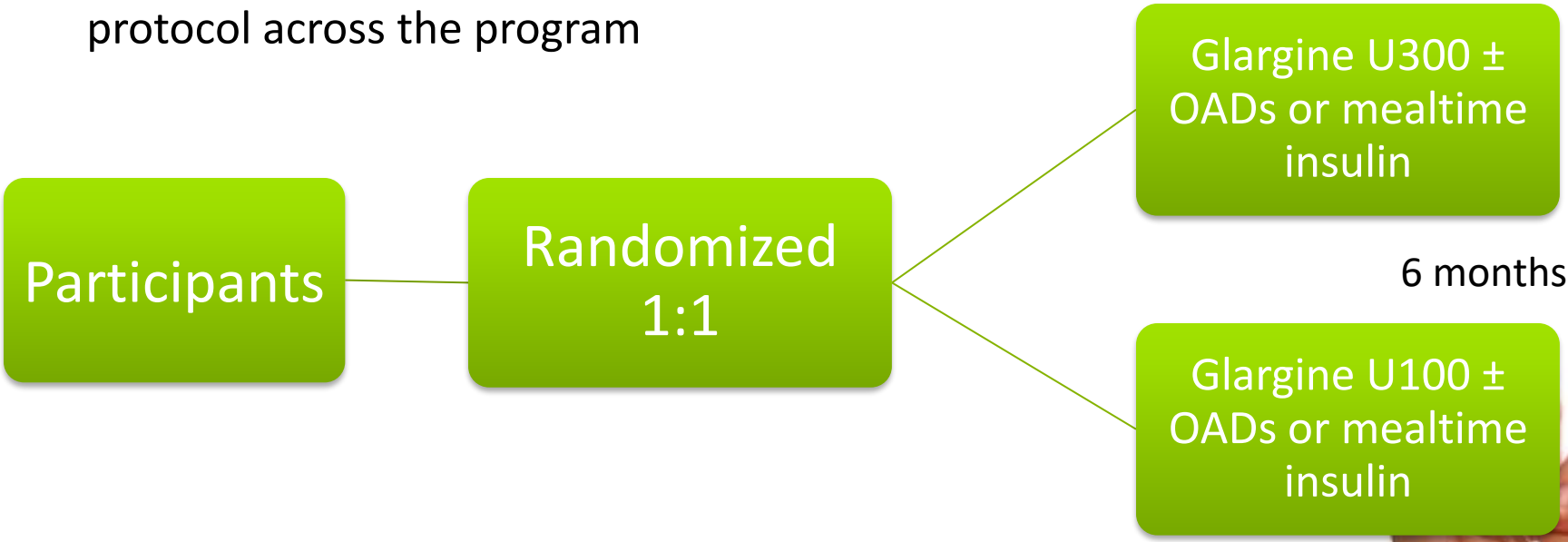
Pharmacodynamic of Glargine U-300 versus U-100 in Clamp Studies in T1D After 8 Days of Treatment



Becker RH, et al. *Diabetes Care*. 2015;38:637-643.

EDITION studies Glargine U300 vs U100 design was consistent across all 4 trials

- Randomized 1:1, open – label, parallel – group, multinational study
- The EDITION clinical studies had a similar design and titrate – to – target protocol across the program



- Primary endpoint: No inferiority of Glargine U300 to Glargine U100 in A1C reduction

Summary of Edition Trials

	T1DM		T2DM					
	Edition 4		Edition 1		Edition 2		Edition 3	
	Previously on basal and mealtime insulin regimen		Previously on basal and mealtime insulin +/- metformin		Previously on basal Insulin + OADs		Insulin-Naïve + OADs	
	With mealtime insulin analog		With mealtime insulin analog +/- metformin		With non-insulin antidiabetic drugs			
	U-300 Glargine	U-100 Glargine	U-300 Glargine	U-100 Glargine	U-300 Glargine	U-100 Glargine	U-300 Glargine	U-100 Glargine
Patients Treated (n)	273	273	404	400	403	405	432	430
Mean baseline A1C (%)	8.13	8.12	8.13	8.14	8.27	8.22	8.49	8.58
Mean Change A1C at 26 weeks (%)	-0.40	-0.44	-0.90	-0.87	-0.73	-0.70	-1.42	-1.46
Incidence of Severe Hypoglycemia	6.6%	9.5%	5%	5.7%	1.0%	1.5%	1.0%	1.0%
Incidence of documented symptomatic hypoglycemia	68%	69.8%	37%	41%	20.6%	26.8%*	8%	14%*
Mean Baseline FPG (mg/dL)	186	199	157	160	149	142	179	184
Mean FPG change from baseline (mg/dL()	-17	-20	-29	-30	-18	-22	-61	-68

Statistically Significant $p < .05$ Hypoglycemia < 54 mg/dL

Edition Trials Nocturnal Hypoglycemia: Percent Reduction in U300 vs U100 Glargine

Edition 4 T1DM on Basal Bolus	Edition 1 T2DM Previously on Basal Bolus	Edition 2 Previously on Basal Insulin + OAD	Edition 3 Insulin Naive plus OAD
10%	21%*	23%*	11%

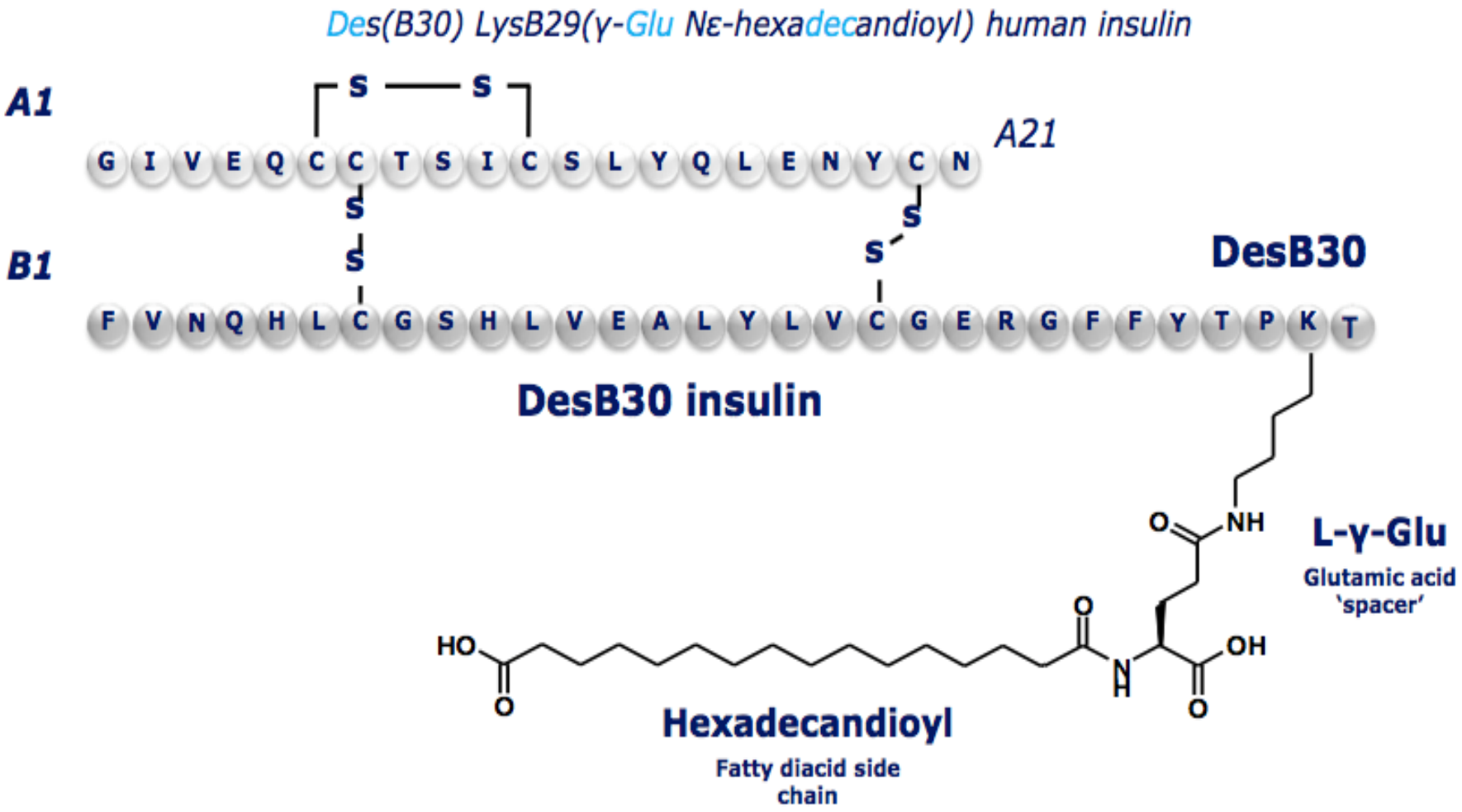
* Statistically Significant p<.05

EDITION Trials Summary

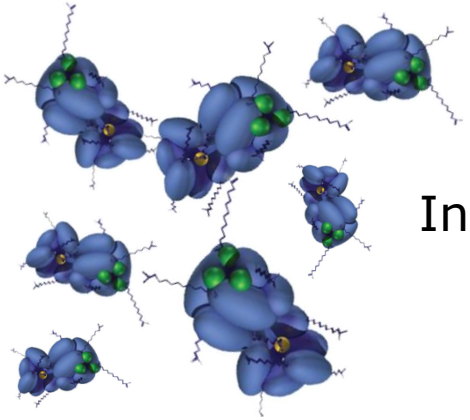
- Efficacy
  - Insulin glargine U300 achieved comparable glycemic control to insulin glargine U100 in patients with T1DM and T2DM
- Safety
  - Less, or comparable, nocturnal hypoglycemia with insulin glargine U300 vs U100
  - Comparable hypoglycemia at any time of day with insulin glargine U300 vs U100
- Comparable, or lower, weight gain with insulin U300 vs U100
- Higher dose with insulin glargine U300 vs U100 by the end of 6 month studies

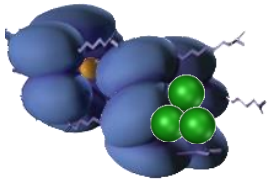
Riddle MC, et al. Diabetes Care. 2014;27:2755-2762; Yki-Jarvinen H, et al. Diabetes Care. 2014;37:3235-3243; Bolli GB, et al. Diabet Obes. Metab. 2015; Home PD, et al. Diabetes 2014;63(Suppl1):LB19(abstr 80-LB); Ritzel RA et al Diabetologia 2014;57(Suppl 1):S394-395

Degludec Molecule



Insulin Degludec
Multi – Hexamer formation after injection





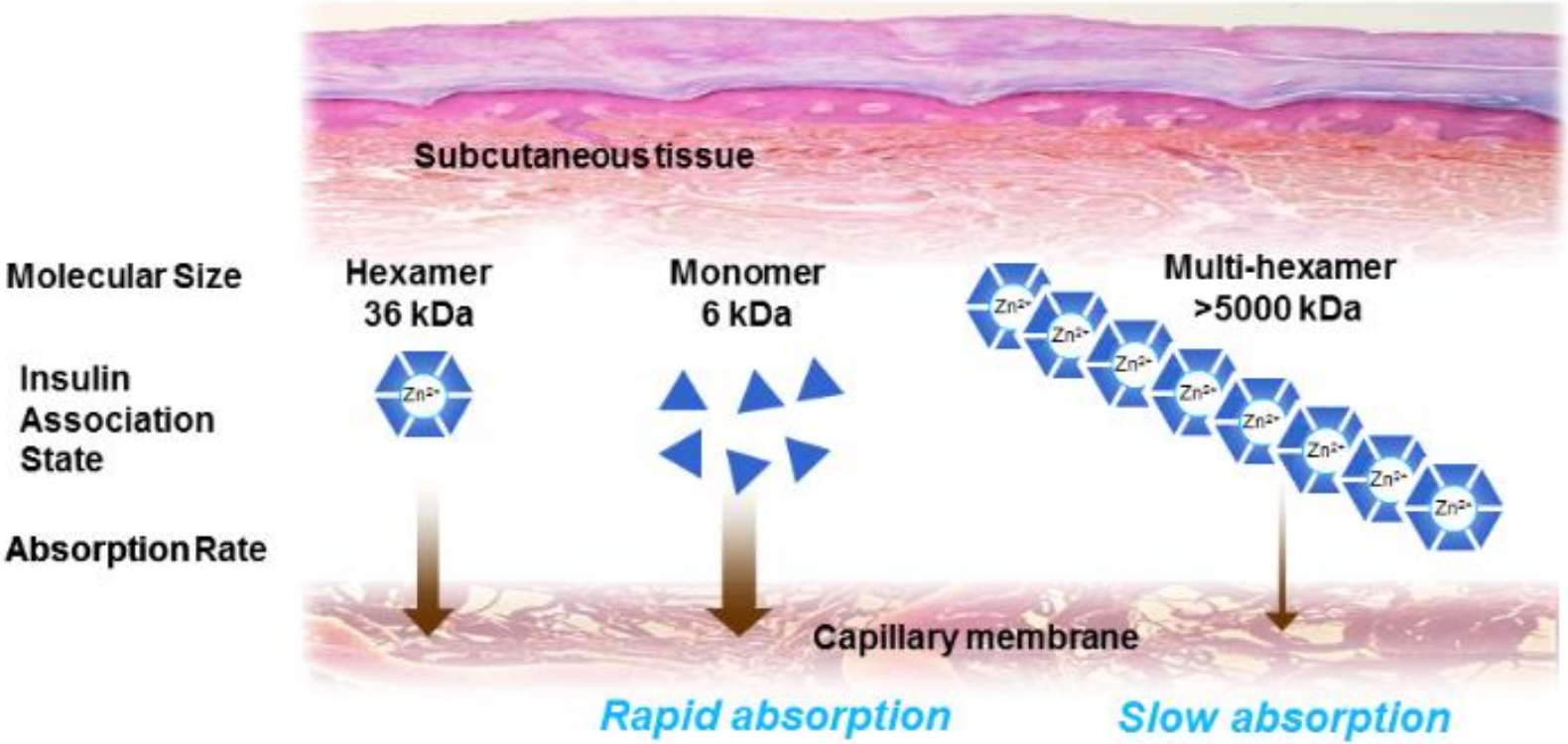
Phenol Zn^{2+}

Insulin degludec injected

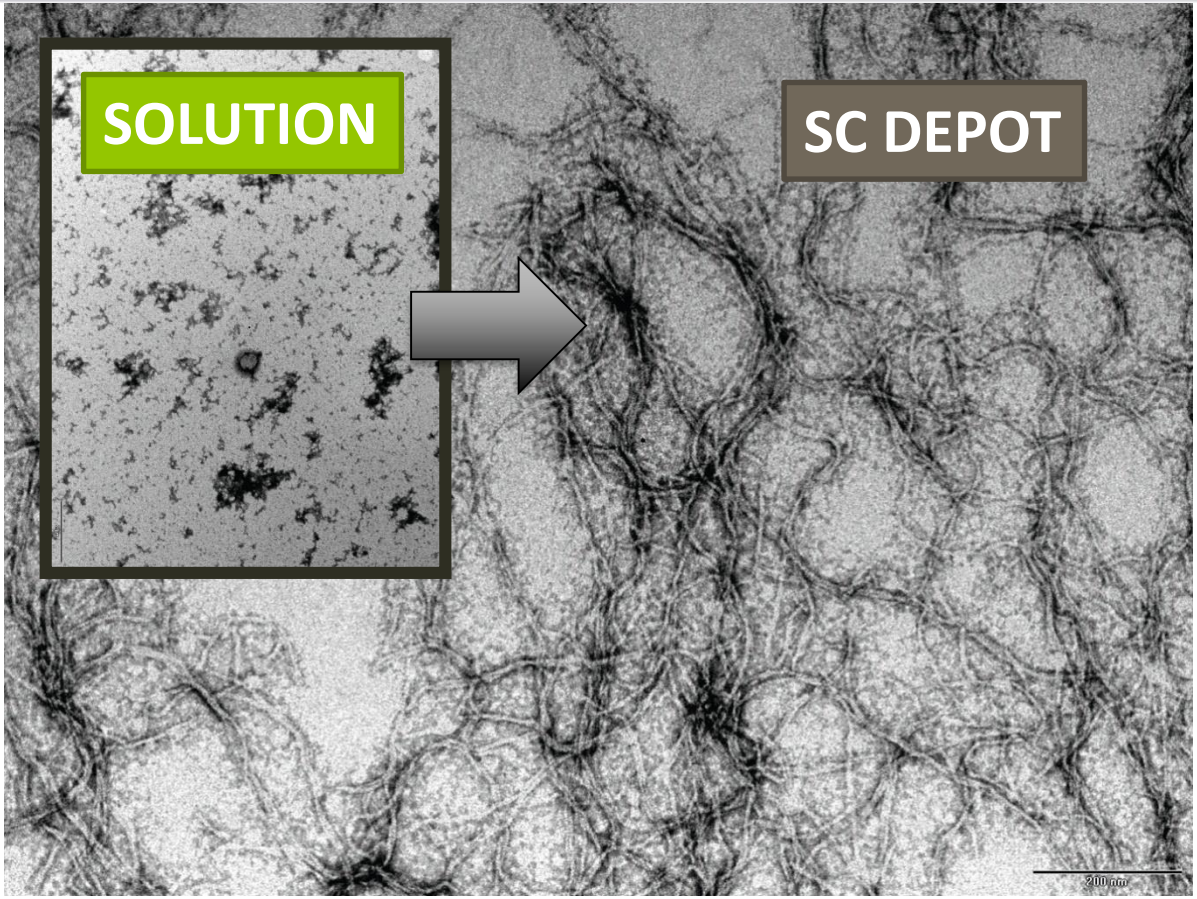
As phenol from the vehicle diffuses degludec hexamers link up via single side-chain contacts

Long multi-hexamers assemble

Insulin Degludec
Multi – Hexamer formation after injection



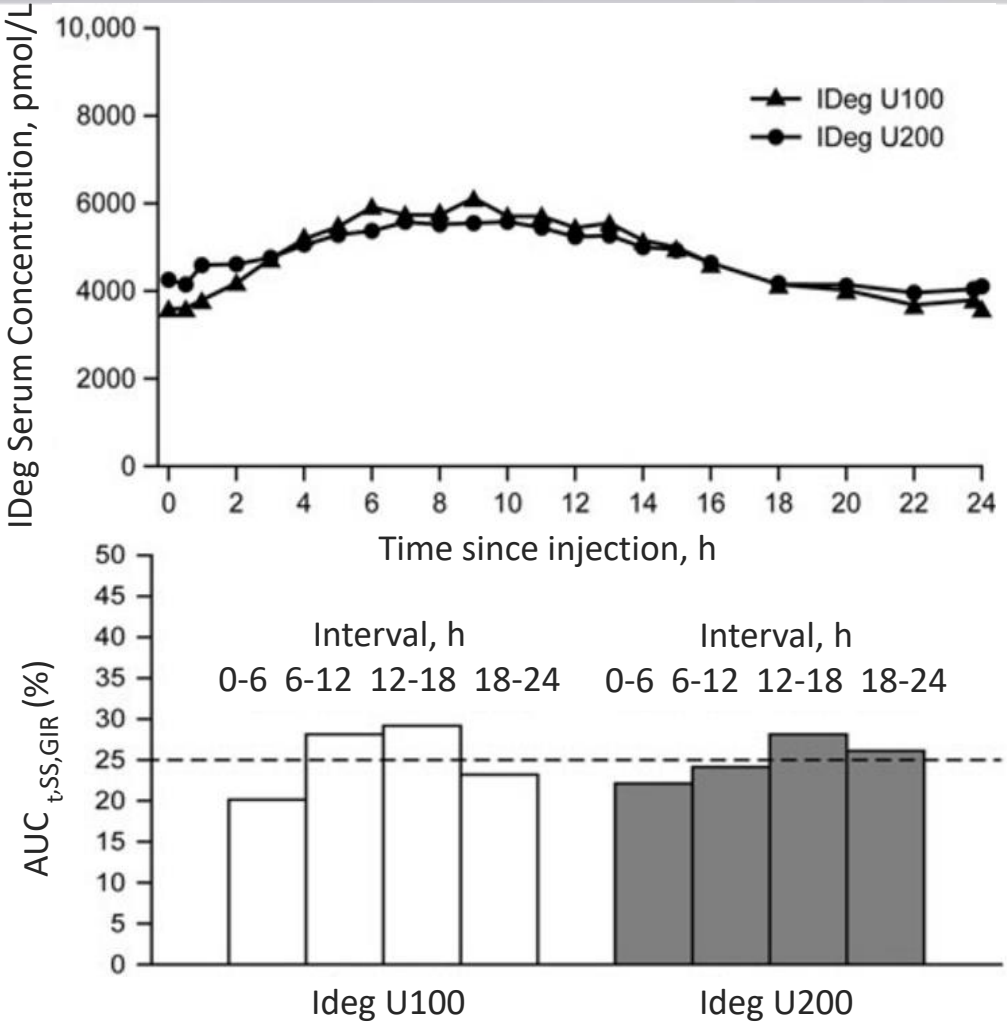
Insulin degludec multi-hexamers visible with transmission electron microscopy



Main picture shows elongated insulin degludec structures in absence of phenol; inset shows absence of elongated insulin degludec structures in presence of phenol

Kurtzhals *et al*. *Diabetes* 2011;60(Suppl . 1):LB12 (Abstract 42-LB) (NN1250-1993 + MOA)

PK/PD Profile of U200 Degludec Is Bioequivalent to U100 Degludec

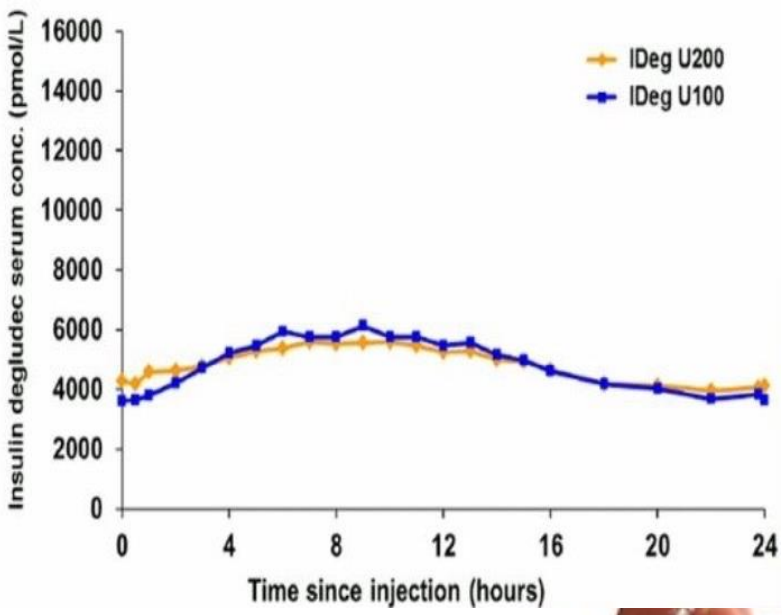


- 8-day crossover euglycemic clamp study comparing PK profile of U100 to U200 IDeg at 0.4 U/kg in patients with T1D (n = 33) showed flat, stable PK/PD profiles for both insulin concentrations

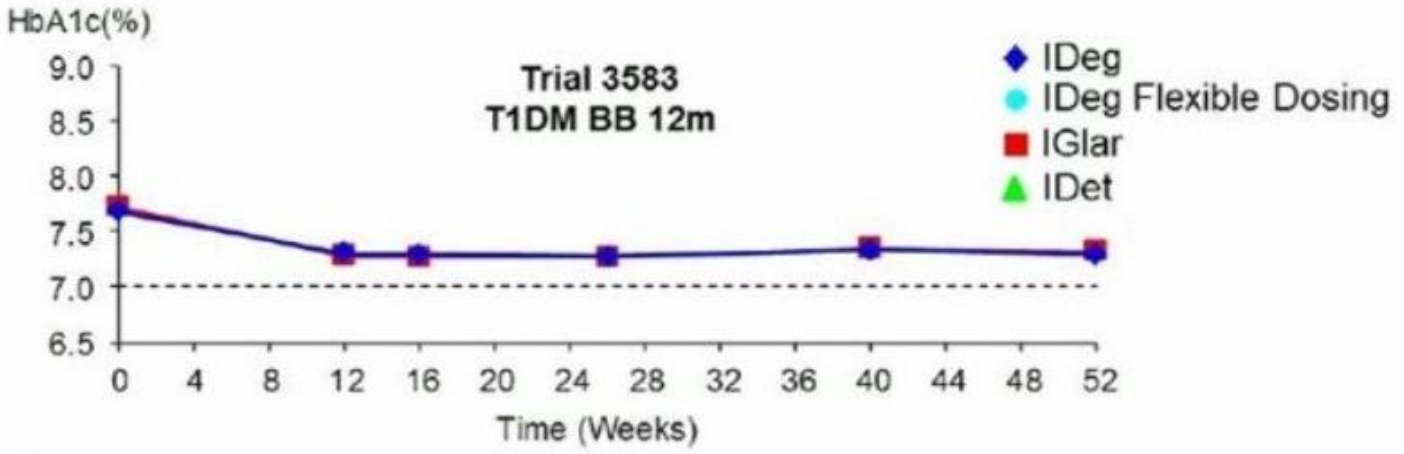
Korsatko S, et al. *Clin Drug Investig*. 2013;33:515-521.

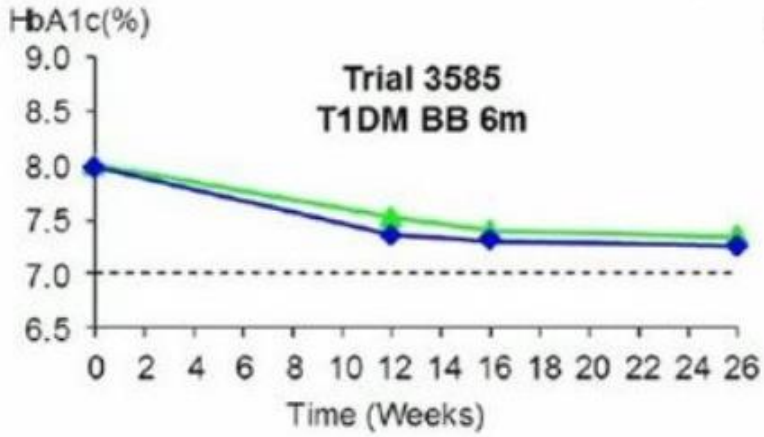
BEGIN Trials Degludec vs Glargine U-100

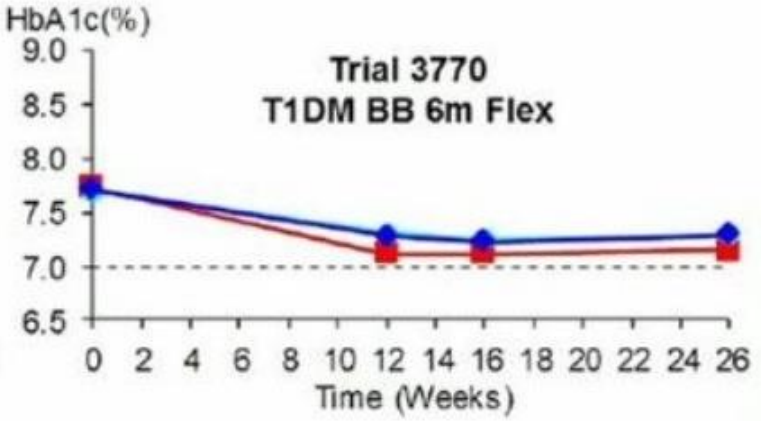
- Flat time – action profile in type 1 diabetes at steady state in 33 subjects
- Degludec longer duration of action & four – fold lower variability than Glargine
- Similar A1C reduction with less hypoglycemia than Glargine

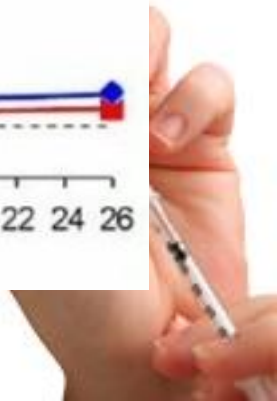


Mean HbA1c (%) by Treatment Week – Degludec T1DM Trials









Summary of Insulin Degludec U – 100 vs Glargine U – 100 BEGIN Basal – Bolus T1DM Long 104 – Wk Results

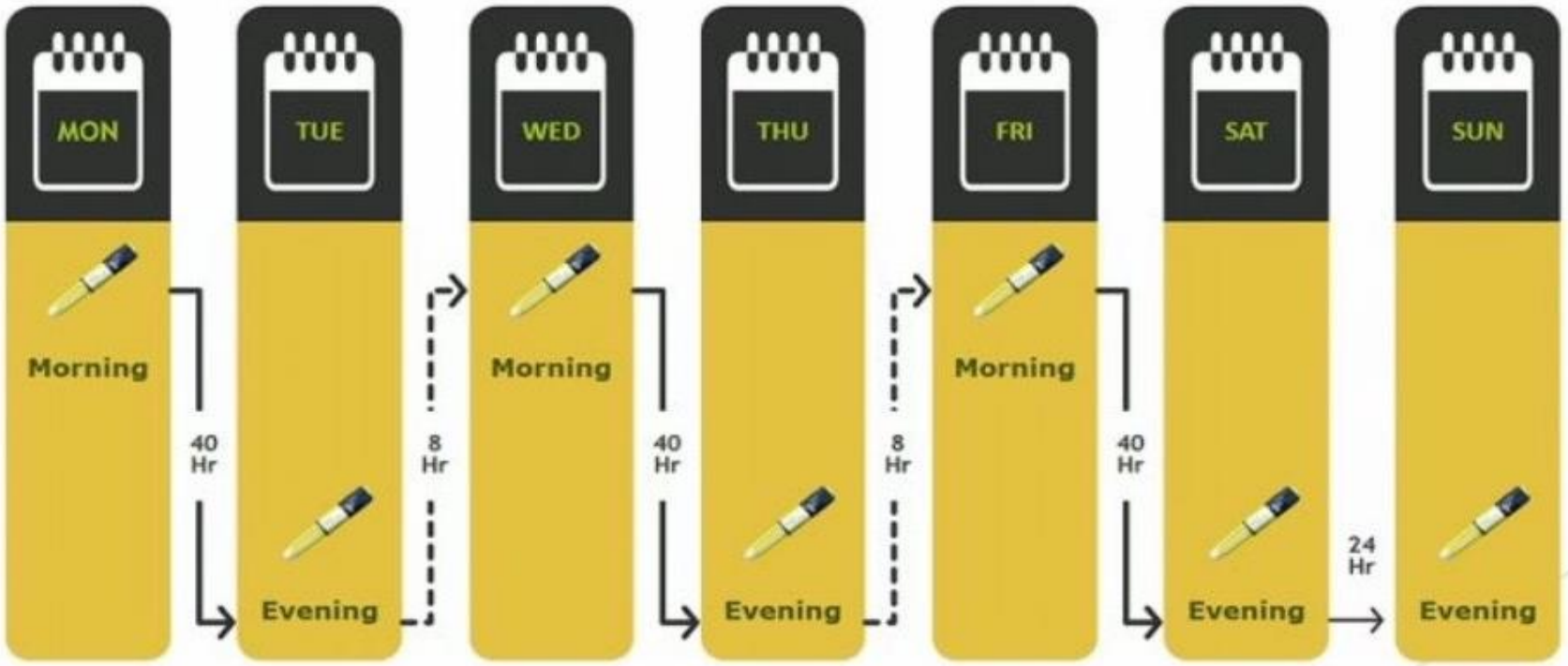
- Similar HA1c lowering
- Overall hypoglycemia and severe hypoglycemia numerically lower, but not statistically significant
- Nocturnal hypoglycemia reduced by 25%
- Similar fasting and 9-point self-measured plasma glucose
- At study end lower insulin requirements
  - 12% less basal insulin
  - 9% less total daily insulin
  - 6% less bolus insulin

Bode BW et al. Diabetic Medicine Published online: 17 JUN 2013

BEGIN FLEX T1D Study:

- Degludec U-100 Alternating times once daily AM vs. PM, 8-h to 40-h intervals
- Degludec U-100 Fixed timing once daily
- Glargine U-100 Fixed dose, once daily

Open label Randomized



1. J Clin Endocrinol Metab. 2013 Mar;98(3):1154-62. doi: 10.1210/jc.2012-3249, Epub 2013 Feb 7.
2. Tresiba (package insert). Plainsboro,NJ: Novo Nordisk Inc: September 2015

Degludec Alternating Times Achieved Comparable A1C Efficacy and Degludec Fixed Numerically Lower FPG vs Insulin Glargine U-100 and Degludec Alternating Times

A1C %

	Degludec U-100 Alternating	Degludec U-100 Fixed	Glargine, Fixed
A1C Reduction	-0.40	-0.41	-0.58

FBG (mg/dl)

	Degludec U-100 Alternating	Degludec U-100 Fixed	Glargine, Fixed
FBS Reduction	-23.04	-45.72	-23.04

Hypoglycemia Rates of BEGIN FLEX T1D Study (week 26):

- Confirmed hypoglycemia rates or severe hypoglycemia rates were similar in all three groups.
- Nocturnal hypoglycemia was lower with Degludec ForcedFlex vs Degudec Fixed (37% p=.003)
- Nocturnal hypoglycemia was lower with Degludec ForcedFlex vs Glargine Fixed (40% p=.001)

1. J Clin Endocrinol Metab. 2013 Mar;98(3):1154-62. doi: 10. 1210/jc.2012-3249, Epub 2013 Feb 7.
2. Degludec [package insert]. Plainsboro, NJ: Novo Nordisk Inc: September 2015.

Glycemic Control in Insulin-naïve Patients with Type 2 Diabetes: Insulin Degludec U-100 vs Insulin Glargine U-100, Begin T2DM Long-52 Wk Results

Insulin-naïve patients with type 2 diabetes (n=1030)

- **IDeg OD + metformin ± DPP-4 (n=773)**
- **IGlar OD + metformin ± DPP-4 (n=257)**

0 — **52 weeks**

Inclusion criteria

- Type 2 diabetes ≥6 months
- Insulin naïve treated with metformin ± SU, DPP-4 or acarbose for ≥3 months
- HbA_{1c} 7.0–10.0%
- BMI ≤40 kg/m^2
- Age ≥18 years

Randomised 3:1 (IDeg OD:IGlar OD)
Open label

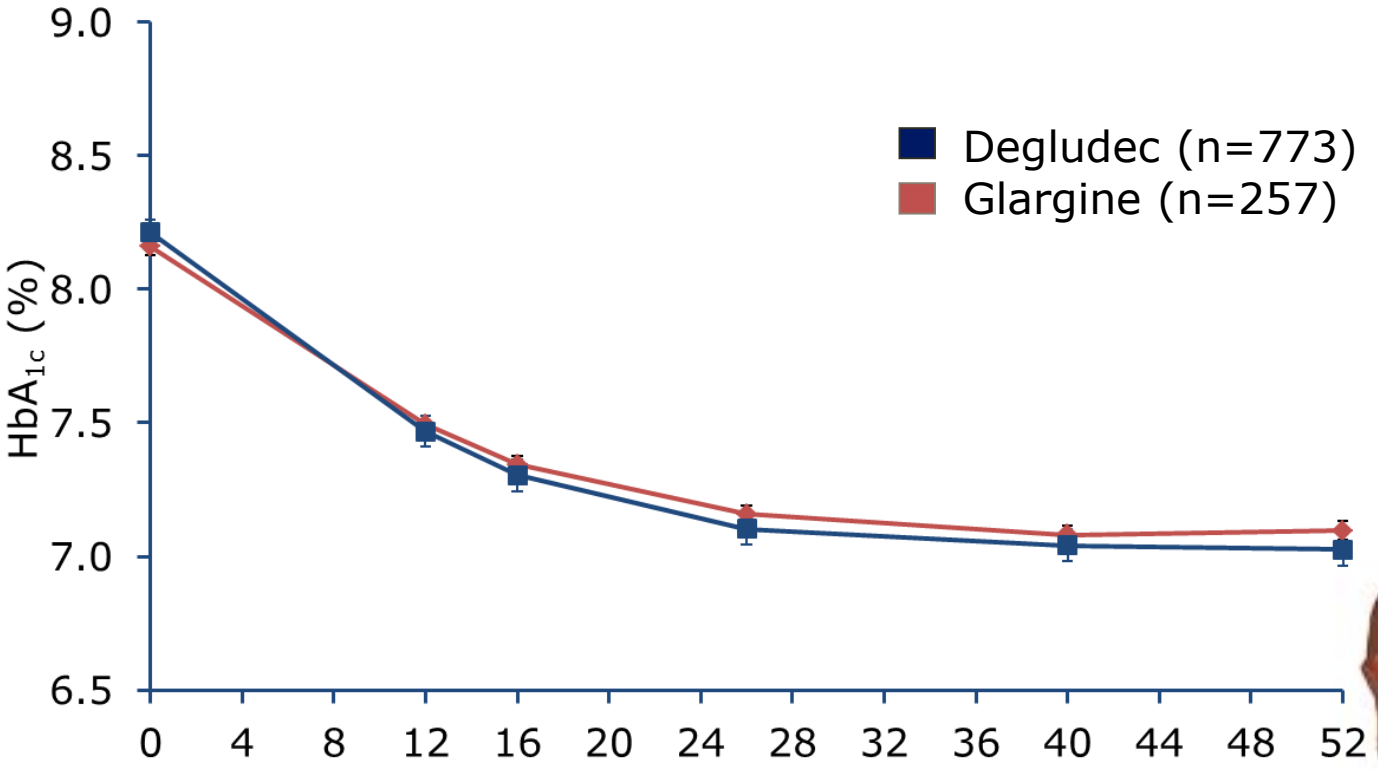
DPP-4, dipeptidyl peptidase-4 inhibitor
SU, sulphonylurea
OD, once daily
Data on file: NN1250-3579; Accepted for presentation at ADA 2012

Weekly titration algorithm for insulin Degludec and insulin Glargine in T2DM

Pre-breakfast plasma glucose[a]		Adjustment
mmol/L	mg/dL	U
<3.1[b]	<56[b]	–4
3.1–3.9[b]	56–70[b]	–2
4.0–4.9	71–89	0
5.0–6.9	90–125	+2
7.0–7.9	126–143	+4
8.0–8.9	144–161	+6
≥9.0	≥162	+8

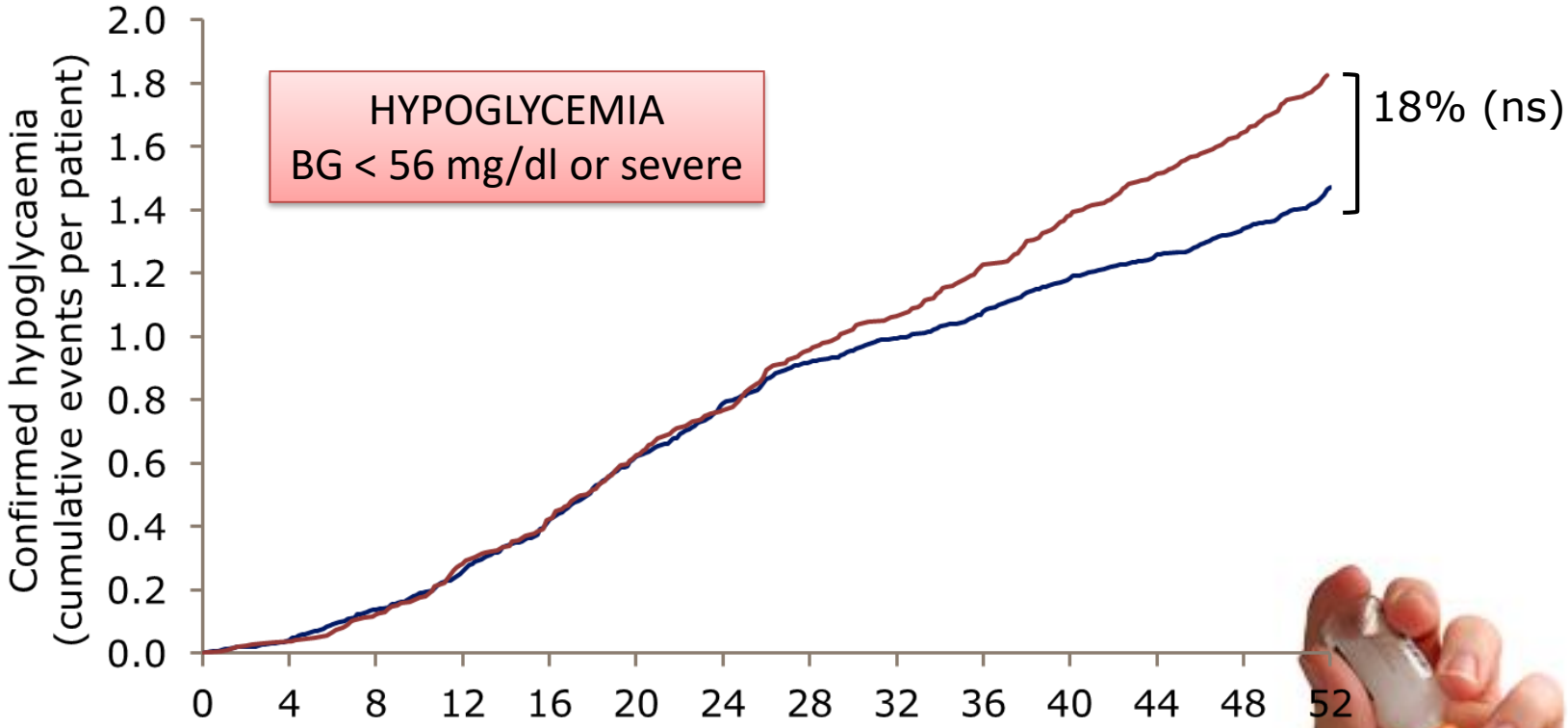
[a] Mean of 3 consecutive days' measurements for up titration.
[b] Unless there is obvious explanation for the low value, such as a missed meal

Glycemic Control in Insulin-naïve Patients with Type 2 Diabetes: Insulin Degludec U-100 vs Insulin Glargine U-100, Begin T2DM Long-52 Wk Results

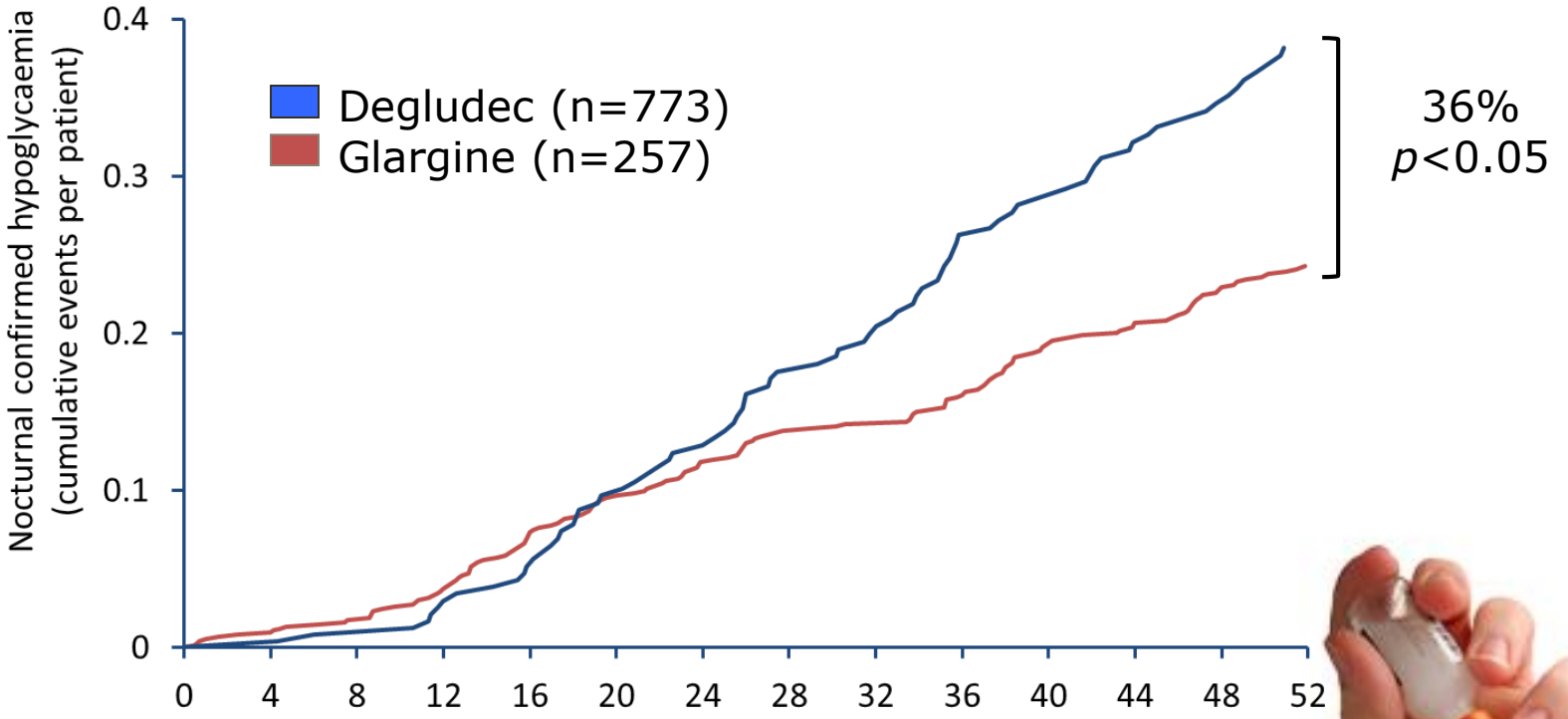


Zinman B et. al; Diabetes Care. 2012 Dec; 35(12):2464-71

Overall Confirmed Hypoglycemia in Insulin-naïve Patients with Type 2 Diabetes: Insulin Degludec U-100 vs Insulin Glargine U-100



Nocturnal Confirmed Hypoglycemia in Insulin-naïve Patients with Type 2 Diabetes: Insulin Degludec U-100 vs Insulin Glargine U-100

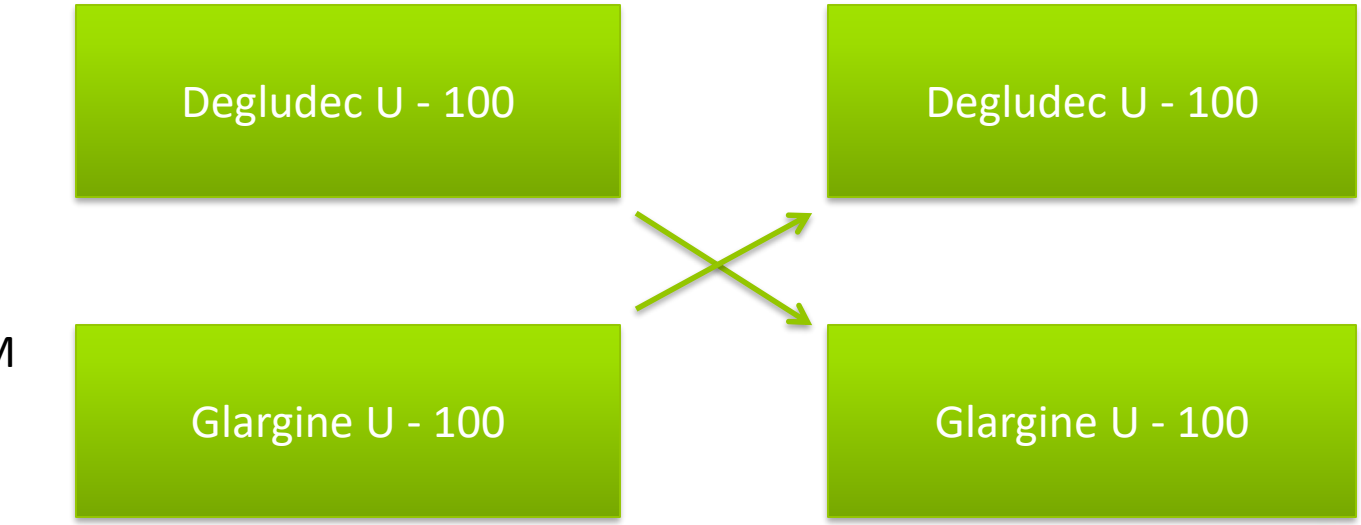


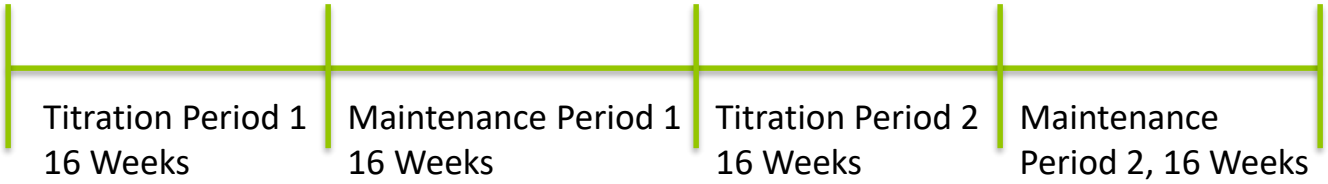
SWITCH – 1 & SWITCH – 2 Trials

- 64 weeks randomized double blind cross over Phase 3b trial
- SWITCH-1: Type 1 DM on basal insulin
- SWITCH-2: Type 2 DM on basal insulin with or without OHA (excluding SU and Meglitinides)
- Patients assigned 1:1 ratio either Degludec U-100 vs Glargine U-100 for 32 weeks, then crossed over to the other basal insulin for another 32 weeks
- Primary Endpoint was demostrate superiority in rates of severe or confirmed hypoglycemia in maintenance phase of study
- Secondary Endpoint was to demostrate superiority in rates of nocturnal hypoglycemia in maintenance phase of study

SWITCH – 1 Trial Design

Patients with Type 1 DM N = 501





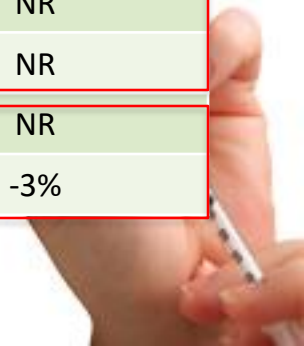
Treatment Period 1

Treatment Period 2

SWITCH – 1 Results

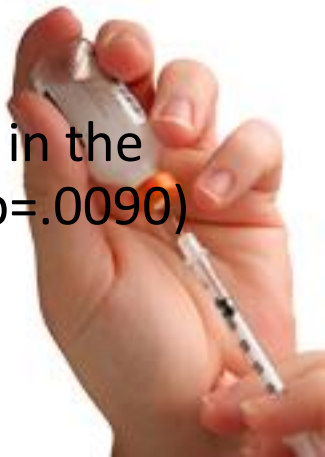
		U-100 Degludec	U-100 Glargine	Treatment Comparisons (ERR) 95% CI
Overall Hypoglycemia Rate (PYE)	MP	22.01	24.63	11% 0.89[.85, .94] p<.001
	FTP	22.44	21.68	.94 [.91, .98] p<.05
Overall Nocturnal Hypoglycemia Rate (PYE)	MP	2.77	4.29	36% .64 [.56, .73] p<.0001
	FTP	2.81	3.72	.75 [.68, .83] p<.005
Severe Hypoglycemia Rate (PYE)	MP	.69	.92	35% .65 [.48, .89]p<.05
	FTP	.86	1.05	.74 [.61. .90] p<.05
Mean A1C	Period 1	6.92	6.78	ETD .03% [-.10. .15]
	Period 2	6.95	6.97	ETD .11% [.00. .23]
Mean Weight Change (lb)	Period 1	5.73	5.95	NR
	Period 2	1.54	0.00	NR
Mean Total Daily Dose (units)	Period 1	69	63	NR
	Period 2	64	69	-3%

MP – Maintenance Phase, FTP – Full Treatment Phase, PYE – Patient Year of Exposure,
ERR – Estimated Relative Risk, CI – Confidence Interval, ETD – Estimated Treatment Difference



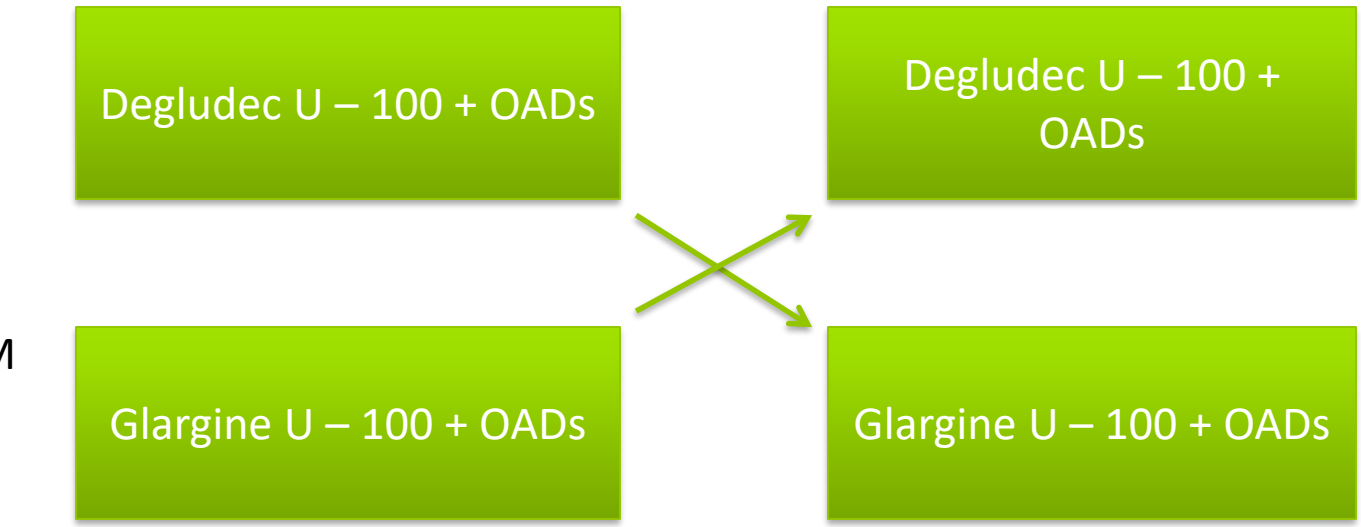
Conclusion of SWITCH – 1 Trial

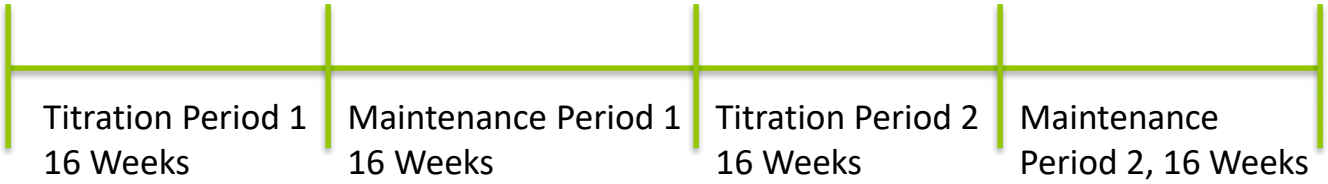
- After 32 weeks of treatment similar reductions of A1C and FPG with Degludec U-100 and Glargine U-100
- Non – inferiority and superiority for the primary endpoint of overall hypoglycemia (11% reduction during Maintenance Phase)
- Non – inferiority and superiority for the secondary endpoint of overall nocturnal hypoglycemia (36% reduction during Maintenance Phase)
- Superiority for secondary endpoint of severe hypoglycemia in the Maintenance Phase (p=.0016) and Total Treatment Phase (p=.0090)



SWITCH – 2 Trial Design

Patients with Type 2 DM N = 721





Treatment Period 1

Treatment Period 2

SWITCH – 2 Results

		U-100 Degludec	U-100 Glargine	Treatment Comparisons (ERR) 95% CI
Number of Patients	MP	632	618	
	FTP	671	665	
Overall Hypoglycemia (PYE)	MP	1.86	2.65	30% .70 [.61, .80] p< .0001
	FTP	2.19	2.75	.77 [.70, .85] p< .0001
Overall Nocturnal Hypoglycemia Rate (PYE)	MP	.55	.94	42% .58 [.46, .74] p< .0001
	FTP	.72	.88	.75 [.64, .89] p = .007
Severe Hypoglycemia Rate (PYE)	MP	.05	.09	.54 [.21, 1.42] p = NS
	FTP	.04	.09	.49 [.26, .94] p < .0306
Mean A1C	Period 1	7.06	6.98	NR
	Period 2	7.08	7.11	NR
Mean Weight Changes (lb)	Period 1	3.30	4.00	NR
	Period 2	1.98	1.10	NR
Mean Total Basal Daily Dose (units)	Period 1	70	74	-4
	Period 2	83	83	0

Conclusion of SWITCH – 2 Trial

- After 32 weeks of treatment similar reductions of A1C and FPG with Degludec U – 100 and Glargine U – 100
- Superiority for the primary endpoint of overall hypoglycemia during Maintenance Phase (30% reduction)
- Superiority for the secondary endpoint of nocturnal hypoglycemia during the Maintenance Phase (42% reduction)
- The proportion of patients experiencing severe hypoglycemia during the Maintenance Phase was numerically lower, but not significantly lower

General Rule of Switching

Dose of:

U300 glargine > U100 glargine

> U100/U200 degludec

Lantus® [package insert]. Bridgewater, NJ: sanofi-aventis US; 2016.
Toujeo® [package insert]. Bridgewater, NJ: sanofi-aventis US; 2016.

Clinical Experience: Switching to and From Concentrated Insulins

Current Therapy	Switch to U100 Glargine	Switch to U300 Glargine	Switch to Degludec
U100 Glargine	--	Switch dose for dose the same; likely need to uptitrate	Consider downtitrating by 10%
U300 Glargine	Consider downtitrating by 15%	--	Consider downtitrating by 20%
Degludec	Switch dose for dose the same; likely need to uptitrate	Switch dose for dose the same; likely need to uptitrate	--

Need for Guidelines: Transitions

From Glargine U100 to U300

- Increase dose by 10%-15%
- Timing to allow for 6-hour overlap to accommodate delayed onset

From Glargine U300 to U100

- Decrease dose by 15%

From Glargine U300 to insulin pump

- Start insulin pump basal 36 hours after last glargine U300 dose and 48 hours after last degludec dose

Acute and procedural care

- Maintain home long-acting insulin to keep up the steady state?

From IV insulin infusion

- Not recommended?
- To Glargine 300: Must ensure 6-hours overlap – requires education and built-in physicians and nursing instructions

Comparison of Pen Features

	U-300 Glargine	U-200 Degludec	U-100 Degludec
Units Per Pen	450	600	300
Units Dose Increments	1	2	1
Max units Per Pen in One Dose	80	160	80
Duration once opened at room temp	42 days	56 days	56 days
Plunger	Push	Spring	Spring

So why change from your present basal to longer acting concentrated basal insulin?

- Reduce Variability of Glucose Levels
- Convenience of Increased Amount of Insulin in Pens
- Improve Adherence
- Get Rid of Split Basal Dosing
- Reduction in Overall, Nocturnal and Severe Hypoglycemia

Thank you!

http://co9to25.org/

References

Upon Request!!!

Surfing the Wave of Life!!!