New generation in basal insulins: safety and efficacy of glargine U300

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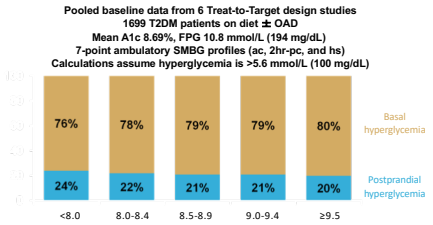
Disclosures

- Speaker: Astra Zeneca, Abbott Nutrición, Novartis Oncology, Novartis Pharma, Novo Nordisk, Merck Sharp & Dohme, Roche, Glaxo SmithKline, Sanofi Aventis, Bayer, Boehringer Ingelheim, Janssen
- Advisory Board: Sanofi Aventis, Astra Zeneca, Novo Nordisk, Pfizer
- Clinical investigation: Astra Zeneca, Novartis Oncology, Novartis Pharma Logistics Inc., Merck Sharp & Dohme, Glaxo SmithKline, Organon, Boehringer Ingelheim, Roche, Novo Nordisk

Agenda

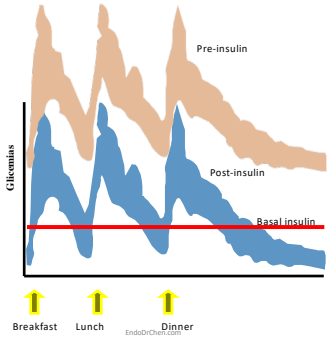
- Why do we need new basal insulins?
- Insulin glargine U300
  - Differences with glargine U100
  - Differences with degludec based on RCT

Basal and postprandial contributions to hyperglycemia by A1c range



On oral therapy, fasting hyperglycemia dominates over a wide range of A1c

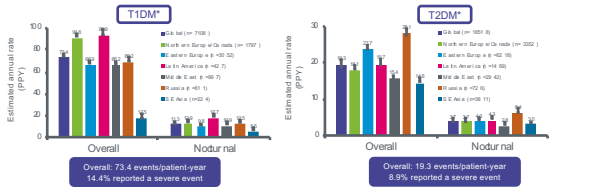
Riddle et al, Diabetes Care 34:2508–2514, 2011



General thoughts

- Why clinical trials have not shown superiority of insulin analogues?
- Definition of 1 unit of insulin
- Study design
- Most of basal insulin studies have been designed to reach a fasting glucose target that is the same in both groups, therefore we would not expect a difference in Hba1c
- Difference would be safety!

Rates of hypoglycemia are high for patients using insulin in the real world



- Hypoglycemia incurs morbidity and increased health care utilization
- Hypoglycemia is a limiting factor in achieving good glycemic control

Non-interventional 6-month retrospective and 4-week prospective global Hypoglycaemia Assessment Tool (HAT) study of 27,585 patients with T1DM or T2DM treated with insulin for <12 months from 24 countries
*During the prospective period
PPY, per patient-year; Khunti K et al. Diabetes Obes Metab. 2016;18:907–15

Hospitalization due to hypoglycemia has an impact upon healthcare utilization costs

The percentage of patients admitted to hospital for hypoglycemia was considerable in all regions

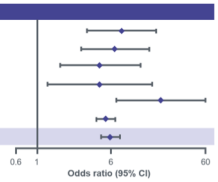
Estimated costs for inpatient care for people with diabetes was approximately $327 billion in 2017[2]
Mean cost of a hypoglycemia visit is approximately $17,564 for an inpatient admission[3]

SD, standard deviation; SE, south east; T1DM, type 1 diabetes; T2DM, type 2 diabetes.
1. Anonsen K et al. Diabetes Res Clin Pract 2018;138:35–41;
2. ADA Diabetes Care. 2018 May;41(5):917-928;
3. Quilliam BJ, et al. Am J Manag Care 2011;17:673–80

Hypoglycemia during first 3 months of BI therapy is a predictor for long-term hypoglycemia risk in real world clinical practice

Risk of hypoglycemia after 24 months if patient experiences hypoglycemia within first 3 months of initiating a BI treatment

Country	OR	95% CI
France	7.84	3.40–18.06
Germany	6.72	2.92–15.44
Italy	4.69	1.76–12.47
Spain	4.58	1.27–16.48
UK	19.97	6.85–58.19
USA	5.30	4.22–6.66
Overall	**5.71**	**4.67–6.99**



- Hypoglycemia during the initial 3 months post-basal insulin initiation is predictive of longer-term risk of hypoglycemia over the ensuing 3 to 24 months
- Over 24 months, 8.9% of patients experienced a hypoglycemic event

Observational, retrospective analysis of insulin-naïve patients (n=40,627) with T2D initiating basal insulin in 5 European countries and the USA. Hypoglycemic episodes were identified using electronic medical records.
Mauricio D. et al. Diabetes Obes Metab 2017;19:1155–1164.

Introduction

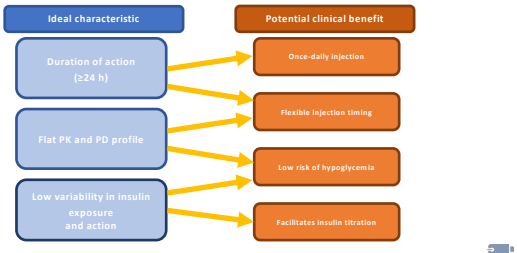
- Unmet needs of actual basal insulins:
  - In some patients, it does not last 24 hours, some patients need a twice a day dosing, specially in T1DM
  - Variability in effect:
    - Insulin
    - device
  - Still some risk of hypoglycemia
  - Some patients need flexibility

Basal insulins

Insulin	Start time	Peak time	Duration
NPH	1-2 hours	5-7 hours	13-18 hours
Glargine U100	6-8 hours	---	20 hours
Glargine U300		A flatter effect	24 hours
Detemir		6-7 hours	12-20 hours
Degludec			40 hours

Second generation basal insulin analogues

Clinical benefits of an ideal PK/PD profile



Becker RH et al. Diabetes Care. 2015 Apr;38(4):637-43; Riddle M et al. Diabetes Technol Ther. 2016 Apr;18(4):252-7

SANOFI

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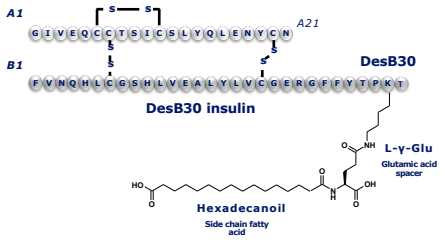
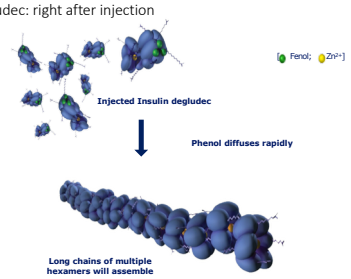
Insulin degludec

Degludec insulin

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

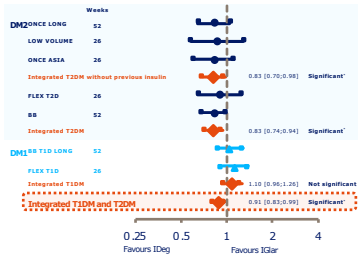


Insulin degludec: right after injection



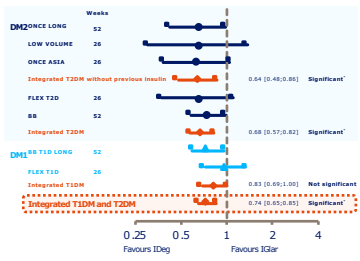
Jonassen *et al. Pharm Res* 2012;29:2104–14

Meta analysis: confirmed general hypoglycemia



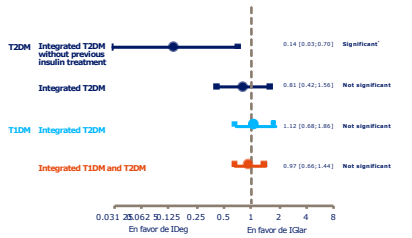
Ajustado para el ensayo, tipo de diabetes, terapia antidiabética al momento de la selección, género, región y edad. El brazo de dosificación flexible no fue incluido en el análisis.
*Riesgo significativamente más bajo con base en IC 95%. Ratner *et al. Diabetes Obes Metab* 2013;15:175–84

Meta analysis: confirmed nocturnal hypoglycemia



Ajustado para el ensayo, tipo de diabetes, terapia antidiabética al momento de la selección, género, región y edad. El brazo de dosificación flexible no fue incluido en el análisis.
*Riesgo significativamente más bajo con base en IC 95%. Ratner *et al. Diabetes Obes Metab* 2013;15:175–84

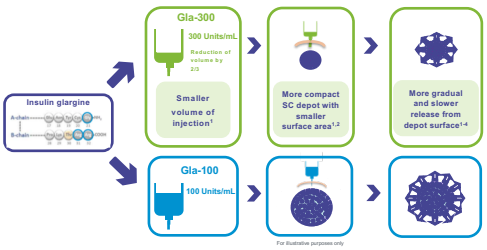
Meta analysis: severe hypoglycemia in T1DM and T2DM



Ajustado para el ensayo, tipo de diabetes, terapia antidiabética al momento de la selección, género, región y edad. El brazo de dosificación flexible no fue incluido en el análisis.
*Riesgo significativamente más bajo con base en IC 95%. Rahner *et al. Diabetes Obes Metab* 2013;15:175-84

Glargine U300

Compact depot formation results in more gradual insulin release with Gla-300 vs Gla-100



1. Peltus J et al. Diabetes Metab Res Rev. 2016 Sep;32(6):478-96; 2. Adapted from Sutton G et al. Expert Opin Biol Ther. 2014 Dec;14(12):1849-60; 3. Steinstraesser A et al. Diabetes Obes Metab. 2014 Sep;16(9):873-6; 4. Becker RH et al. Diabetes Care. 2015 Apr;38(4):637-43

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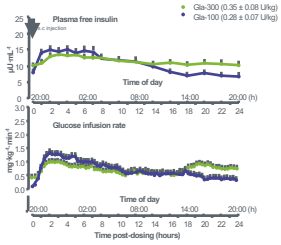
Gla-300 exhibits a more stable profile with lower variability compared with Gla-100 after dose optimization in T1DM patients



PK and PD within-day variability was 50% and 17% lower with Gla-300

24-hr insulin profile for Gla-300 is flatter and more constant over 24 hrs compared with Gla-100

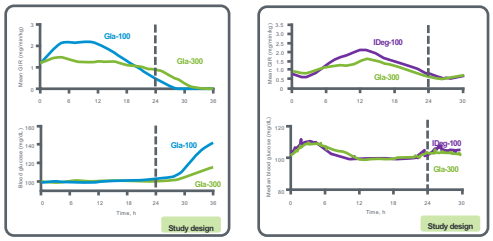
Glucose infusion rate was more consistent over 24 hr with Gla-300 vs Gla-100

An euglycemic clamp study characterizing the PK, PD, and endogenous glucose production of clinical doses of Gla-300 and Gla-100 under steady state conditions in T1DM patients (N=18)

Porcellati F, et al. Diabetes Care. 2019 Jan;42(1):85-92

Study design

More stable **glucose-lowering (PD) profile** with Gla-300 vs Gla-100 and Gla-300 vs IDeg-100



Study design

Study design

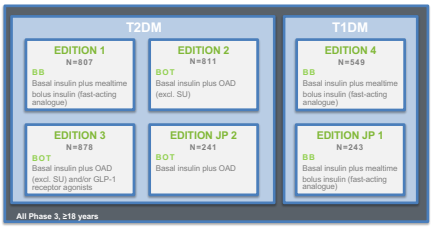
GIR, glucose infusion rate

Adapted from Becker RH et al. Diabetes Care. 2015 Apr;38(4):637-43; Bailey TS et al. Diabetes Metab. 2018 Feb;44(1):15-21

EDITION: CLINICAL DEVELOPMENT PROGRAM OF GLARGINE U300

EDITION program

Testing Toujeo® vs Lantus® in several populations

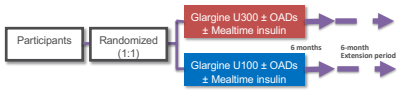


BB, Basal-bolus therapy; BOT, basal only therapy

Riddle MC et al. Diabetes Care. 2014;37:2755-62; Yki-Järvinen H et al. Diabetes Care. 2014 Sep 5. pii: DC_140590 [Epub ahead of print]; Bolli GB et al. Poster presentation at EASD 2014; Abstract 947; Terauchi Y et al. Poster presentation at EASD 2014; Abstract 976; Home PD et al. Oral presentation at EASD 2014; Abstract 148; Matsuhisa M et al. Poster presentation at EASD 2014; Abstract 975

EDITION study design is consistent across the program

- Randomized 1:1, open-label, parallel-group, multinational studies
- EDITION program built with similar study design across trials to confirm results



Non-inferiority to glargine U100 in HbA_{1c} reduction was the primary endpoint in all trials

Riddle MC et al. Diabetes Care. 2014;37:2755-62; Yki-Järvinen H et al. Diabetes Care. 2014 Sep 5. pii: DC_140590 [Epub ahead of print]; Bolli GB et al. Poster presentation at EASD 2014; Abstract 947; Terauchi Y et al. Poster presentation at EASD 2014; Abstract 976; Home PD et al. Oral presentation at EASD 2014; Abstract 148; Matsuhisa M et al. Poster presentation at EASD 2014; Abstract 975; Riddle MC et al. Poster presentation at EASD 2014; Abstract 980; Yki-Järvinen H et al. Poster presentation at EASD 2014; Abstract 946

Basal insulin titration in EDITION 1, 2 & 3

Glargine U300 was always given in the evening
Titration steering committee was in place
Adjustments at investigators' discretion for safety

Titration algorithm	
Median fasting SMPG from last 3 days in the range of:	Dose adjustment for glargine U100 or Glargine U300, U/day
≥140 mg/dL (≥7.8 mmol/L)	+6
>100 and <140 mg/dL (5.6–7.8 mmol/L)	+3
Glycemic target:	
80–100 mg/dL (4.4–5.6 mmol/L)	No change
≥60 and <80 mg/dL (3.3–4.4 mmol/L)	-3
<60 mg/dL (<3.3 mmol/L) or occurrence of ≥2 symptomatic or 1 severe hypoglycemia episode(s) in the preceding week	-3 or at investigator's discretion

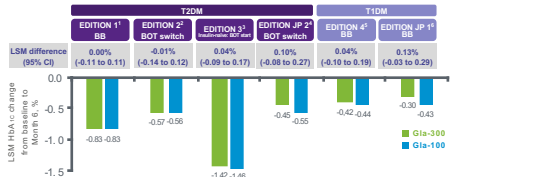
- In EDITION 1 and 2, basal dose unchanged at entry unless two daily NPH injections were previously used, when dose was reduced by 20%

Data on file, EDITION 1 CSR pg 16, 27, 28; EDITION 2 CSR pg 16, 26-28; EDITION 3 CSR pg 27, 30-32

8-point SMPG profiles

Consistently effective glycemic control

- **Non-inferior change in HbA1c** for Gla-300 vs Gla-100 at **Month 6** in the EDITION program

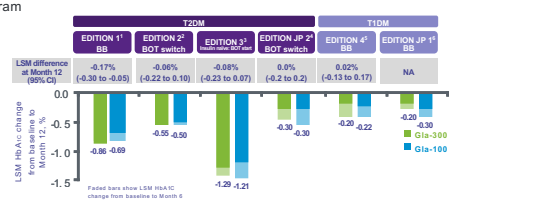


Modified intention-to-treat population; BB, basal-bolus therapy; BOT, basal-oral therapy; CI, confidence interval; LSM, least squares mean

1. Riddle MC et al. Diabetes Care. 2014 Oct;37(10):2755-62. 2. Yki-Järvinen H et al. Diabetes Care. 2014 Dec;37(12):3235-43.
3. Bolli GB et al. Diabetes Obes Metab. 2015 Apr;17(4):386-94. 4. Terauchi Y et al. Diabetes Obes Metab. 2016 Apr;18(4):366-74 (main article and Supplementary Table 2);
5. Home PD et al. Diabetes Care. 2015 Dec;38(12):2217-25. 6. Matsuhisa M et al. Diabetes Obes Metab. 2016 Apr;18(4):375-83 (main article and Supplementary Table 1);

Consistently effective glycemic control

- **Non-inferior change in HbA1c** for Gla-300 vs Gla-100 at **Month 12** in the EDITION program

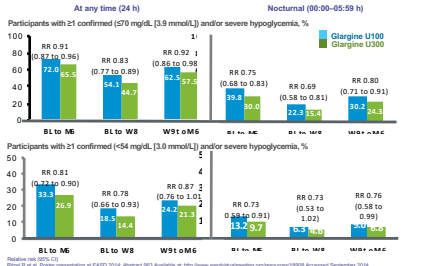


Modified intention-to-treat population

1. Riddle MC et al. Diabetes Care. 2014 Oct;37(10):2755-62. 2. Yki-Järvinen H et al. Diabetes Care. 2014 Dec;37(12):3235-43.
3. Bolli GB et al. Diabetes Obes Metab. 2015 Apr;17(4):386-94. 4. Terauchi Y et al. Diabetes Obes Metab. 2016 Apr;18(4):366-74 (main article and Supplementary Table 2);
5. Home PD et al. Diabetes Care. 2015 Dec;38(12):2217-25. 6. Matsuhisa M et al. Diabetes Obes Metab. 2016 Apr;18(4):375-83 (main article and Supplementary Table 1);

EDITION 1-2-3 T2DM Pooled Analysis

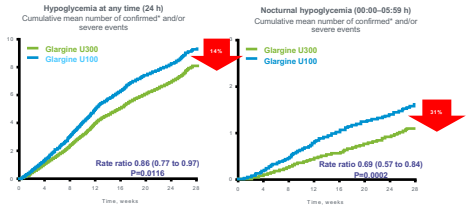
Generally lower confirmed and/or severe hypoglycemia with Glargine U300 vs Glargine U100 at any time (24 h) and at night



Relative risk (95% CI)
Rosenstock J et al. Poster presentation at EASD 2014; Abstract 963 Available at: http://www.easdvirtualmeeting.org/resources/18908 Accessed September 2014

EDITION 1-2-3 T2DM Pooled Analysis

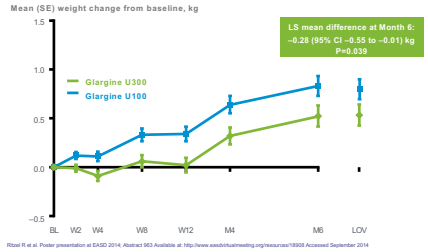
Lower confirmed and/or severe hypoglycemia with glargine U300 vs glargine U100 at any time (24 h) and at night



*Confirmed events based on plasma glucose ≤70 mg/dL (3.9 mmol/L)
Ritzel R et al. Poster presentation at EASD 2014; Abstract 963 Available at: http://www.easdvirtualmeeting.org/resources/18908 Accessed September 2014

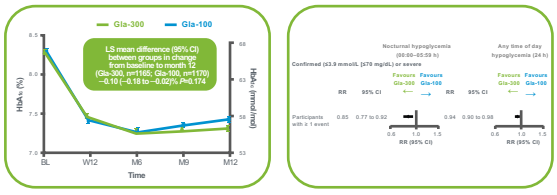
EDITION 1-2-3 T2DM Pooled Analysis

Small but significant difference in weight gain with Glargine U300 vs Glargine U100



Ritzel R et al. Poster presentation at EASD 2014; Abstract 963 Available at: http://www.easdvirtualmeeting.org/resources/18908 Accessed September 2014

Similar HbA_{1C} reduction with lower incidence of hypoglycemia Gla-300 vs Gla-100 in EDITION T2DM studies* from baseline to Month 12

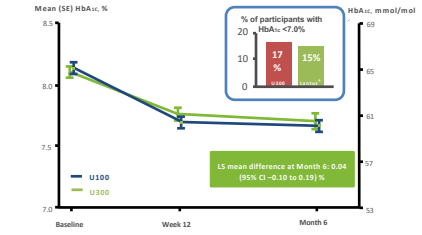


*Patient-level meta-analysis of EDITION 1 (BB), EDITION 2 (BOT switch) and EDITION 3 (BOT start) studies in a broad population of patients with T2DM
SE, standard error
Ritzel R et al. Diabetes Obes Metab. 2018 Mar;20(3):541-548

TYPE 1 DIABETES: EDITION 4

EDITION 4

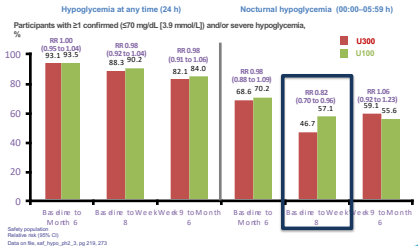
U300 met the primary endpoint of non-inferiority to Lantus® for reduction in HbA1c at Month 6



mITT population
Home PD et al. Oral presentation at EASD 2014; Abstract 148 Available at: http://www.easdvirtualmeeting.org/resources/16864 Accessed September 2016
Data on file, EDITION 4 CSR, pg 95

EDITION 4

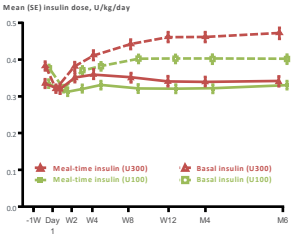
Similar confirmed and/or severe hypoglycemia
Lower nocturnal hypoglycemia with U300 vs U100 during the first 8 weeks



Safety population
Relative risk (95% CI)
Data on file, saf_hypo_pt2_3, pg 219, 273
Home PD et al. Poster presentation at ADA 2014; Abstract 80-LB Available at: http://ada.appriorc.org/epa/AbstractADA.cfm?id=1 Accessed June 2014

EDITION 4

Slight increase in basal insulin dose with U300

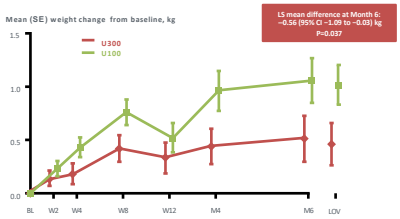


mITT population

Home PD et al. Oral presentation at EASD 2014; Abstract 148 Available at: http://www.easdvirtualmeeting.org/resources/16864 Accessed September 2014

EDITION 4

Less weight gain with U300 vs U100

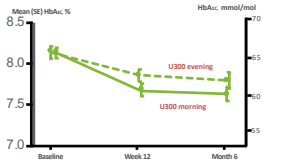


Home PD et al. Oral presentation at EASD 2014; Abstract 148 Available at: http://www.easdvirtualmeeting.org/resources/16864 Accessed September 2014
Home PD et al. Poster presentation at ADA 2014; Abstract 80-LB Available at: http://cdn.appinvor.org/wp4/abstractADA.cfm?id=1 Accessed June 2014

BENEFITS OF LONG DURATION OF ACTION: FLEXIBLE DOSING

EDITION 4

Similar HbA1c reductions by injection time



U300 morning vs evening
LS mean difference: −0.15
(95% CI −0.35 to 0.05)

mITT population
Home PD et al. Oral presentation at EASD 2014; Abstract 148 Available at: http://www.easdvirtualmeeting.org/resources/16964 Accessed September 2014

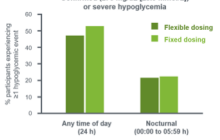
Flexible dosing time of Gla-300 had no effect on glycemic control and incidence of hypoglycemia vs fixed dosing time

Pooled EDITION 1 and 2 substudies in T2DM (Months 6–9)

HbA1c, %	Flexible dosing* n=99	Fixed dosing n=95
Month 6, mean (SD)	7.30 (0.93)	7.30 (0.96)
Month 6–9, LS mean change (SE)	0.05 (0.06)	0.00 (0.07)
LS mean difference (95% CI)	0.05 (–0.13 to 0.23)	

Gla-300 may allow some flexibility in timing injections to deal with the situational variability experienced in daily life

Confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe hypoglycemia



Sub studies design

*Flexible dosing time: Once-daily injection intervals of 24 ± 3 h
Adapted from Rüdiä M et al. Diabetes Technol Ther. 2016 Apr;18(4):252-7

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IF NEWER BASAL INSULIN LASTS FOR MORE THAN 24 HOURS, WILL THERE BE DOSE STACKING AND HYPOGLYCEMIA?

Steady state

- Ensues after 4-5 half lives
- By definition, it is when the amount of a given drug is the same as the amount that is cleared
- With drugs that have a long half life, it will take a longer time to reach this steady state but there will be no dose stacking
  - Levothyroxine has a half life of 7 days!

Para una insulina con vida media de 24 horas

	Given dose	Amout that is circulating	Amount that is cleared	Amount that remains
Day 1	10	10	5	5
Day 2	10	15	7.5	7.5
Day 3	10	17.5	8.75	8.75
Day 4	10	18.75	9.37	9.37
Day 5	10	19.37	9.69	9.69
Day 6	10	19.69	9.84	9.84
Day 7	10	20	10	10
Day 8	10	20	10	10

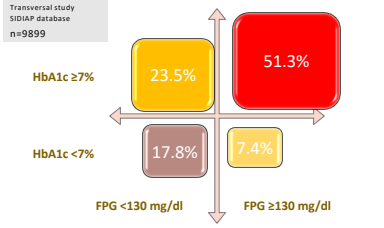
Therefore… there is no stacking effect but it will take longer to reach the steady state. Blood glucose may take initially a longer time to decrease

Starting glargine U300 and dose titration

Treatment with basal insulins: failure in dose optimization

Distribution of patients treated with basal insulin according to their FPG and Hba1c

Transversal study
SIDIAP database
n=9899

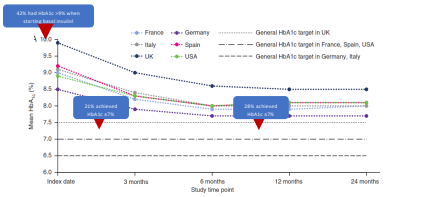


1. Adapatado de Mata-Cases M. et al. *Journal of Diabetes* 9 (2014), 34–44

Insulina Glargina (100 U/mL) + Lixisenatida

Glucose response during the first 3 months treatment with basal insulin is a predictor of glucose control on the long term

- May patients will start basal insulin with HbA1c >9% = delay in treatment intensification
- Average HbA1c decreased more during the first 3 months of treatment and then remained stable



Análisis observacional retrospectivo de Cegedim Strategic Data de 40.527 pacientes con DM T2 + CMO / GLP-1RA iniciando insulina basal de Francia, Alemania, Italia, España, Reino Unido y EE. UU. (2008-2012)

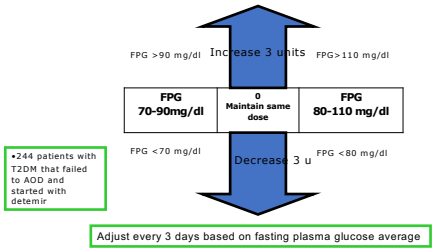
Mauricio Cett al. Diabetes Obes Metab. 2017;19:1151–64

BI, insulina basal; CMO, fármaco antidiabético oral; GLP-1 RA, agonista del receptor del péptido-1 similar al glucagón

What's the difference in dose titration with the usual basal insulins?

- Start with 10 u daily or 0.1-0.2 u/kg
- Due to their longer half life, it will take a longer time to reach steady state
- With the usual basal insulins (NPH, detemir, glargine U100), dose titration was recommended every 3 days
- With newer basal insulins (glargine U300, degludec), current recommendations are to titrate once weekly
  - BRIGHT: 80-100 mg/dl
  - CONCLUDE 70-90 mg/dl
- Usual target is between 90 and 120 mg/dl

Basal insulin: dose adjustment



•244 patients with T2DM that failed to AOD and started with detemir

Adjust every 3 days based on fasting plasma glucose average

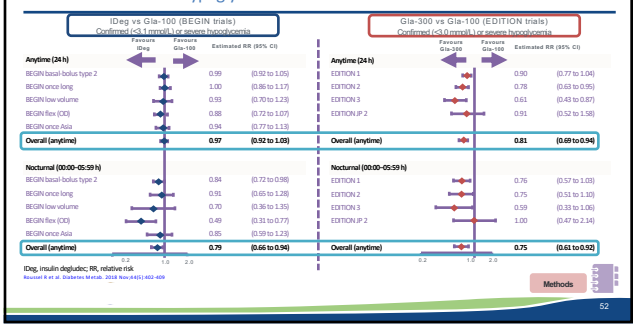
Diabetes Obes Metab. Jun 2009;11(6):623-631

Switching from other basal insulins

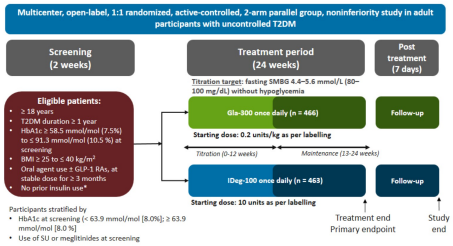
- If switching from another basal insulin analogue, keep the same dose (1:1 exchange)
- If switching from NPH, decrease the dose by 10-20% and titrate
- During the first few days, fasting glucose may rise a little
  - Tell the patients so they won't be scared!
  - Due to longer half lives needing more days to reach steady state
- Titrate once weekly

COMPARISON BETWEEN GLARGINE U300 AND DEGLUDEC BASED ON RANDOMISED CONTROLLED TRIALS

Relative risk of ≥1 hypoglycemic event in EDITION and BEGIN trials in T2DM



BRIGHT: Head-to-Head Comparison of Gla-300 and Deg-100



*With the exception of a maximum of 8 consecutive days or 15 days total prior insulin use.

Cheng AYY. ADA 2018. Oral presentation 301-OR.

BRIGHT: Study Endpoints and Glycemic Targets

Primary efficacy endpoint:
- Change in HbA1c from baseline to week 24
  - Analyzed using a MMRM approach, adjusted for covariates including baseline HbA1c
  - Non-inferiority margin was 0.3% (HbA1c units)

Secondary efficacy endpoints included:
- Change in FPG, fasting SMBG, and 8-point SMBG profiles from baseline to week 24
- Variability of 8-point SMBG profiles

Safety endpoints included:
- Incidence and annualized rates of hypoglycemia (≤ 3.9 mmol/L [70 mg/dL] and ≤3.0 mg/dL [54 mg/dL]) over the full 24-week period, and during weeks 0-12 (the active titration period) and weeks 13-24 (the maintenance period)
- TEAEs

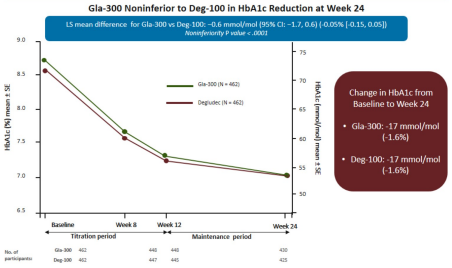
Gla-300 and Deg-100 titrated weekly* to SMBG target of 4.4-5.6 mmol/L (80-100 mg/dL)

Median† fasting SMPG, mmol/L (mg/dL)	Dose change
> 7.8 (> 140)	+ 6 units
> 6.7 to ≤ 7.8 (> 120 to ≤ 140)	+ 4 units
> 5.6 to ≤ 6.7 (> 100 to ≤ 120)	+ 2 units
≥ 4.4 to ≤ 5.6 (≥ 80 to ≤ 100)	0
< 4.4 (80)‡	- 2 units§

*But no more than every 3 days; †From last 3 measurements ‡or 1 symptomatic confirmed hypoglycemia episode in preceding week §or at investigator's discretion.

Cheng AYY. ADA 2018. Oral presentation 301-OR.

BRIGHT: Primary Endpoint: Glycemic Control

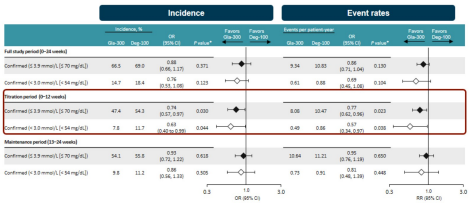


Change in HbA1c from Baseline to Week 24

- Gla-300: -17 mmol/mol (-1.6%)
- Deg-100: -17 mmol/mol (-1.6%)

Cheng AYY. ADA 2018. Oral presentation 301-OR.

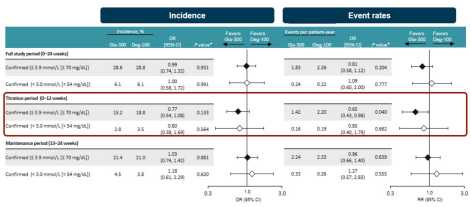
BRIGHT: Anytime (24 h) Hypoglycemia



Confirmed hypoglycemia included documented symptomatic or asymptomatic hypoglycemia (≤ 3.9 mmol/L or < 3.0 mmol/L [≤ 70 mg/dL or < 54 mg/dL]), and severe events if any; only 1 participant experienced severe hypoglycemia (1 event), in the Gla-300 group, due to a skipped evening meal and not reducing her insulin dose after a non-severe event 2 days earlier.
All *P* values presented are nominal, not adjusted for multiplicity. Safety population (Gla-300, n = 463; Deg-100, n = 462).

Cheng AYY. ADA 2018. Oral presentation 301-OR.

BRIGHT: Nocturnal (00:00–06:00 h) Hypoglycemia



Confirmed hypoglycemia included documented symptomatic or asymptomatic hypoglycemia (≤ 3.9 mmol/L or < 3.0 mmol/L [≤ 70 mg/dL or < 54 mg/dL]), and severe events if any; only 1 participant experienced severe hypoglycemia (1 event), in the Gla-300 group, due to a skipped evening meal and not reducing her insulin dose after a non-severe event 2 days earlier.
All *P* values presented are nominal, not adjusted for multiplicity. Safety population (Gla-300, n = 463; Deg-100, n = 462).

Cheng AYY. ADA 2018. Oral presentation 301-OR.

BRIGHT: Insulin Dosage and Body Weight Over 24 Weeks

Mean Daily Insulin Dose

	Gla-300 (n = 462)		Deg-100 (n = 462)	
	Units	Units /kg	Units	Units /kg
Initial	16.9 ± 4.4	0.19 ± 0.04	10.2 ± 1.9	0.12 ± 0.04
Between-treatment difference at baseline		0.07 units/kg		
Week 24	50.5 ± 25.6	0.54 ± 0.26	39.2 ± 23.3	0.43 ± 0.24
Between-treatment difference at week 24		0.11 units/kg		
Change from baseline to week 24	33.6 ± 24.4	0.36 ± 0.25	29.1 ± 23.3	0.31 ± 0.24

Data are mean ± SD, except for between-treatment differences (only mean presented)

Mean Body Weight

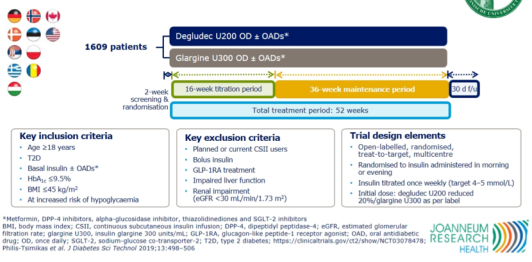
	Gla-300 (n = 462)	Deg-100 (n = 462)
	Kg	Kg
Initial	90.6 ± 16.1	88.7 ± 15.9
Week 24	92.5 ± 16.6	91.4 ± 16.7
Change from baseline to week 24	2.0 ± 3.8	2.3 ± 3.6

Data are mean ± SD

Cheng AYY. ADA 2018. Oral presentation 301-OR.

CONCLUDE: DEGLUDEC VS GLARGINA U300

Trial design



Key inclusion criteria
- Age ≥18 years
- T2D
- Basal insulin ± OADs*
- HbA_{1c} ≤9.5%
- BMI ≤45 kg/m²
- At increased risk of hypoglycaemia

Key exclusion criteria
- Planned or current CSII users
- Bolus insulin
- GLP-1RA treatment
- Impaired liver function
- Renal impairment (eGFR <30 mL/min/1.73 m²)

Trial design elements
- Open-labelled, randomised, treat-to-target, multicentre
- Randomised to insulin administered in morning or evening
- Insulin titrated once weekly (target 4–5 mmol/L)
- Initial dose: degludec U200 reduced 20%/glargine U300 as per label

*Metformin, DPP-4 inhibitors, alpha-glucosidase inhibitor, thiazolidinediones and SGLT-2 inhibitors
BMI, body mass index; CSII, continuous subcutaneous insulin infusion; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; glargine U300, insulin glargine 300 units/mL; GLP-1RA, glucagon-like peptide-1 receptor agonist; OAD, oral antidiabetic drug; OD, once daily; SGLT-2, sodium-glucose co-transporter-2; T2D, type 2 diabetes; https://clinicaltrials.gov/ct2/show/NCT03078478; Philis-Tsimikas *et al. J Diabetes Sci Technol* 2019;13:498–506

JOANNEUM RESEARCH HEALTH

Titration algorithm

Pre-breakfast (fasting) SMBG*		Total daily dose adjustment of degludec U200 and glargine U300
mmol/L	mg/dL	Units
<3.1	<56	−4
3.1–3.9	56–70	−2
4.0–5.0	**71–90**	**0**
5.1–7.0	91–126	+2
7.1–8.0	127–144	+4
8.1–9.0	145–162	+6
>9.0	>162	+8

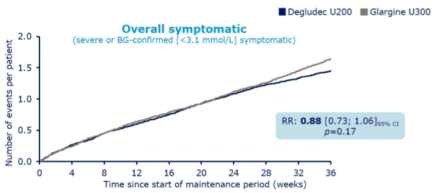
*For dose increases the mean of 3 pre-breakfast SMBG measurements were used. For dose reductions the lowest SMBG measurement was used
Glargine U300, insulin glargine 300 units/mL; SMBG, self measured blood glucose

JOANNEUM RESEARCH HEALTH

Hypoglycaemia endpoints

MAINTENANCE period – primary endpoint

Prespecified analysis



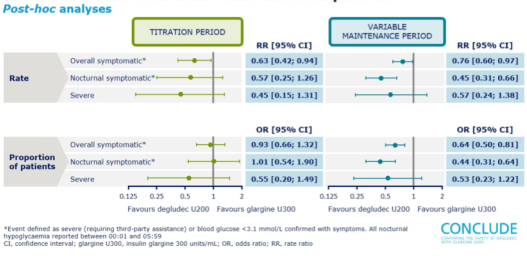
BG, blood glucose; CI, confidence interval; glargine U300, insulin glargine 300 units/mL; RR, rate ratio

CONCLUDE

Hypoglycaemia endpoints

TITRATION and VARIABLE MAINTENANCE periods

***Post-hoc* analyses**



*Event defined as severe (requiring third-party assistance) or blood glucose <3.1 mmol/L confirmed with symptoms. All nocturnal hypoglycaemia reported between 00:01 and 05:59
CI, confidence interval; glargine U300, insulin glargine 300 units/mL; OR, odds ratio; RR, rate ratio

CONCLUDE

How do we explain the different results?

- BRIGHT
  - Sponsored by Sanofi
  - Insulin naive patients
  - Glargine U300 vs degludec
  - Tiration to 80-100 mg/dl
  - Primary endpoint reached (non inferiority in Hba1c)
  - Lower incidence of hypoglycemia during titration period favouring glargine U300 (safety endpoint)
- CONCLUDE
  - Sponsored by Novo Nordisk
  - Insulin users at high risk for hypoglycemia
  - Glargine U300 vs degludec
  - Titration to 70-90 mg/dl
  - No difference in primary endpoint (overall hypoglycemia) but a difference was seeen during maintenance period favouring degludec

SPECIAL POPULATIONS: CHILDREN, SENIORS AND RENAL FAILURE

Edition junior

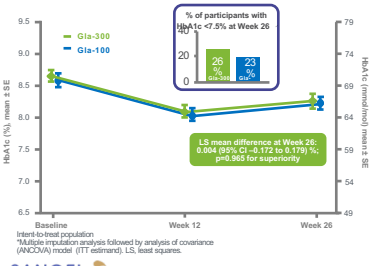
SANOFI

EDITION Junior:
6-month, multicenter, randomized, open-label, 2-arm, parallel-group study comparing the efficacy and safety of Gla-300 and Gla-100 in children and adolescents age 6-17 years with T1D with a 6-month safety extension period

Danne T, et al. *Pediatr Diabetes* 2019;20(Suppl 28):P240; https://clinicaltrials.gov/ct2/show/results/NCT02735044 (Last accessed October 11, 2019).
INNs:Gla-300, insulin glargine 300 U/mL; Gla-100, insulin glargine 100 U/mL; T1D, type 1 diabetes mellitus

Gla-300 met the primary endpoint of non-inferiority to Gla-100 for reduction in HbA1c at week 26

EDITION JUNIOR – 6 M



Gla-300 was non-inferior to Gla-100 in HbA1c change from baseline to Week 26 (the upper bound of the 95% CI was lower than the predefined non-inferiority margin of 0.3%)

Hba1c (%)	Gla-300 n=233	Gla-100 n=236
Baseline mean (SD)	8.65 (0.88)	8.61 (0.87)
Change from baseline to Week 26		
Combined LS Mean (95% CI)	-0.399 (-0.522 to -0.275)	-0.402 (-0.527 to -0.278)
Combined LS Mean difference vs. Gla-100 (95% CI)	0.004 (-0.172 to 0.179)	
p-value for the superiority test	0.965	

Intent-to-treat population
*Multiple imputation analysis followed by analysis of covariance (ANCOVA) model (ITT estimand). LS, least squares.

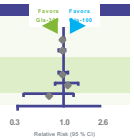
Danne T, et al. Pediatr Diabetes 2019;20(Suppl 28):P240; https://clinicaltrials.gov/ct2/show/results/NCT02763644 (Last accessed October 11, 2019).

SANOFI

Gla-300 showed a similar incidence of anytime and nocturnal hypoglycemia vs Gla-100 in children/adolescents (6-17 years) with T1D

EDITION JUNIOR – 6 M

Hypoglycemia category	Number of participants (%) Gla-300 N=233	Gla-100 N= 228	Hypoglycemia Anytime (24 h) & Nocturnal (00:00–05:59 h) Relative Risk (95%CI) Gla-300 vs Gla-100
Anytime hypoglycemia (24 h)			
Severe and/or documented ≤70 mg/dL (≤3.9 mmol/L)	226 (97.0)	223 (97.8)	0.99 (0.96–1.02)
<54 mg/dL (<3.0 mmol/L)	187 (80.3)	191 (83.8)	0.96 (0.88–1.04)
Nocturnal hypoglycemia (00:00–05:59 h)			
≤70 mg/dL (≤3.9 mmol/L)	163 (70.0)	160 (70.2)	1.00 (0.88–1.12)
<54 mg/dL (<3.0 mmol/L)	63 (27.0)	57 (25.0)	1.09 (0.80–1.47)
Severe hypoglycemia (24 h)	14 (6.0)	20 (8.8)	0.68 (0.35–1.30)



Incidence of severe hypoglycemia was numerically lower in Gla-300 vs Gla-100 groups

Safety population. CI, confidence interval. T1D, type 1 diabetes. Based on relative risk stratified by randomization strata of screening HbA1c (<8.5 or ≥8.5%) and age group at screening visit (<12 years and ≥12 years, using Cochran-Mantel-Haenszel methodology. Percentage of patients with at least one event of hypoglycemia during the 6-month main treatment period according to different ADA and ISPAD-2018 categories is shown.

Severe hypoglycemia: an event in which the child/adolescent having altered mental status and cannot assist in their care, is semiconscious or unconscious, or in coma o convulsions and may require parenteral therapy (glucagon or glucose).

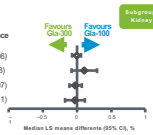
Danne T, et al. Pediatr Diabetes 2019;20(Suppl 28):P240.

SANOFI

Comparable glucose control and fewer nocturnal hypoglycemia with GLA300 regardless of renal function

Similar reduction in Hba1c with Gla-300 and Gla-100 independent of renal function

Subgroup analysis: Kidney function



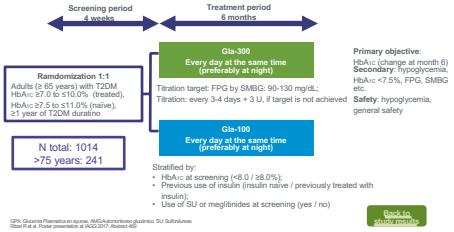
Lower incidence of hypoglycaemia with Gla-300 vs Gla-100 regardless of renal function

Subgroups by basal GFR (mL/min/1.73 m²)	nocturnal (00:00–05:59 h) Participants with ≥1 event, n (%) Gla-300	Gla-100	Any time (24 h) Participants with ≥1 event, n (%) Gla-300	Gla-100
Total (n=2,468)	30.0	39.7	65.7	71.7
≥30 to <60 (n=399)	39.5	51.3	79.5	80.4
≥60 to <90 (n=1,386)	32.1	40.0	67.0	71.4
≥90 (n=683)	20.1	32.7	54.8	67.3

FG: Filtrado glomerular
*Post hoc patient-level meta-analysis of people with T2DM treated with Gla-300 or Gla-100 for 6 months in the EDITION 1, 2 and 3 studies by estimated glomerular filtration rate (eGFR).
Adapted from Hahn S et al. Poster presentation at ATTD 2017

SENIOR: Study design

- **Design:** 1:1 randomization, open label, parallel group, multinational
- **Objective: To demonstrate non inferiority of Gla-300 vs Gla-100 in changes of Hba1c at 26 weeks in older adults with T2DM**

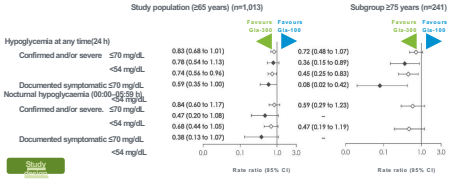


GPA: Glucemia Plasmatica en ayunas, AMG:Autocontrolmo glucémico. SU: Sulfonilureas
Ribal R et al. Poster presentation at IAGG 2017; Abstract 469

Pacientes ≥65años con DM2

Comparable glucose control and lower documented symptomatic hypoglycemia with Gla-300 vs Gla-100 in older patients with T2DM

- In SENIOR RCT, Gla-300 was effective in older adults (>65 years) with low documented symptomatic hypoglycemia vs Gla-100, specially in ≥75 years [1]



RCT, randomized controlled trial; RR, rate ratio
1. Ribal R et al. Poster presentation at IAGG 2017; Abstract 469; 2. Yale JF et al. Poster presentation at ADA 2015; Abstract 991-P

Key messages: various populations

T1DM adult patients	Gla-300 provides **comparable glycemic control and reduced hypoglycaemia (nocturnal) risk during the titration period** vs Gla-100 in adults with T1DM[1]
Patients with impaired renal function	Gla-300 provides **comparable glycemic control and a reduced hypoglycemia risk** vs Gla-100 in T2DM patients **regardless of renal function**[2]
Older patients	Gla-300 results in **comparable reductions in HbA1c** and low or lower risk of documented **symptomatic hypoglycemia** vs Gla-100 in older patients with T2DM, particularly those ≥ 75 years[3]
Pregnancy	The use of **Gla-100 or Gla-300** during pregnancy is **not associated with any specific adverse events**[4]
EDITION JUNIOR*	RCT designed to assess the efficacy and safety of Gla-300 vs Gla-100 in **children and adolescents** with T1DM[5] (Study design)

*Gla-300 is only indicated in adults; Risk criteria for developing hypoglycemia: 1. Experienced at least 1 severe hypoglycemic episode within the past year; 2. Moderate chronic renal failure (estimated glomerular filtration rate of 30-59 mL/min/1.73m²); 3. hypoglycemic symptom unawareness; 4. Exposure to insulin for longer than 5 years; or 5. An episode of hypoglycemia (symptoms and/or blood glucose level ≤70 mg/dL within the last 12 weeks

Home PD et al. Diabetes Obes Metab. 2018 Jan;20(1):121-128; [2]Ocaladi J et al. Diabetes Obes Metab. 2018 Dec;20(12):2860-2868; [3]Ribal R et al. Diabetes Care 2018 Aug;41(8):1672-1680; [4]Bertolini M et al. Poster presentation at EASD 2017; Abstract 917; [5]https://clinicaltrials.gov/ct2/show/NCT02750384 (last accessed March 2019)

Conclusions

- Insulin glargine U300 has a longer duration of action compared to glargine U100
- Lower rate of hypoglycemia (<70 mg/dl) specially during the first 8 weeks of treatment
  - Similar Hba1c
  - A slightly higher insulin requirement
  - Lower body weight
- Safety profile similar to glargine U100

PREGUNTAS…

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Puede descargar la presentación en:

www.EndoDrChen.com