
# New generation insulins

## Basal & Bolus

**Prof Abdulmoen Al Agha**

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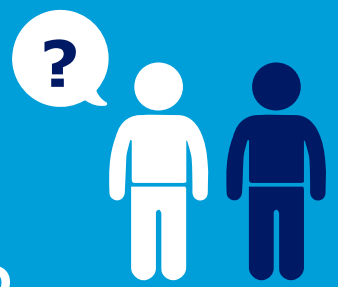
TODAY, more than **425 MILLION** people have diabetes[1]

BY 2045, it's estimated that

# 736 MILLION

people will have diabetes globally[1]




**1** in 2

People with type 2 diabetes **do not know** they have it[1]

**7** in 10

People with diabetes **do not achieve desired treatment outcomes**[2]

**4 MILLION**

**Deaths** were caused by diabetes in 2017[1]

1. International Diabetes Federation. *IDF Diabetes Atlas*, 8th edn. Brussels, Belgium: International Diabetes Federation. 2017. 2. Hart JT. Rule of halves: implications of increasing diagnosis and reducing dropout for future workload and prescribing costs in primary care. *Br J Gen Pract*. 1992;42(356):116–119.

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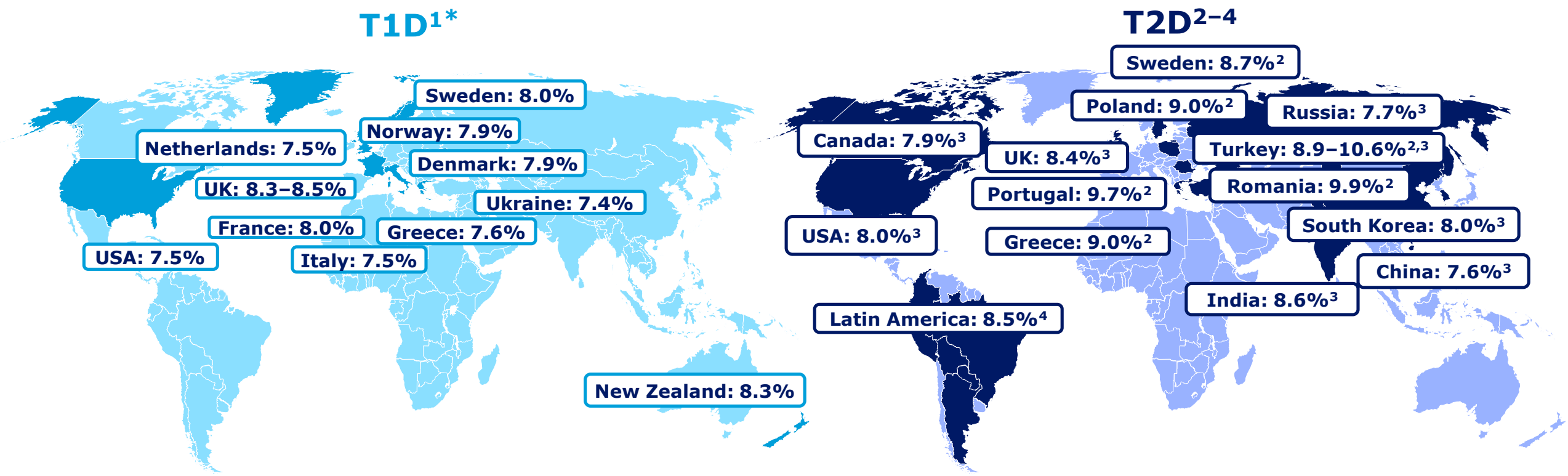
# Prevalence of Type 1 Diabetes

**Table 3.16 Top 10 countries/territories for the incidence rates (per 100,000 population per year) with Type 1 diabetes (<20 years),2017**

| Rank | Country | Incidence rates with type 1 diabetes |
|---|---|---|
| 1 | Finland | 57.2 |
| 2 | Kuwait | 44.5 |
| 3 | Sweden | 39.5 |
| 4 | Saudi Arabia | 33.5 |
| 5 | Norway | 29.8 |
| 6 | Algeria | 26.0 |
| 6 | Morocco* | 26.0 |
| 8 | United Kingdom | 25.9 |
| 9 | Ireland | 24.3 |
| 10 | Denmark | 23.0 |

# The worldwide challenge of glycaemic control

## $HbA_{1c}$ in T1D and T2D




*Data are median and in adults (25+ years)
T1D, type 1 diabetes; T2D, type 2 diabetes

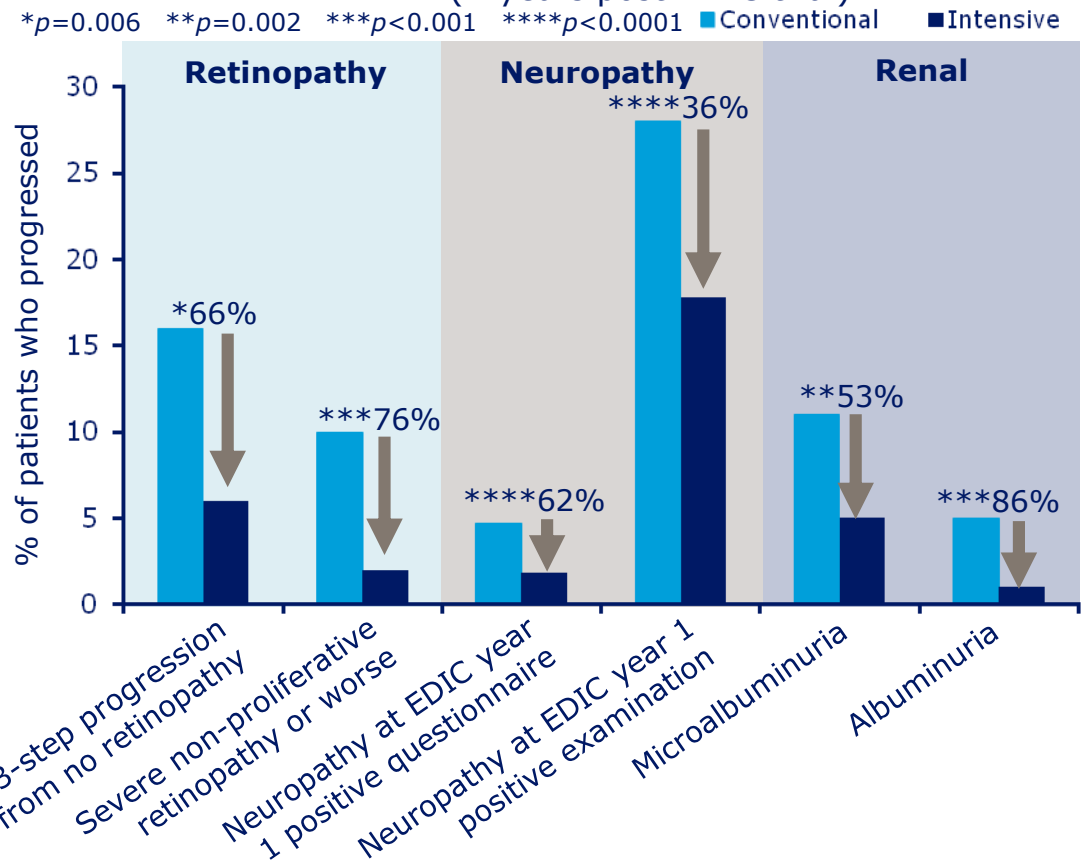
1. McKnight *et al. Diabet Med* 2015;32:1036–50; 2. Oguz *et al. Curr Med Res Opin* 2013;29:911–20; 3. Polinski *et al. BMC Endocr Disord* 2015;15:46; 4. Mendivil *et al. Curr Med Res Opin* 2014;30:1769–76

# Intensive vs. conventional treatment in T1D and T2D

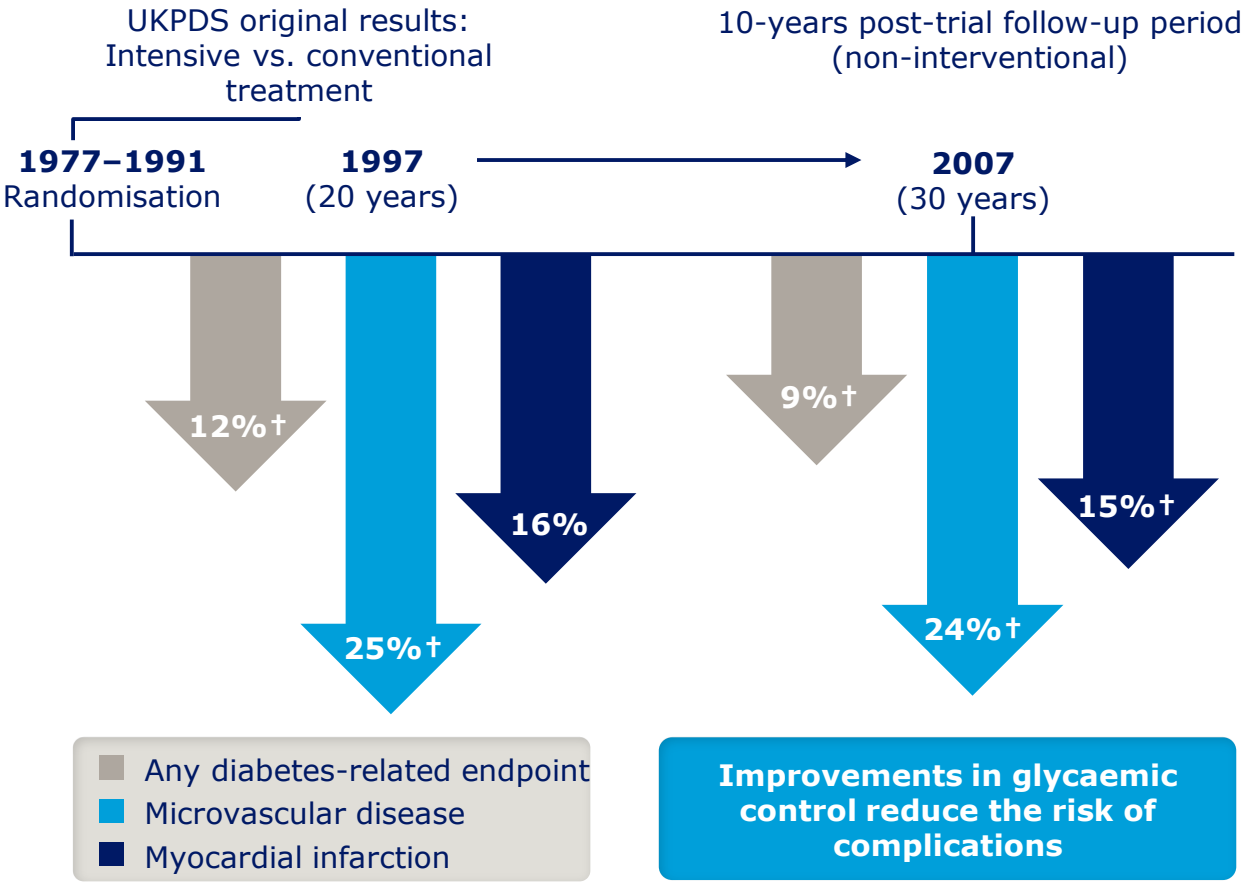
## DCCT/EDIC and UKPDS follow-up data

### T1D
### DCCT/EDIC – microvascular complications[1,2]

(4-years post-EDIC trial)




### T2D
### UKPDS – macrovascular complications[3,4]




**Improvements in glycaemic control reduce the risk of complications**

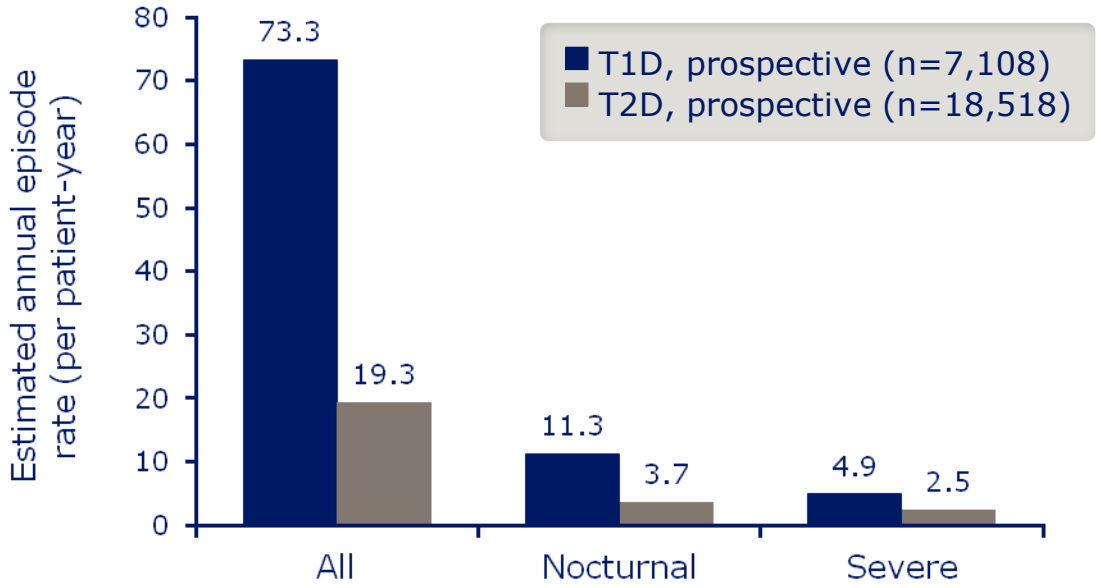
†$p<0.05$; intensive vs. conventional treatment; DCCT, Diabetes Control and Complications Trial; EDIC, European Diploma in Intensive Care Medicine; T1D, type 1 diabetes; T2D, type 2 diabetes; UKPDS, UK Prospective Diabetes Study. 1. DCCT/EDIC Group. *JAMA* 2002;287:2563–9; 2. Martin *et al. Diabetes Care* 2006;29:340–4; 3. UKPDS Study Group. *Lancet* 1998;352:837–53; 4. Holman *et al. N Engl J Med* 2008;359:1577–89

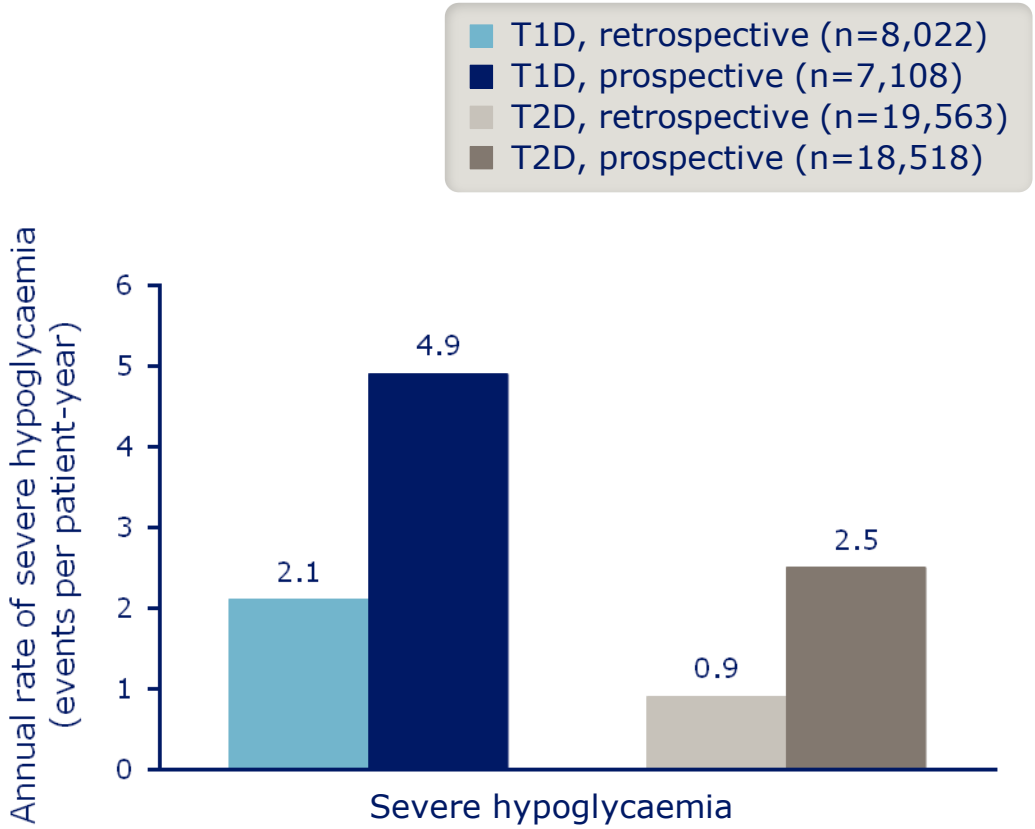
# Patients experience frequent hypoglycaemic events, some of which are severe

## Results from the HAT study

**HAT study**

- Non-interventional, global, 6-month retrospective and 1-month prospective study of patient self-reported hypoglycaemic events
- n=27,585 (T1D: 8,022; T2D: 19,563)



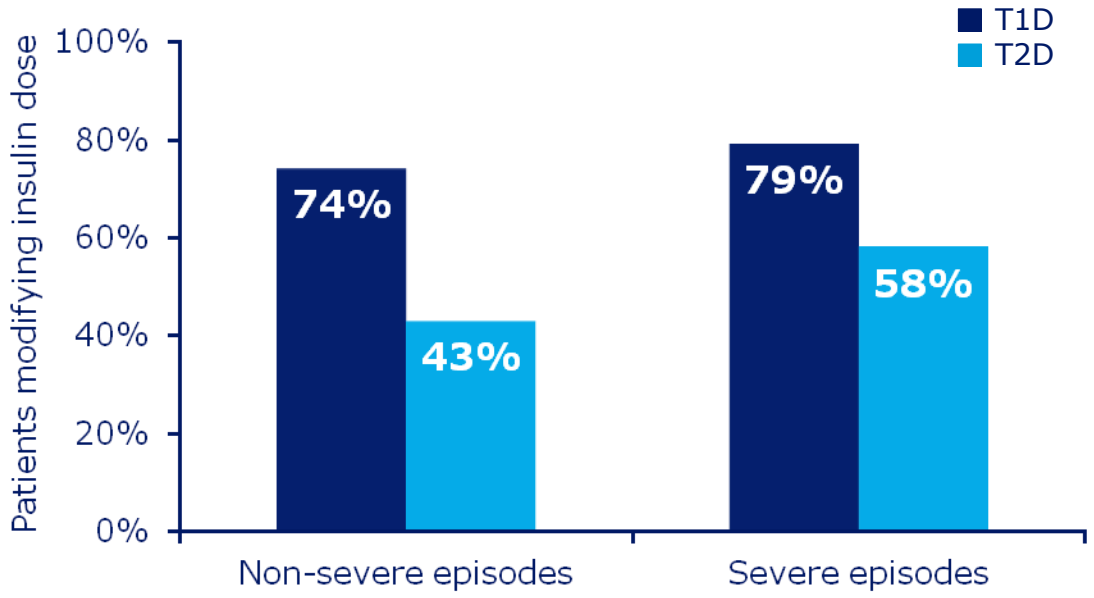




HAT, Hypoglycaemia Assessment Tool; T1D, type 1 diabetes; T2D, type 2 diabetes

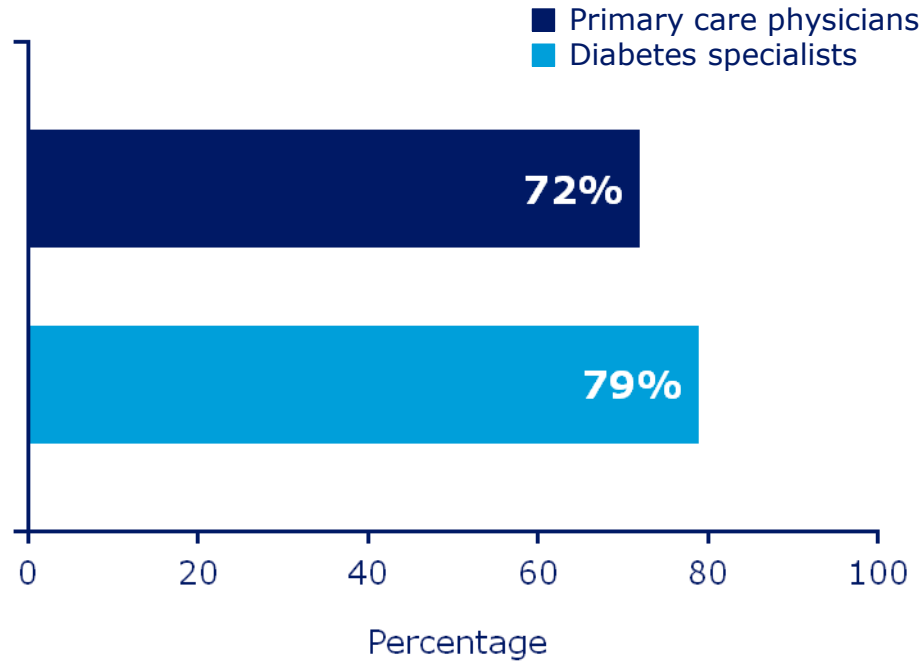
Khunti *et al. Diabetes Obes Metab* 2016;18:907–15; Khunti *et al.* Poster presented at the 10th International Diabetes Federation-Western Pacific Region Congress, 21–24 November 2014, Singapore

# Fear of hypoglycaemia conflicts with treatment success for both patients and clinicians

**Percentage of patients decreasing their insulin dose following a hypoglycaemic event**



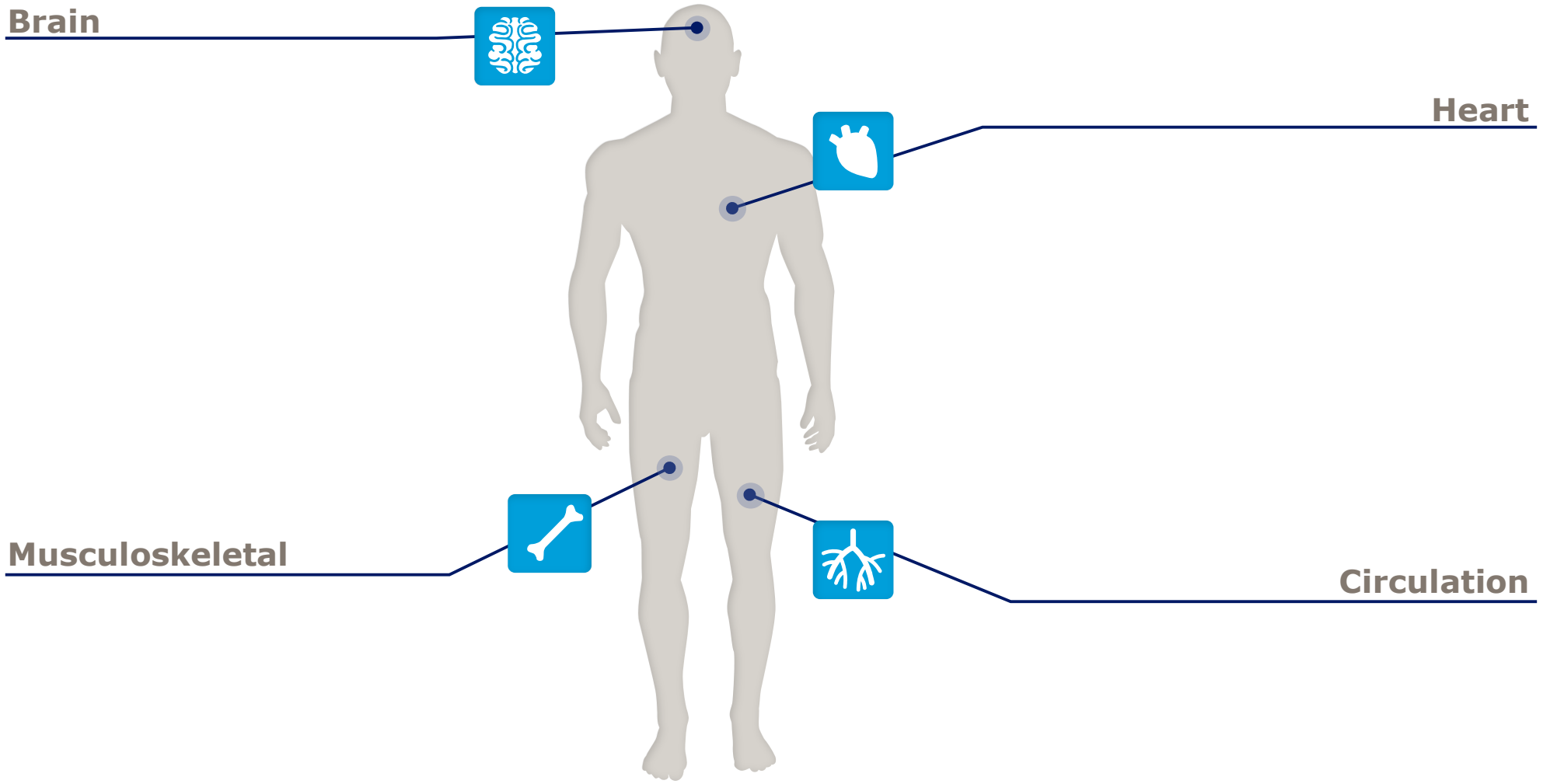

**I would treat my patients more aggressively if there was no concern about hypoglycaemia**




Total patient sample, n=335 (T1D, n=202; T2D, n=133)
T1D, type 1 diabetes; T2D, type 2 diabetes
Leiter *et al. Can J Diabetes* 2005;29:186–92

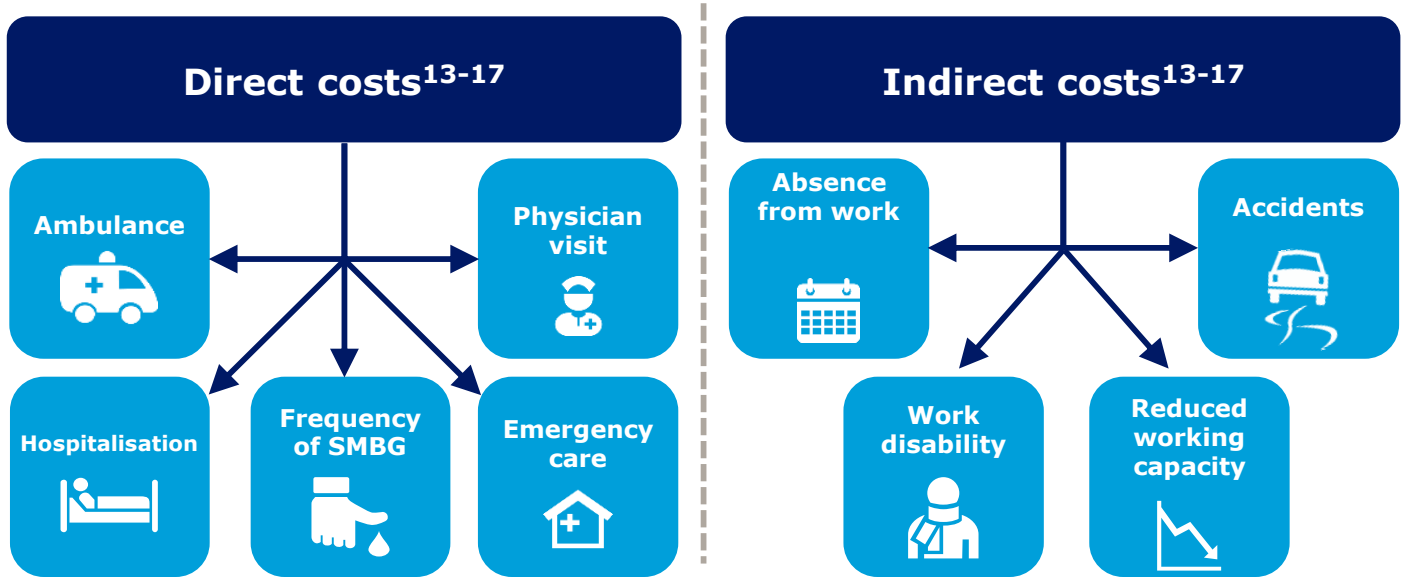
GAPP™ (A global internet survey of patient and physician beliefs regarding insulin therapy): n=1250 physicians
Peyrot *et al. Diabet Med* 2012;29:682–9

# The consequences of hypoglycaemia




Desouza *et al. Diabetes Care* 2010;33:1389–94; Frier *et al. Diabetes Care* 2011;34(Suppl. 2):S132–7; Frier. *Nat Rev Endocrinol* 2014;10:711–22; Gjedde *et al. Diabetologia* 2018;61:551-561

# The consequences of hypoglycaemia present a considerable burden to patients and society


CVE, cardiovascular events; ER, emergency room; SMBG, self-measured blood glucose

1. Heller *et al. Diabet Med* 2016;33:471–7; 2. Johnston *et al. Diabetes Obes Metab* 2012;14:634–43; 3. Ward *et al. J Med Econ* 2014;17:176–83; 4. Khunti *et al. Diabetes Care* 2015;38:316–22; 5. Leiter *et al. Can J Diabetes* 2005;29:186–92; 6. UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:837–53; 7. American Diabetes Association. *Diabetes Care* 2017;40(Suppl. 1):S75–S87; 8. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993;329:977–86; 9. Brod *et al. Value Health* 2011;14:665–71; 10. Davis *et al. Curr Med Res Opin* 2005;21:1477–83; 13. Jönsson *et al*. *J Value Health* 2006;9:193–198; 14. Farmer *et al. Curr Med Res Op* 2008;24:3097–3104; 15. Amiel *et al. Diabet Med* 2008;25:245–254. 16. Leese *et al. Diabetes Care*. 2003;26:1176–80; 17. Curkendall *et al. JCOM* 2011;18:455–62

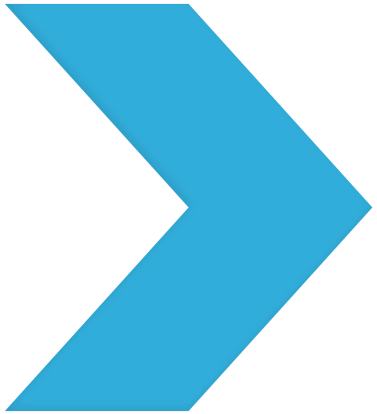
# Objectives of developing the ideal basal insulin

Glycaemic control

Simplicity
(once-daily and flexible dosing)

Predictability

Low risk of hypoglycaemia



**Ideal PK/PD profile**

Flat time–action profile

Low variability

Half-life >24 hours

Potency (total glucose-lowering effect)

PD, pharmacodynamic; PK, pharmacokinetic

# Discovery of insulin

## First human patient

**Leonard Thompson**
14 year-old boy with diabetes

- Weighed 65 pounds
- Urine full of acetone and sugar
- Ketotic breath

**First injection**
January 11th 1922

- Blood sugar drops from 440 to 320mg
- Inflammation at injection sites due to allergic reaction

**Second injection**
Cleaner extract made by Collip
January 23rd 1922

- Improved health
- Lived for another 13 years with regular insulin injections

Karamitsos, D.T. (2011). The story of insulin discovery. *Diabetes Res Clin Pract, 93,* S2-S8; Rosenfeld, L. (2002). Insulin: discovery and controversy. *Clin Chem, 48*(12), 2270-88.

# Significant space for innovation within insulin

Isolation of Insulin (Banting & Best)

1922

Animal Insulin Preparations

1950s

Premixed animal insulin

Recombinant Human Insulin

1977

NovoRapid® (insulina aspart)

Rapid-acting analogues

1980s

Premixed human insulin

NovoLog® Mix 70/30
70% insulin aspart protamine suspension and 30% insulin aspart injection, (rDNA origin)

Biphasic analogues

1990s

LANTUS
insulin glargine (rDNA origin) injection

Levemir®
insulin detemir (rDNA origin) injection

Basal analogues

2000s

Premixed insulin analogue

2002

Fiasp®
fast-acting insulin aspart

Xultophy®
insulin degludec 100 units and liraglutide 3.6 mg per mL injection

TRESIBA®
insulin degludec injection 100 U/mL, 200 U/mL

RYZODEG®
30% insulin degludec and 70% insulin aspart (rDNA origin) injection

Toujeo®
insulin glargine injection 300 Units/mL

New generation analogues

2010s

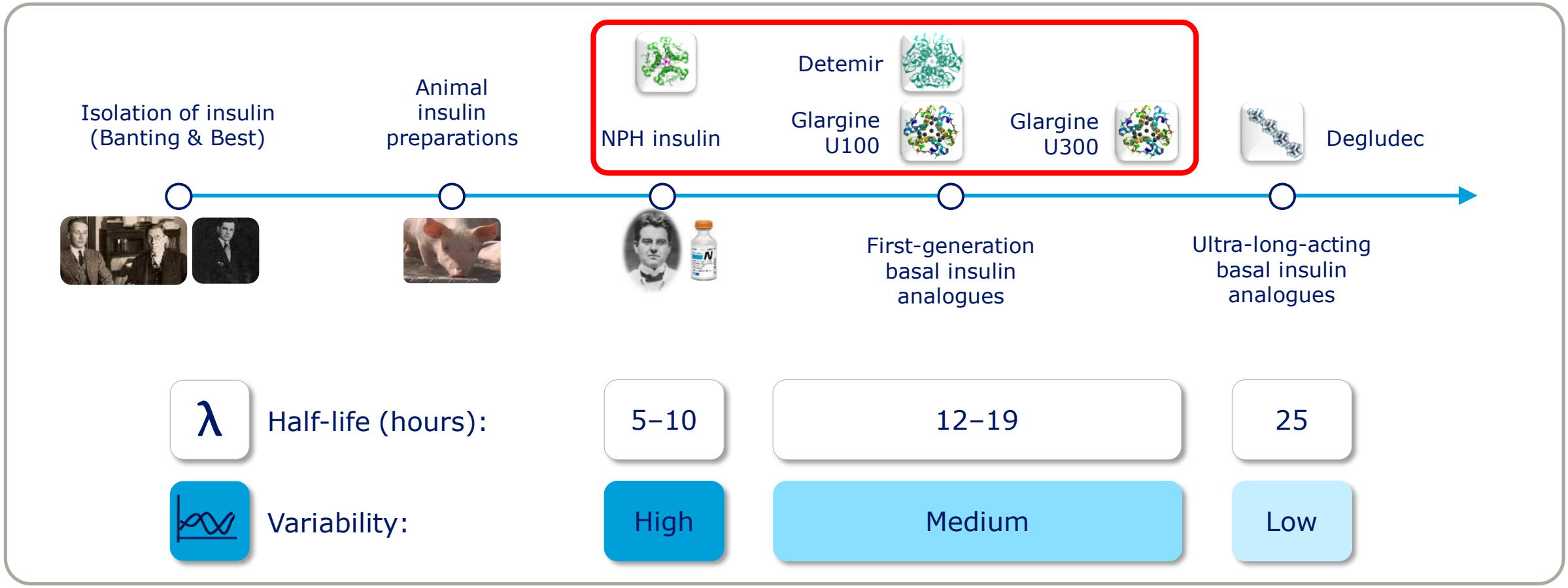
IDegAsp co-formulation

2013

## Evolution of combination insulins

IDegAsp, insulin degludec/insulin aspart

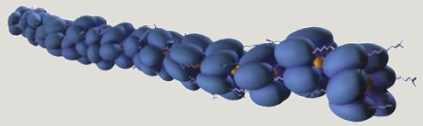
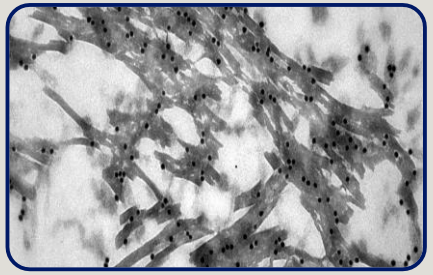
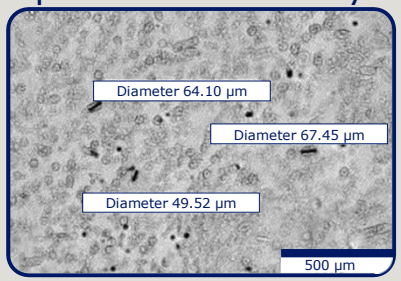
# The quest for the ideal basal insulin




Detemir, insulin detemir; glargine U100, insulin glargine 100 units/mL; glargine U300, insulin glargine 300 units/mL; NPH, neutral protamine Hagedorn; SmPC, summary of product characteristics; NPH insulin SmPC. https://www.ema.europa.eu/documents/product-information/insulatard-epar-product-information_en.pdf; Detemir SmPC. https://www.ema.europa.eu/documents/product-information/levemir-epar-product-information_en.pdf; Glargine U100 SmPC. https://www.ema.europa.eu/documents/product-information/lantus-epar-product-information_en.pdf; Glargine U300 SmPC. https://www.ema.europa.eu/documents/product-information/toujeo-epar-product-information_en.pdf; Degludec SmPC. https://www.ema.europa.eu/documents/product-information/tresiba-epar-product-information_en.pdf All accessed December 2018

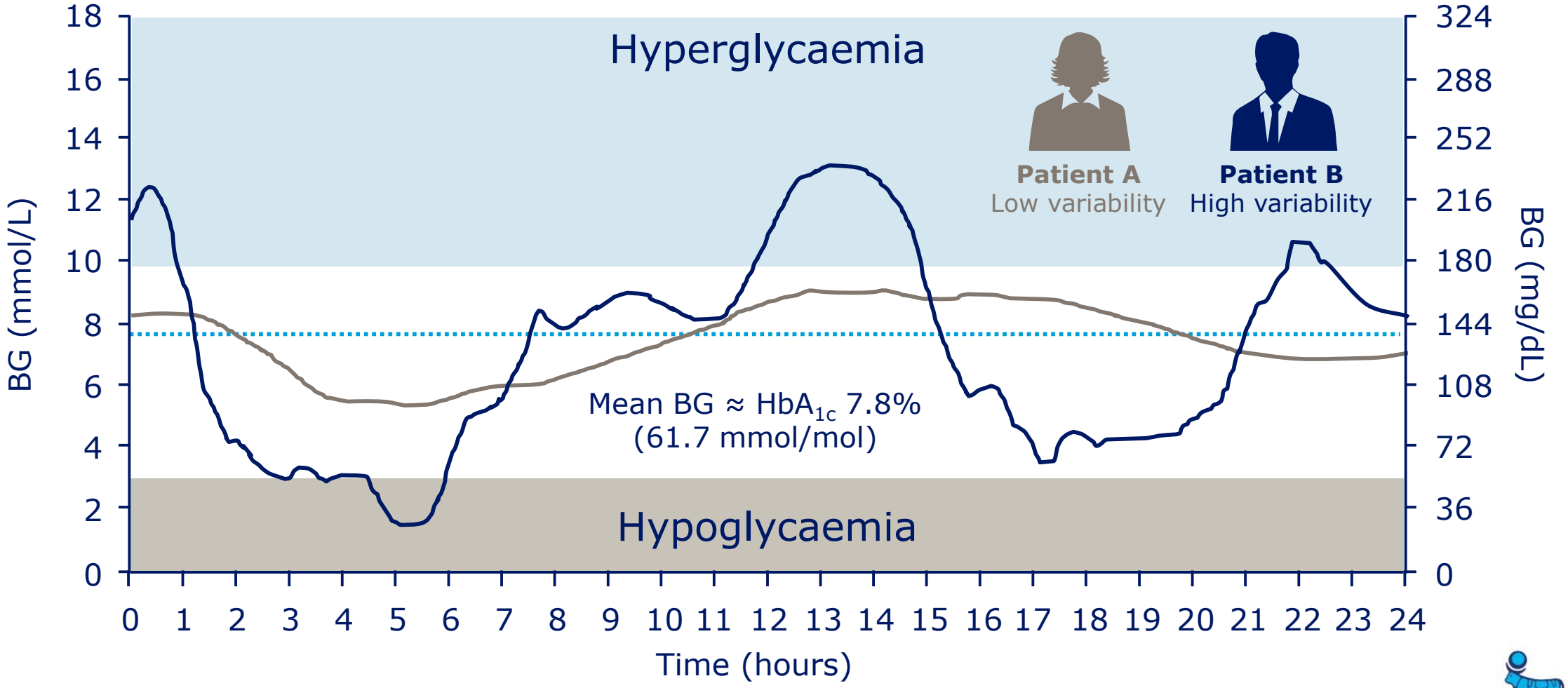
# New Generation of Basal insulins

# Degludec and glargine U100 and U300

| | Degludec | Glargine U100 | Glargine U300 |
|---|---|---|---|
| **Type of insulin** | New-generation long-acting basal insulin analogue | First-generation basal insulin analogue | Up-concentrated formulation of first-generation basal insulin analogue |
| **Mode of protraction** | Forms soluble multihexamers  | Precipitates as microcrystals  | Precipitates as microcrystals   |
| **Half life** | ~25 hours | ~12 hours | ~19 hours |

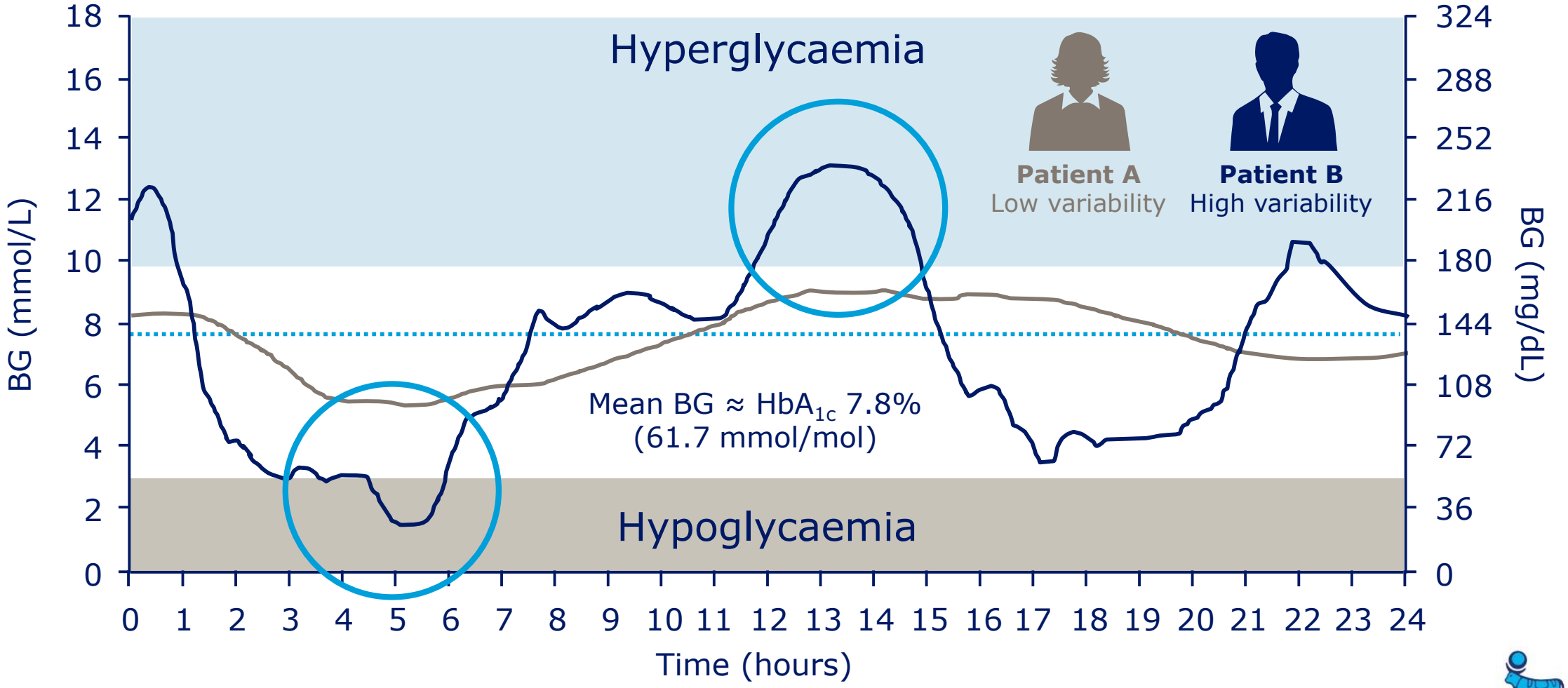
Glargine U100, insulin glargine 100 units/mL; glargine U300, insulin glargine 300 units/mL
Glargine U100 image data on file; glargine U300 optical microscopy images obtained from European patent application http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=EP&NR=2387989A2&KC=A2&date=&FT=D&locale=en_EP
Jonassen *et al. Pharm Res* 2012;29:2104–14; Heise *et al. Expert Opin Drug Metab Toxicol* 2015;11:1193–201; Heise *et al. Diabetes Obes Metab* 2012;14:859–64

# Glycaemic control: variability



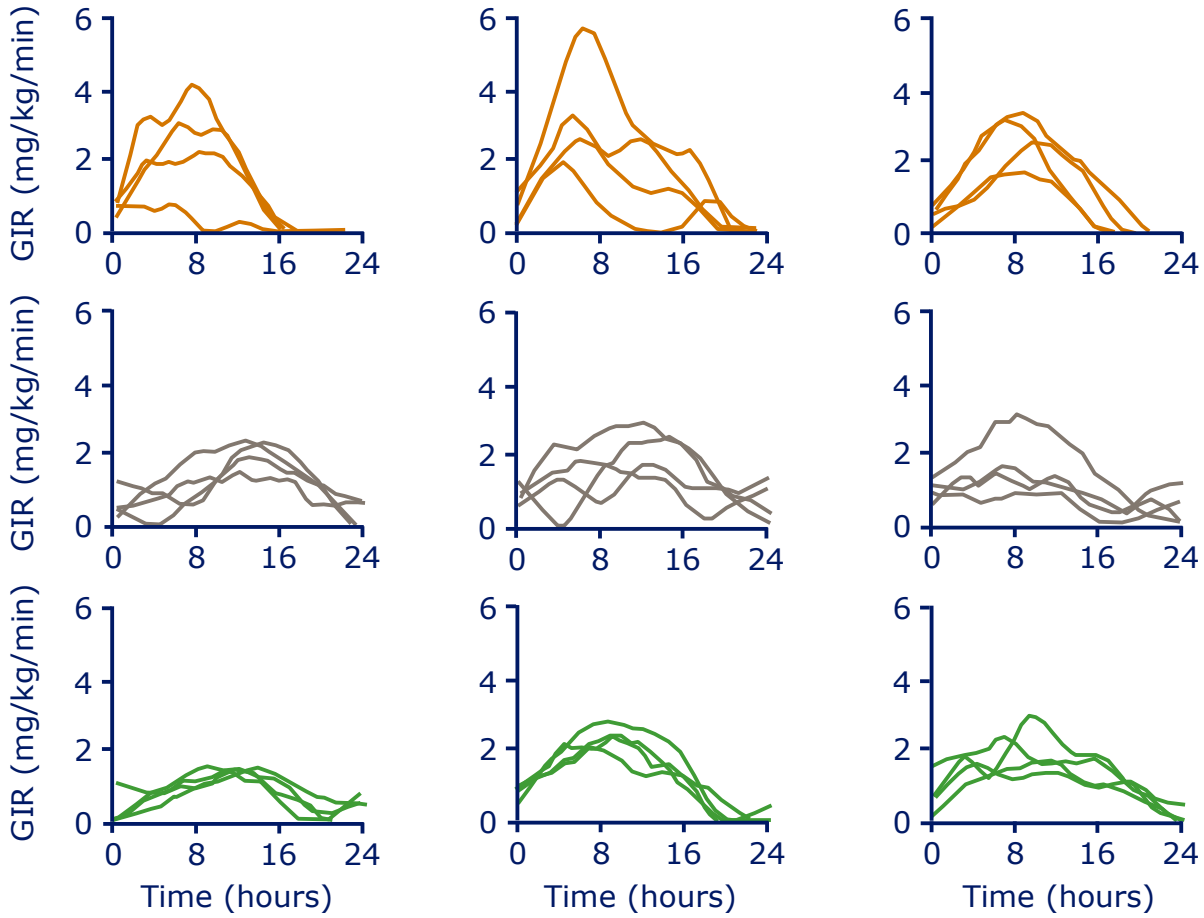

BG, blood glucose; $HbA_{1c}$, glycated haemoglobin.
Image adapted from Penckofer S et al. *Diabetes Techno Ther* 2012;14:303–10; Vora J & Heise T. *Diabetes Obes Metab* 2013;15:701–12.

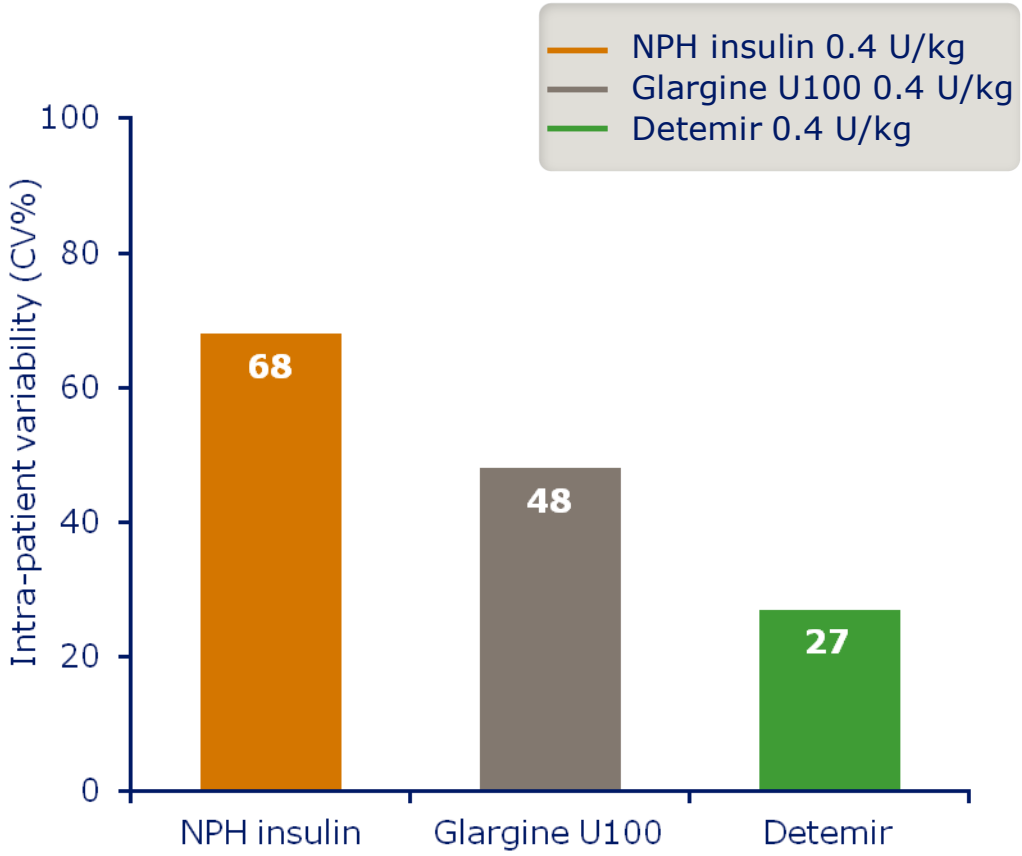
# Glycaemic control: similar $HbA_{1c}$, different profile




BG, blood glucose; $HbA_{1c}$, glycated haemoglobin.
Image adapted from Penckofer S et al. *Diabetes Techno Ther* 2012;14:303–10; Vora J & Heise T. *Diabetes Obes Metab* 2013;15:701–12.

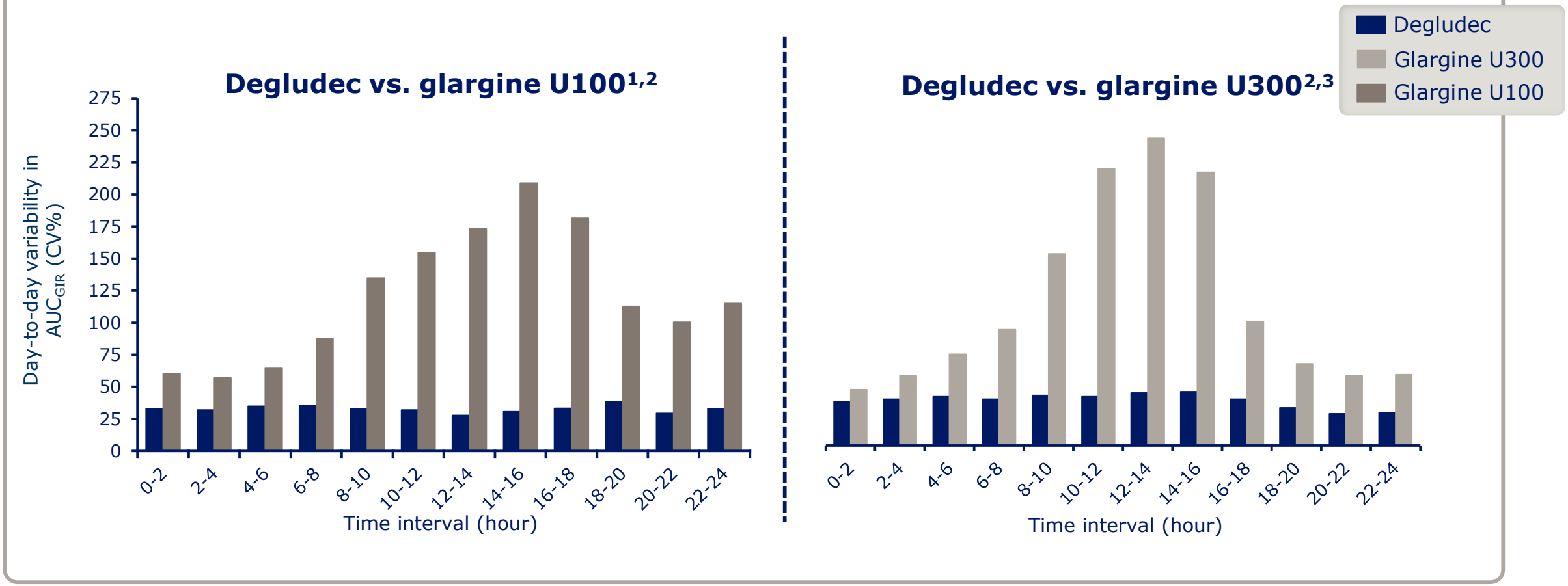
# Lower day-to-day glucose variability with first-generation basal insulin analogues versus NPH insulin




CV, coefficient of variation; detemir, insulin detemir; GIR, glucose infusion rate; glargine U100; insulin glargine 100 units/mL; NPH, neutral protamine Hagedorn; Heise *et al. Diabetes* 2004;53:1614–20

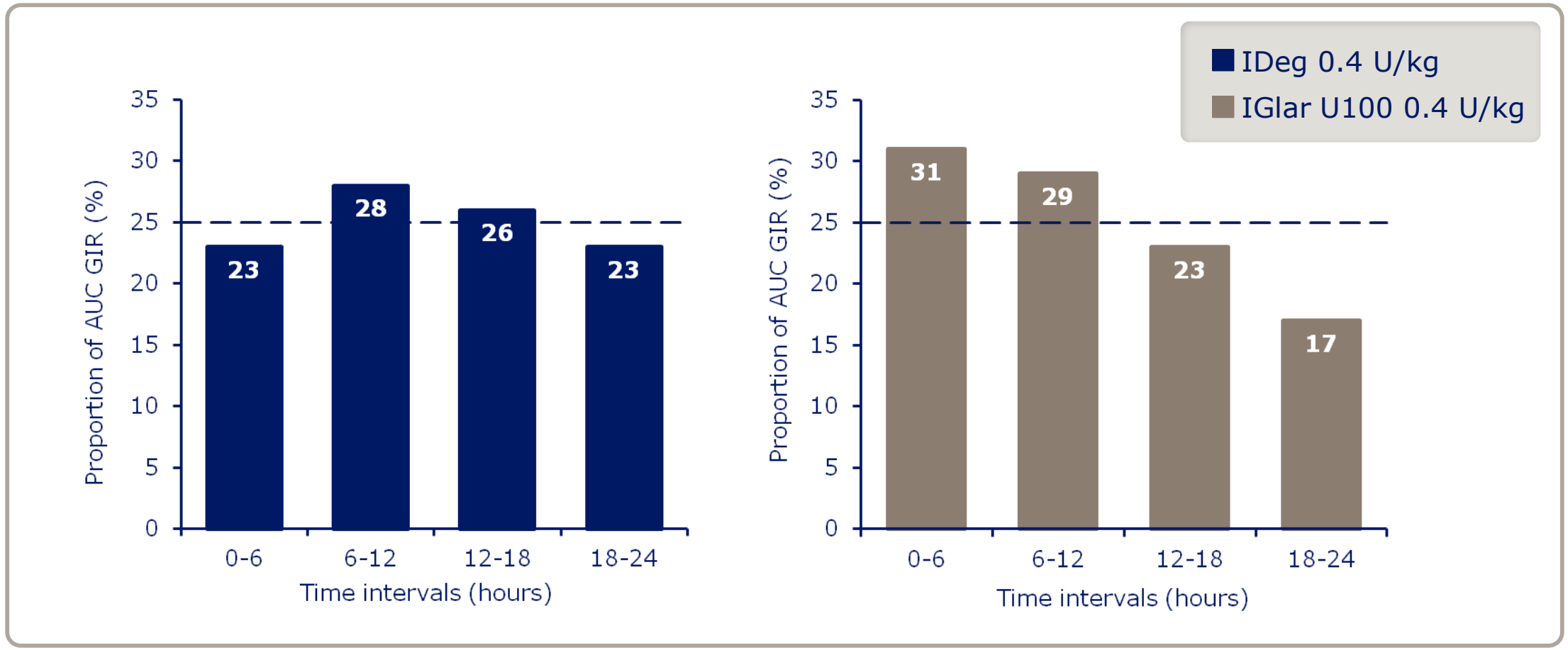
# Lower day-to-day variability in glucose-lowering effect for degludec versus glargine U100/U300




AUC, area under the curve; CV, coefficient of variation; GIR, glucose infusion rate; glargine U100, insulin glargine 100 units/mL; glargine U300, insulin glargine 300 units/mL

1. Heise *et al. Diabetes Obes Metab* 2012;14:85–64; 2. Heise *et al. J Diabetes Sci Technol* 2018;12:356-363; 3. Heise *et al. Diabetes Obes Metab* 2017;19:1032–9

# Glucose-lowering effect is more consistent with IDeg than IGlar U100




Proportion of effect in 6-hour time intervals across one dosing interval (%)
Patients with T1D (n=66)
AUC, area under the curve; GIR, glucose infusion rate; IDeg, insulin degludec; IGlar U100, insulin glargine U100; T1D, type 1 diabetes
Heise *et al. Expert Opin Drug Metab Toxicol* 2015;11:1193–201

# Degludec phase 3 clinical trial programme overview

## Type 2 diabetes

- EARLY
  Basal start, n=458
- ONCE LONG
  Basal start, n=1030
- ONCE ASIA
  Basal start, n=435
- ADD-ON TO GLP-1
  BOT, n=346
- LOW VOLUME
  U200 basal start, n=460
- BB
  Basal–bolus, n=1006
- HIGH DOSE
  degludec U200 vs. glargine U100, n=145
- VICTOZA® ADD-ON
  BOT, n=413
- SWITCH 2
  Basal switch, n=721
- DEVOTE
  Cardiovascular outcomes study
- FLEX
  BOT, n=687
- Flexibility and simple titration in Japan, n=458
- COMPARE
  BOT, n=373
  degludec U100 vs. U200
- ONCE SIMPLE USE
  Basal start, n=222
  Simple vs. step-wise

## Type 1 diabetes

- BB T1 LONG
  Basal–bolus, n=629
- BB T1
  Basal–bolus, n=456
- FLEX T1
  Basal–bolus, n=493
- YOUNG 1
  Basal–bolus, n=350
- Exercise study
  n=40
- SWITCH 1
  Basal switch, n=501

### Comparators

- vs. detemir
- Degludec + liraglutide
- vs. DPP-4 inhibitors
- vs. degludec*

T1D and T2D vs. glargine U100

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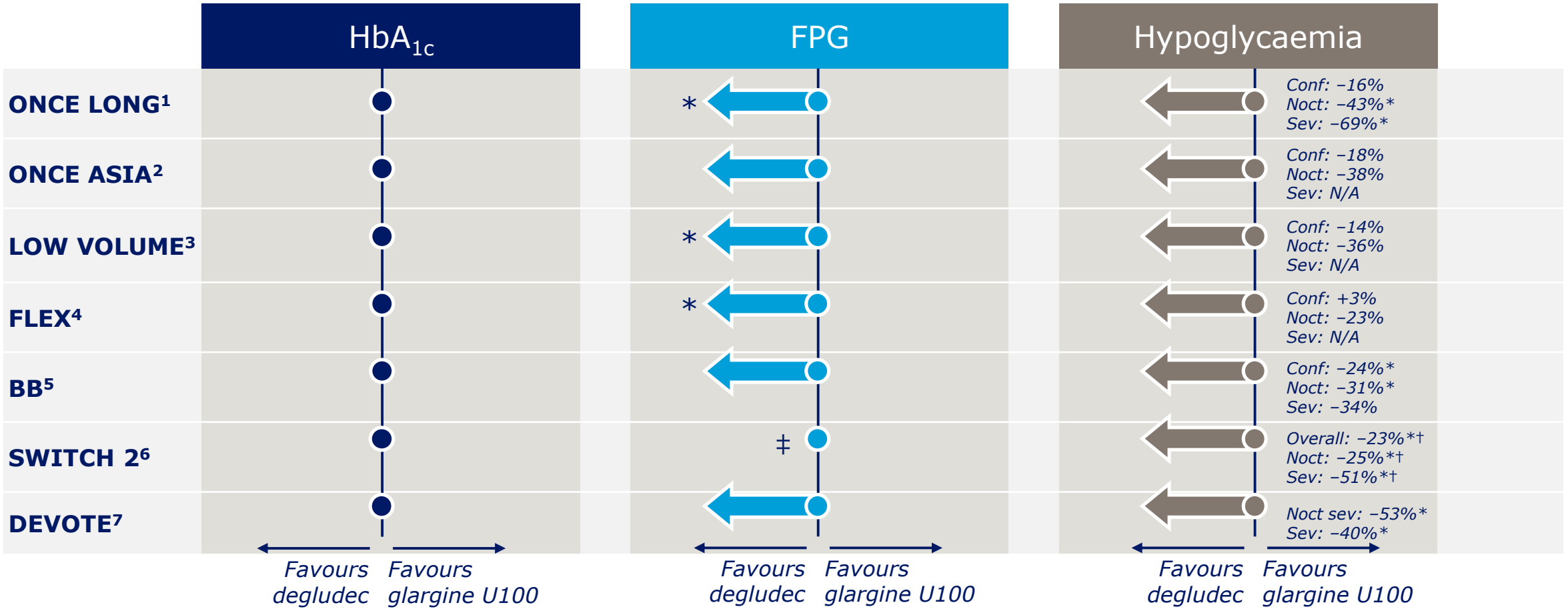
BB, basal–bolus; BOT, basal-oral therapy; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; T1D, type 1 diabetes; T2D, type 2 diabetes

# Degludec phase 3 T2D trial overview




*Statistically significant difference; †full treatment period; ‡at the end of treatment period 1, mean FPG was 5.96 mmol/L for degludec and 5.94 mmol/L for IGla U100 At the end of treatment period 2, mean FPG increased slightly to 5.97 mmol/L for degludec, whereas FPG increased to 6.33 mmol/L for glargine U100
Conf, confirmed; FPG, fasting plasma glucose; N/A, not analysed due to few or no severe events recorded; noct, nocturnal; sev, severe

1. Rodbard *et al. Diabet Med* 2013;30:1298–304; 2. Onishi *et al. J Diab Invest* 2013;4:605–12; 3. Gough *et al. Diabetes Care* 2013;36:2536–42; 4. Meneghini *et al. Diabetes Care* 2013;36:858–64; 5. Hollander *et al. Diabetes Obes Metab* 2014;17:202–6; 6. Wysham *et al. JAMA* 2017;318:45–56; 7. Marso *et al. N Engl J Med* 2017;377:723–32

NN1250-3561

# BEGIN: YOUNG 1 AND EXTENSION


Thalange et al. *Pediatr Diabetes.* 2015;16:164-176.

# YOUNG 1 AND EXTENSION

## Background

### Rationale

- IDeg may offer treatment benefits to pediatric patients with T1DM relative to existing insulin-based therapies
  - IDet is widely used in the treatment of pediatric patients and is a suitable comparator
  - IAsp may be used in children in preference to soluble human insulin when a rapid onset of action might be beneficial

### Objective

- To compare the efficacy and safety of IDeg versus IDet, both given with meal-time IAsp (basal–bolus therapy) in children and adolescents with T1DM

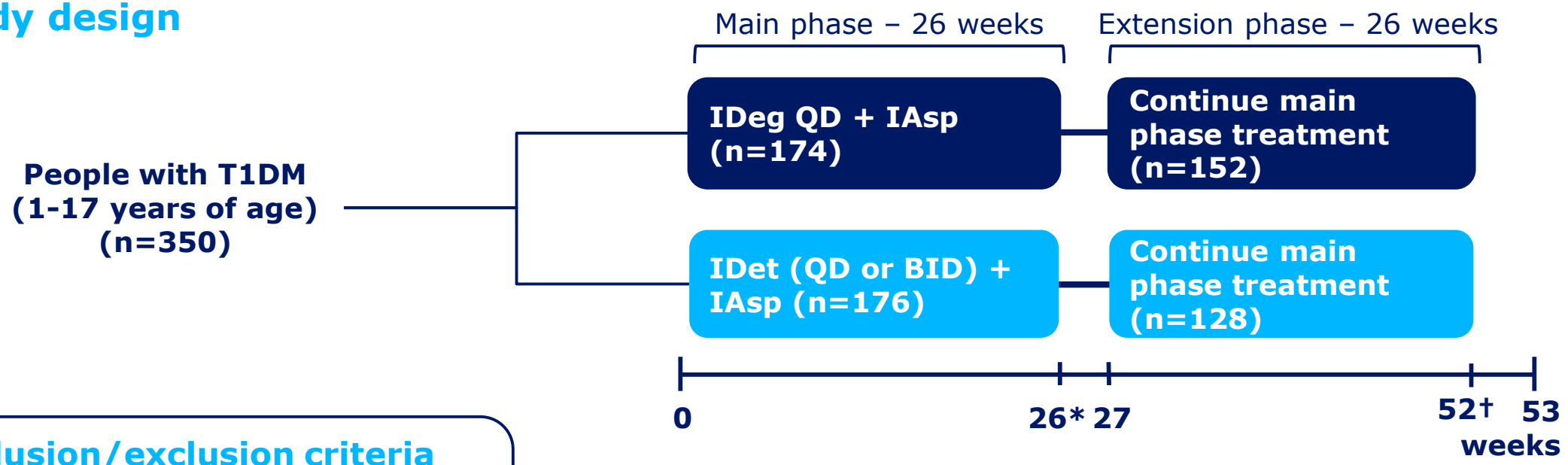
NovoLog® US Prescribing Information: Pediatric: Has not been studied in children with type 2 diabetes. Has not been studied in children with type 1 diabetes <2 years of age (8.4)
Levemir® US Prescribing Information: Pediatric: Has not been studied in children with type 2 diabetes. Has not been studied in children with type 1 diabetes <2 years of age (8.4)

BID, twice-daily; IAsp, insulin aspart; IDeg, insulin degludec; IDet, insulin detemir; QD, once-daily; T1DM, type 1 diabetes mellitus

NovoLog® (insulin aspart) [US Prescribing Information]. Plainsboro, New Jersey: NovoNordisk; Feb 2015.
Levemir (insulin detemir) [US Prescribing Information]. Plainsboro, New Jersey: NovoNordisk; Feb 2015.
Thalange et al. *Pediatr Diabetes.* 2015;16:164-176.

# YOUNG 1 AND EXTENSION

## Study design




### Inclusion/exclusion criteria

- T1DM
- Age 1–17 years
- Ongoing treatment with insulin (any regimen) for ≥3 months
- No OADs allowed
- $HbA_{1c}$ ≤11.0%

Open label

* Follow-up and 1 week NPH + IAsp washout period to minimize interference with antibody measurements taken at Week 27. Only applicable for patients **NOT** continuing in extension period.

† 1 week NPH + IAsp wash out at Week 52

### Age stratification groups

- 1–5 years
- 6–11 years
- 12–17 years

BID: twice-daily; $HbA_{1c}$; glycated hemoglobin; IAsp, insulin aspart; IDeg, insulin degludec; IDet, insulin detemir; NPH: neutral protamine Hagedorn; OAD, oral anti-diabetic drug; QD, once-daily; T1DM, type 1 diabetes mellitus

Thalange et al. *Pediatr Diabetes.* 2015;16:164-176.

# YOUNG 1 AND EXTENSION

## Titration

| Titration algorithm | | IDeg and IDet | | | IAsp (sliding scale) | |
|---|---|---|---|---|---|---|
| Current dose | | <5U | 5–15U | >15U | ≤5U | >5U |
| Pre-breakfast/pre-dinner plasma glucose (IDeg and IDet) or Lowest pre-meal/bedtime plasma glucose (IAsp) | | Adjustment | | | Adjustment | |
| mg/dL | mmol/L | U | | | U | |
| <90 | <5.0 | -½ | -1 | -2 | -1 | -2 |
| 90–145 | 5.0–8.0 | 0 | 0 | 0 | 0 | 0 |
| 146–180 | 8.1–10.0 | +½ | +1 | +2 | +0.5 | +1 |
| 181–270 | 10.1–15.0 | +1 | +2 | +4 | +1 | +2 |
| >270 | >15.0 | +1½ | +3 | +6 | +1.5 | +3 |

Titration of IAsp, IDeg, and IDet was done once weekly based on lowest of SMPG values measured prior to visit/phone contact.

Basal insulin titration was done according to the lowest pre-breakfast SMPG value measured on the three days prior to the visit/ phone contact for IDeg and IDet QD. For IDet BID the morning dose adjustment will be based on the lowest pre-dinner SMPG value measured on the three days prior to the visit/phone contact.

IAsp titration will be done once weekly based on the lowest of three SMPG values measured prior to the next meal and bedtime on the three days prior to the visit/phone contact:

- Pre-breakfast IAsp was adjusted according to lowest SMPG measured pre-lunch
- Pre-lunch IAsp was adjusted according to lowest SMPG measured before main evening meal
- Before main evening meal IAsp was adjusted according to lowest SMPG measured at bedtime

BID, twice daily; IAsp, insulin aspart; IDeg, insulin degludec; IDet, insulin detemir; QD, once-daily, SMPG, self-measured plasma glucose; U, unit

Thalange et al. *Pediatr Diabetes.* 2015;16:164-176.

# YOUNG 1 AND EXTENSION

## Endpoints

**Primary endpoint:** $HbA_{1c}$ change from baseline after 26 weeks

### Key secondary endpoints

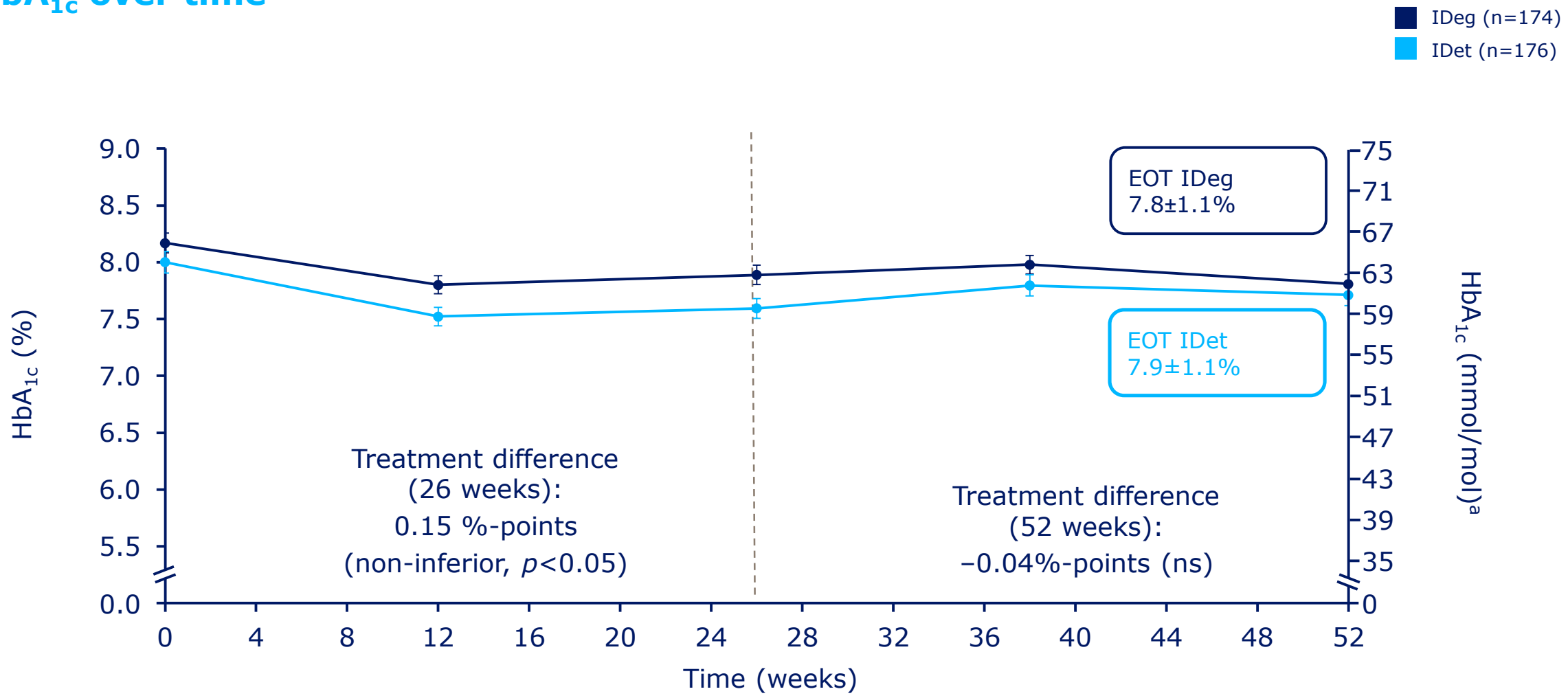
- $HbA_{1c}$ after 52 weeks
- Fasting plasma glucose (FPG)
- 8-point self-measured plasma glucose (SMPG) profiles
- Hypoglycemia
- Hyperglycemia with ketosis
- Adverse events
- Prandial increment
- Insulin dose
- Weight

Achieving good glycemic control in children and adolescents is challenging due lifestyle factors, physiological changes, and developmental changes. Poor control poses a risk of hyperglycemia with ketosis, which may progress to diabetic ketoacidosis and eventually death.

In these results presentations, p-values are shown for results that show statistically significant differences, and not for results that are not statistically significant.
$HbA_{1c}$, glycated hemoglobin
Thalange et al. *Pediatr Diabetes.* 2015;16:164-176.
Halvorson et al. *Diabetes Spectrum.* 2005;18:167-173.
Wolfsdorf JI et al. *Pediatr Diabetes.* 2014;15 Suppl 20:154-179.

# YOUNG 1 AND EXTENSION

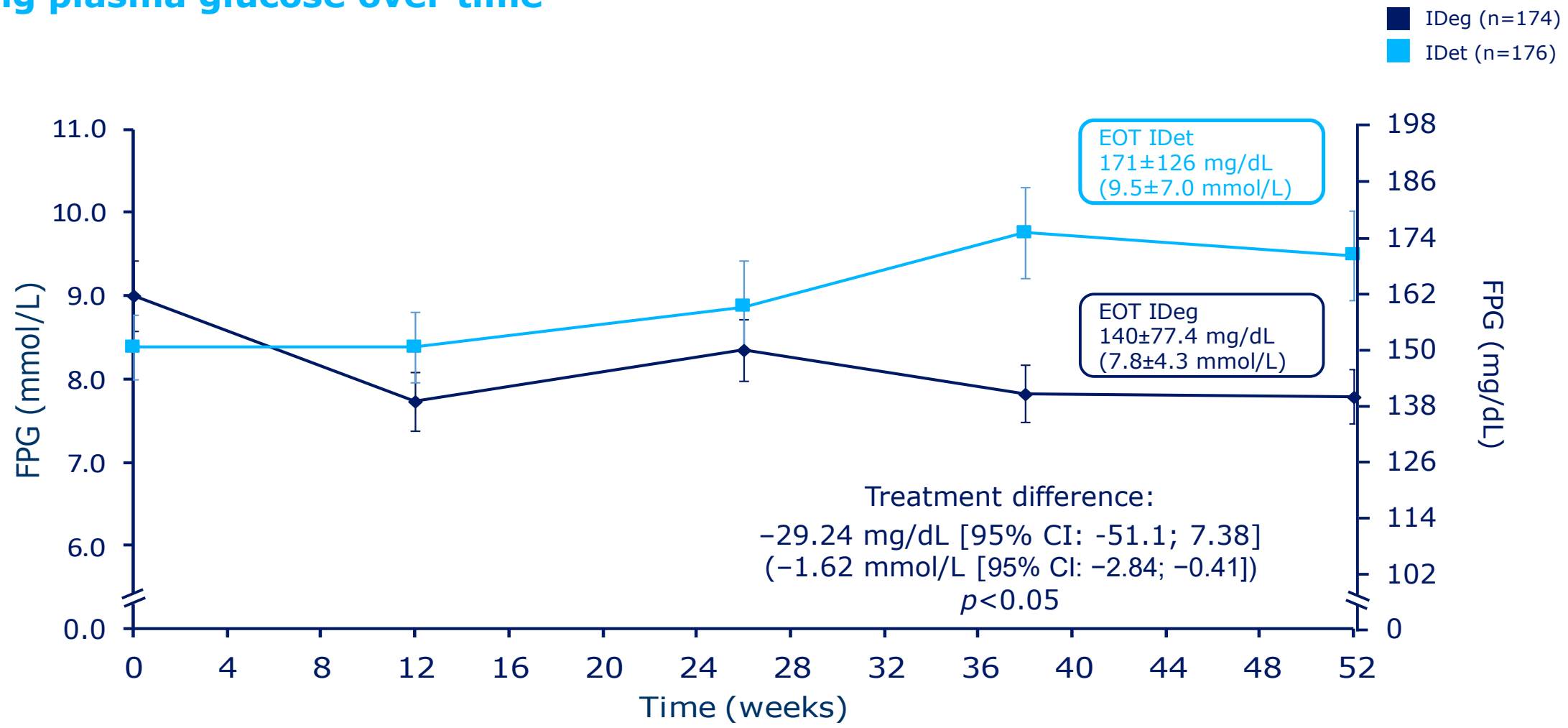
## $HbA_{1c}$ over time




FAS, Full analysis set; LOCF, last observation carried forward; Mean±SEM
$HbA_{1c}$, glycated hemoglobin; IDeg, insulin degludec; IDet, insulin detemir
[a]Calculated, not measured
Comparisons: Estimates adjusted for multiple covariates by ANCOVA
Thalange et al. *Pediatr Diabetes.* 2015;16:164-176.

# YOUNG 1 AND EXTENSION

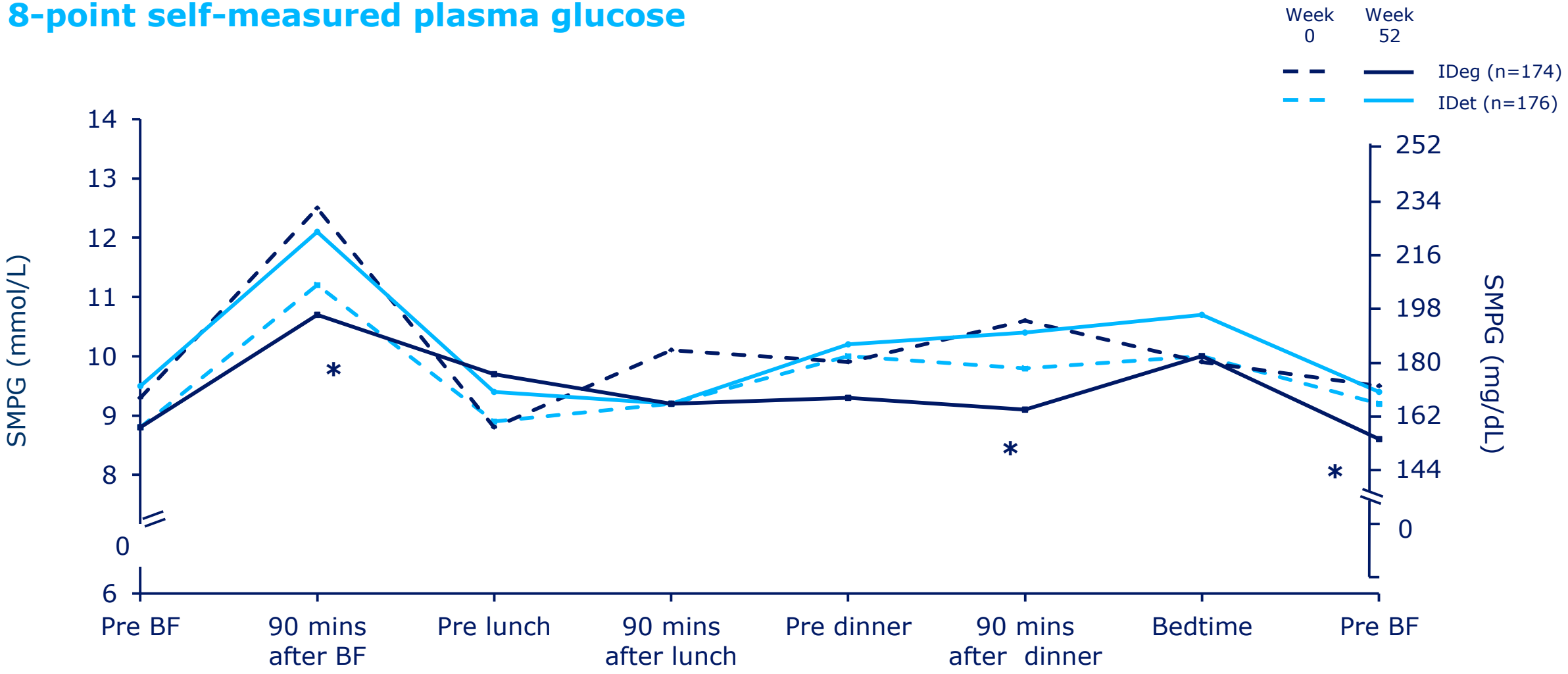
## Fasting plasma glucose over time




FAS, full analysis set; LOCF, last observation carried forward; Mean±SEM
Comparisons: Estimates adjusted for multiple covariates
FPG, fasting plasma glucose; IDeg, insulin degludec; IDet, insulin detemir
Thalange et al. *Pediatr Diabetes.* 2015;16:164-176.

# YOUNG 1 AND EXTENSION

## 8-point self-measured plasma glucose

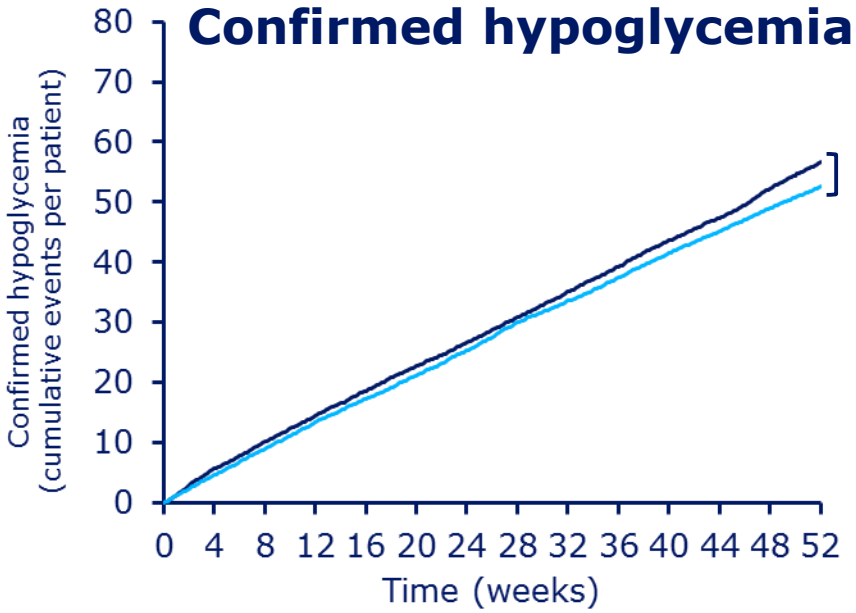



FAS, full analysis set; LOCF, last observation carried forward
*$p<0.05$; Comparisons: Estimates adjusted for multiple covariates
BF, breakfast; IDeg, insulin degludec; IDet, insulin detemir; SMPG, self-measured plasma glucose
Thalange et al. *Pediatr Diabetes.* 2015;16:164-176.

# YOUNG 1 AND EXTENSION

## Hypoglycemia

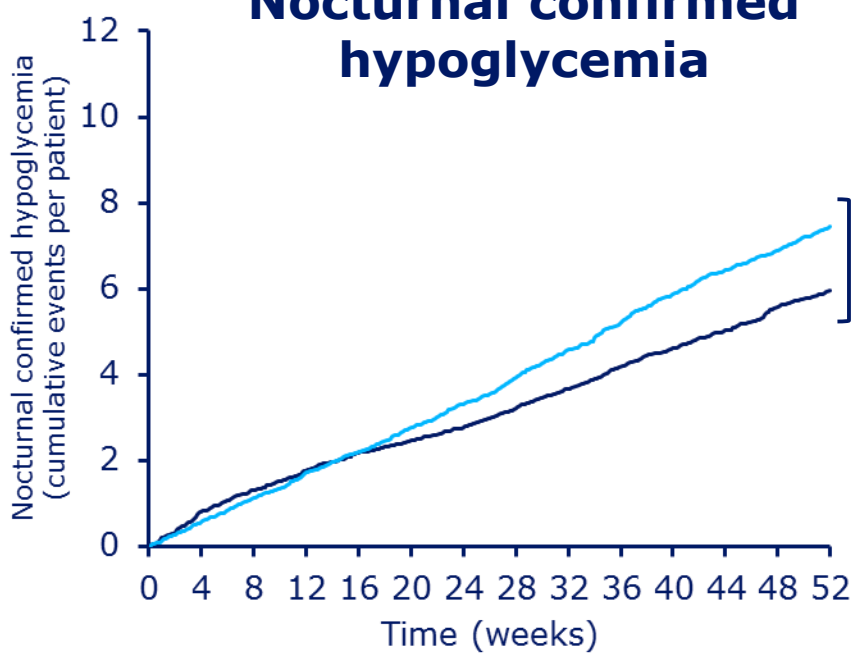
### Confirmed hypoglycemia




End of extension (Week 52)
IDeg rate: 57.7/PYE
IDet rate: 54.1/PYE

ERR (IDeg/IDet): 1.11
[95% CI: 0.89; 1.38]
(ns)

### Nocturnal confirmed hypoglycemia




End of extension (Week 52)
IDeg rate: 6.03/PYE
IDet rate: 7.60/PYE

ERR (IDeg/IDet): 0.99
[95% CI: 0.72; 1.34]
(ns)

Child has altered mental status and cannot assist in his own care, is semi- or unconscious, or in coma ± convulsions and may require parenteral therapy[a]

| | IDeg (n=174) | | IDet (n=175) | | IDeg vs. IDet | |
|---|---|---|---|---|---|---|
| | Incidence % patients (# patients) | Rate episodes/ PYE | Incidence % patients (# patients) | Rate episodes/ PYE | Rate ratio | ΔRisk |
| **Severe** | 17.8% (31/174) | **0.51** | 13.7% (24/175) | **0.33** | 1.30 | **+30%** |

SAS, safety analysis set
Comparisons: Estimates adjusted for multiple covariates
[a]Definition of severe hypoglycemia is according to ISPAD guidelines
Nocturnal hypoglycemia is between 11pm to 7am
% patients, proportion of patients with events; # patients, number of patients with events; ERR, estimated rate ratio; IDeg, insulin degludec; IDet, insulin detemir; PYE, patient-year of exposure, ns, not statistically significant
Statistics based on FAS population
Thalange et al. *Pediatr Diabetes.* 2015;16:164-176.

# YOUNG 1 AND EXTENSION

## Hypoglycemia including pre-specified external classification

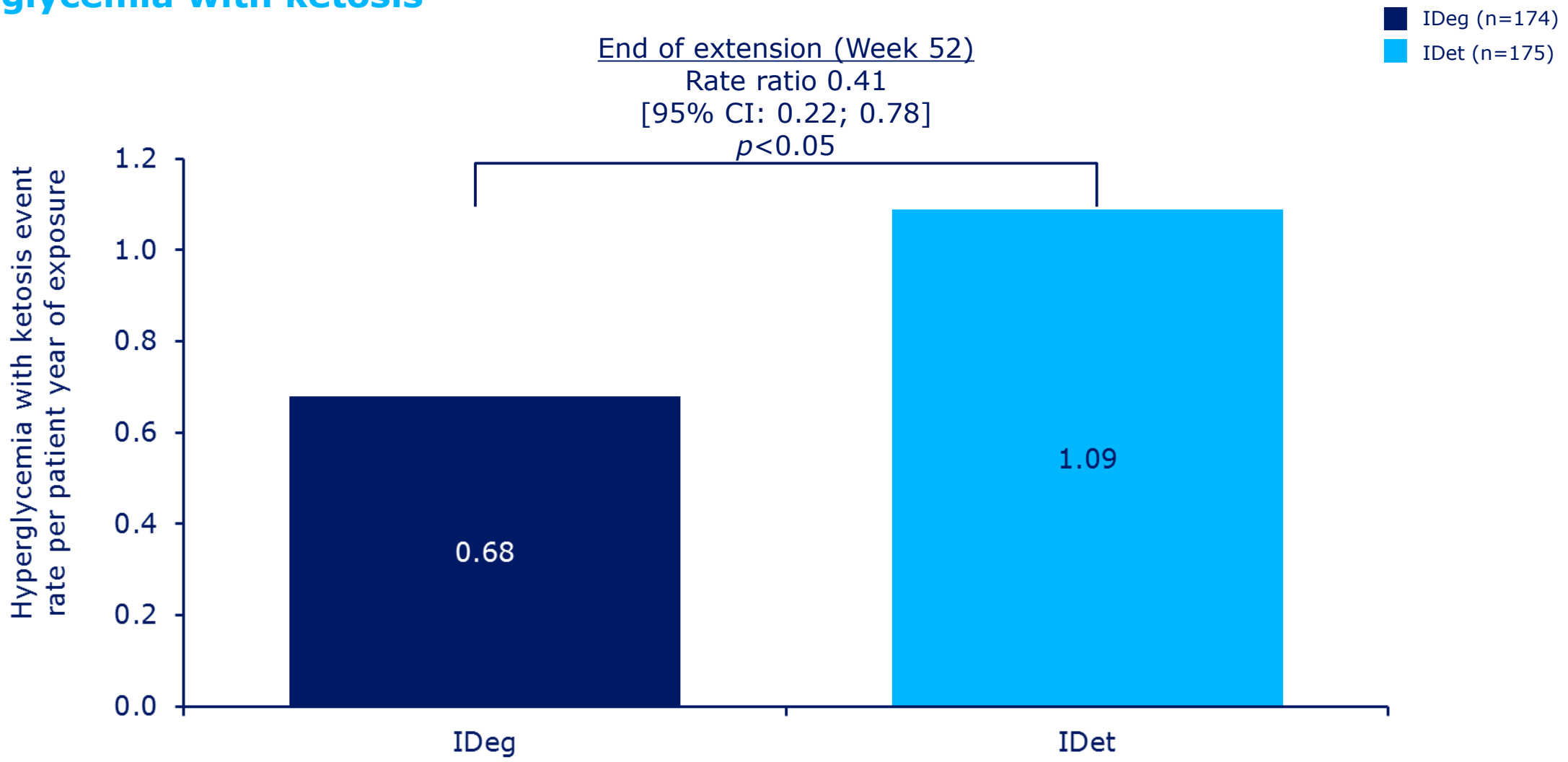
| | Insulin degludec (n=174) | | | | Insulin detemir (n=175) | | | |
|---|---|---|---|---|---|---|---|---|
| | n | % | E | R | n | % | E | R |
| All confirmed hypoglyemia | 171 | 98.3 | 9317 | 5771 | 168 | 96.0 | 7967 | 5405 |
| Nocturnal confirmed hypoglycemia | 133 | 76.4 | 973 | 603 | 125 | 71.4 | 1120 | 760 |
| All reported severe hypoglycemia | 31 | 17.8 | 82 | 51 | 24 | 13.7 | 48 | 33 |
| Externally classified severe episodes | 28 | 16.1 | 61 | 38 | 22 | 12.6 | 38 | 26 |
| Altered mental status and cannot assist in his care | 21 | 12.1 | 46 | 28 | 11 | 6.3 | 18 | 12 |
| Semiconscious or unconscious | 7 | 4.0 | 7 | 4 | 6 | 3.4 | 10 | 7 |
| Coma ±convulsions | 6 | 3.4 | 8 | 5 | 7 | 4.0 | 10 | 7 |
| Not severe hypoglycemia | 5 | 2.9 | 13 | 8 | 5 | 2.9 | 8 | 5 |
| Not possible to classify | 5 | 2.9 | 8 | 5 | 1 | 0.6 | 2 | 1 |

Data are from the end of the extension trial (Week 52).

SAS, safety analysis set
n, number of participants; %, percentage of participants; E, number of events; R, event rate per 100 patient-years of exposure
IDeg, insulin degludec; IDet, insulin detemir
Thalange et al. *Pediatr Diabetes.* 2015;16:164-176.

# YOUNG 1 AND EXTENSION

## Hyperglycemia with ketosis




Mean±SEM
*p*-values are from an ANCOVA model
IDeg, insulin degludec; IDet, insulin detemir
Thalange et al. *Pediatr Diabetes.* 2015;16:164-176.

# YOUNG 1 AND EXTENSION

## Conclusion

- A1c control was comparable between treatment arms
- Overall rates of adverse events, severe adverse events, and safety parameters were comparable between treatment arms
- IDeg offers a new addition to the treatment of T1DM in children

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- Based on this trial, Tresiba® (IDeg) was approved by the EMA for use in pediatric patients who are ≥1 year of age

NovoLog® US Prescribing Information: Pediatric: Has not been studied in children with type 2 diabetes. Has not been studied in children with type 1 diabetes <2 years of age (8.4)
Levemir® US Prescribing Information: Pediatric: Has not been studied in children with type 2 diabetes. Has not been studied in children with type 1 diabetes <2 years of age (8.4)

$HbA_{1c}$, glycated hemoglobin. IDeg, insulin degludec; IDet, insulin detemir; EMA, European Medicines Agency; T1DM, type 1 diabetes mellitus

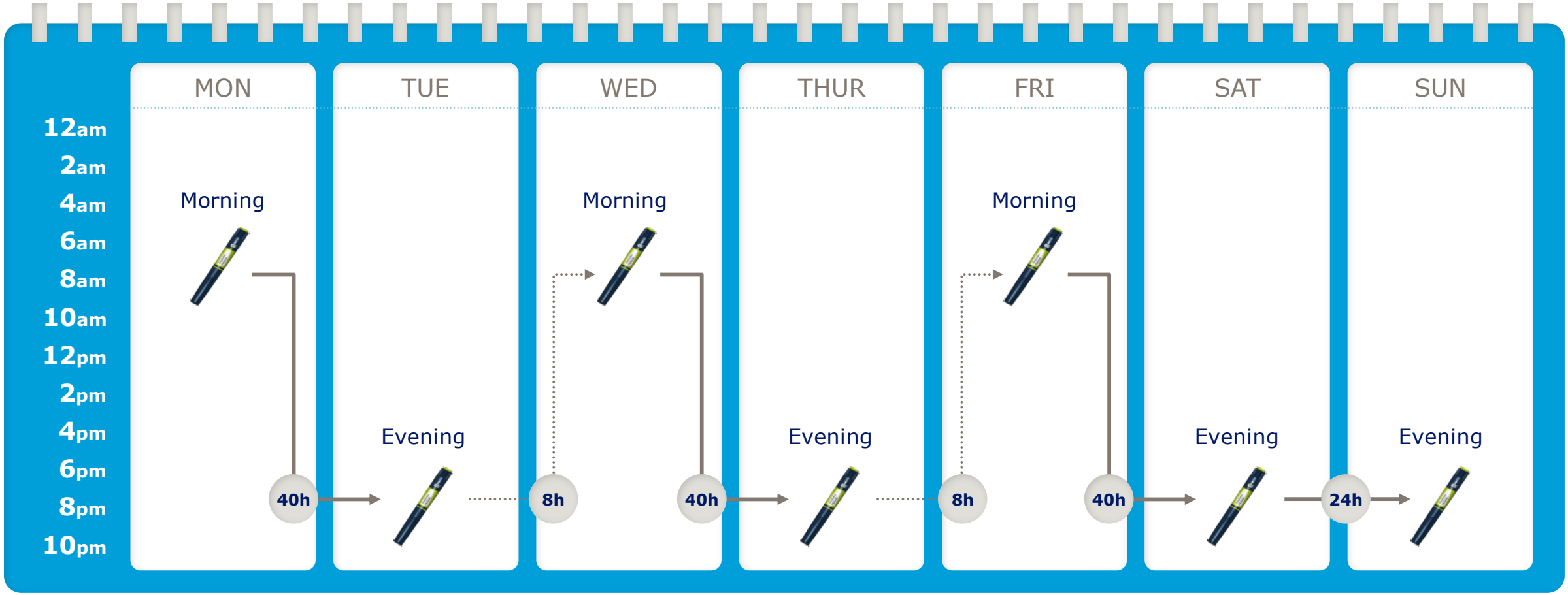
Tresiba© (insulin degludec) [European Public Assessment Report (EPAR)—Product Information]. Bagsværd, Denmark: NovoNordisk; Mar 2015.
NovoLog® (insulin aspart) [US Prescribing Information]. Plainsboro, New Jersey: NovoNordisk; Feb 2015.
Levemir (insulin detemir) [US Prescribing Information]. Plainsboro, New Jersey: NovoNordisk; Feb 2015.
Thalange et al. *Pediatr Diabetes.* 2015;16:164-176.

# Flexibility

## Possible flexible administration

# Flexible administration of IDeg was tested in both T1D and T2D

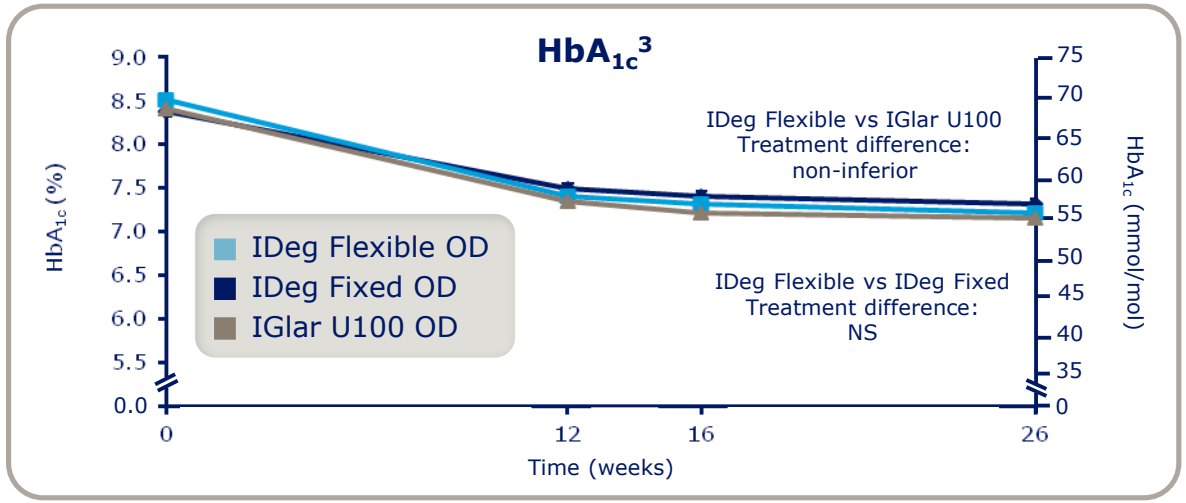
## Two phase 3a clinical trials (6 and 12 months)

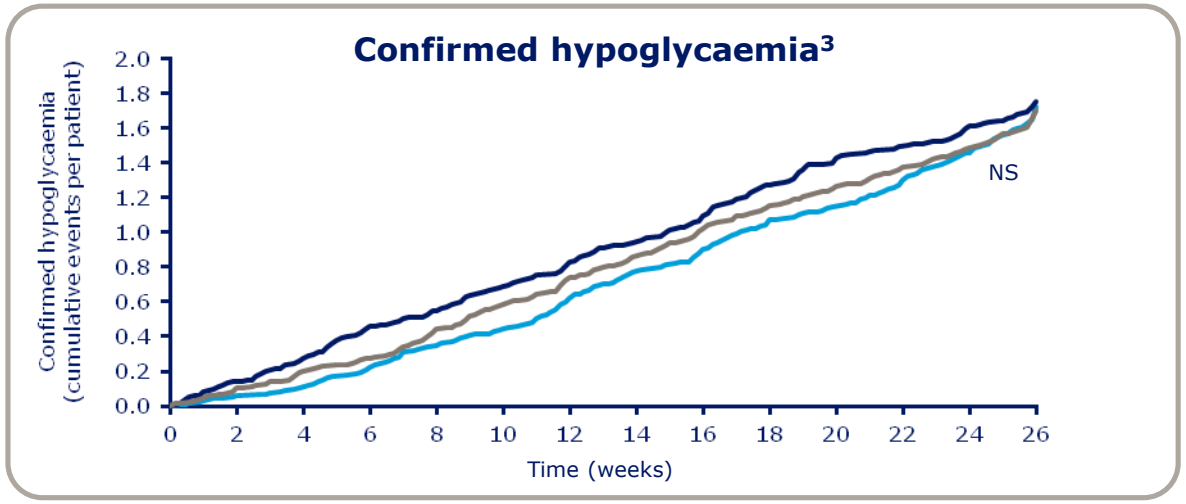


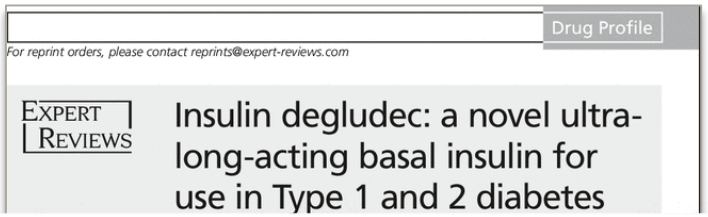

IDeg, insulin degludec; T1D, type 1 diabetes; T2D, type 2 diabetes

Meneghini *et al. Diabetes Care* 2013;36:858–64; Mathieu *et al. J Clin Endocrinol Metab* 2013;98:1154–62

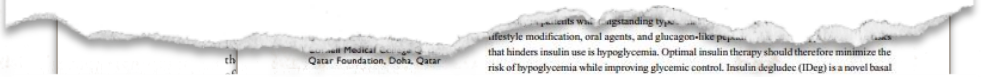
# Flexibility can benefit patients who find it challenging to inject at the same time each day[1,2]



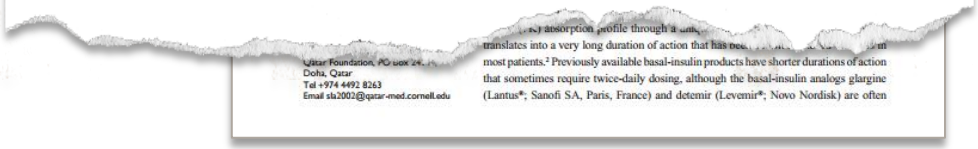




"Flexibility in the timing of insulin administration can benefit **patients who find it challenging to always inject insulin at the same time each day**."[2]



"…In particular, this could include **individuals who travel** regularly … **Shift workers** may also greatly benefit from the freedom to change their dosing schedule…"[1]



IDeg, insulin degludec; IGlar U100, insulin glargine U100; NS, not significant; OD, once daily

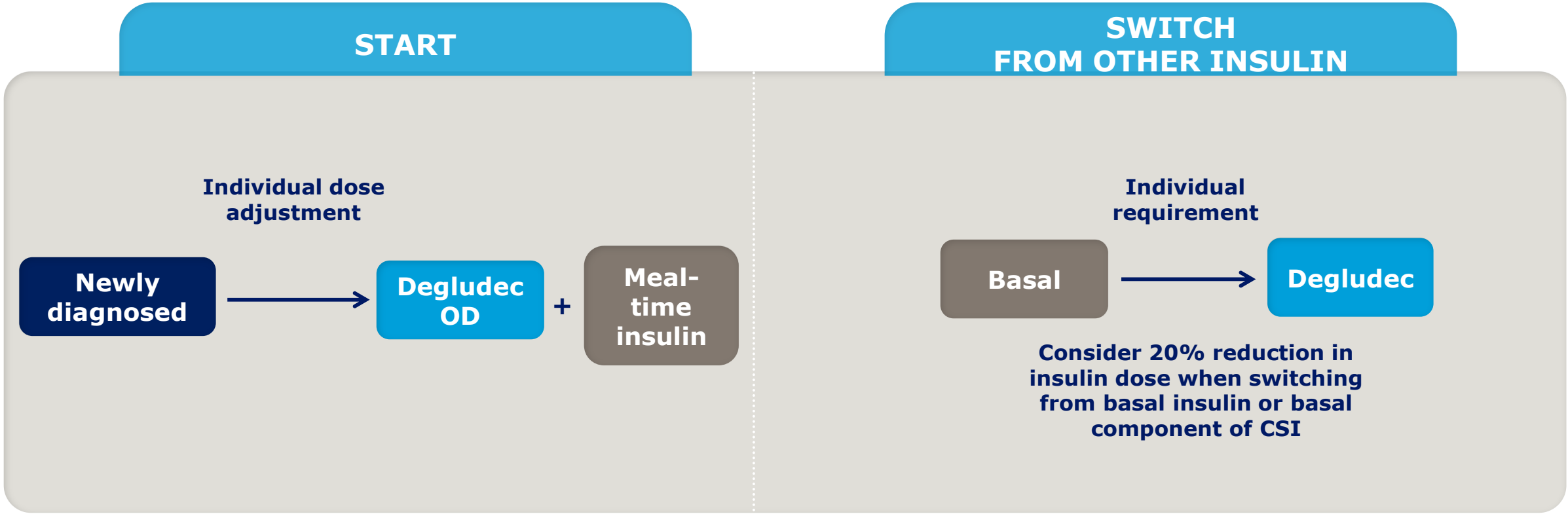
1. Aye & Atkin. *Drug, Healthcare and Patient Safety* 2014;6:55–67; 2. Meneghini *et al. Expert Rev Endocrinol Metab* 2012;7:9–14; 3. Meneghini *et al. Diabetes Care* 2013;36:858–64

# Summary of US and EU labels – subpopulations

| | US | EU |
|---|---|---|
| **Renal indication** | **No clinically relevant differences** in the pharmacokinetics of IDeg were identified in patients with renal impairment vs. healthy patients | **Can be used** in renal impaired patients |
| **Hepatic indication** | **No clinically relevant differences** in the pharmacokinetics of IDeg were identified in patients with hepatic impairment vs. healthy patients | **Can be used** in hepatic impaired patients |
| **Paediatric indication** | • **Can be used** in adolescents and children **from the age of 1 year** | • **Can be used** in adolescents and children **from the age of 1 year**<br>• Safety and efficacy have been demonstrated in a long-term trial in children aged 1 to less than 18 years |
| **Pregnancy** | **No clinical studies** of the use of IDeg in pregnant women. It should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus | **There is no clinical experience** with use of IDeg in pregnant women |
| **Elderly (≥65 years)** | **No differences** in the safety and effectiveness of IDeg in patients ≥65 years vs. younger patients | **Can be used** in elderly patients |
| **Elderly (≥75 years)** | **Greater caution is recommended** in geriatric patients as increased sensitivity in some individuals cannot be ruled out | |

IDeg, insulin degludec
Tresiba® September 2015 (http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/203314lbl.pdf); Tresiba® August 2015 (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002498/WC500138940.pdf)

# Initiation of degludec in T1D

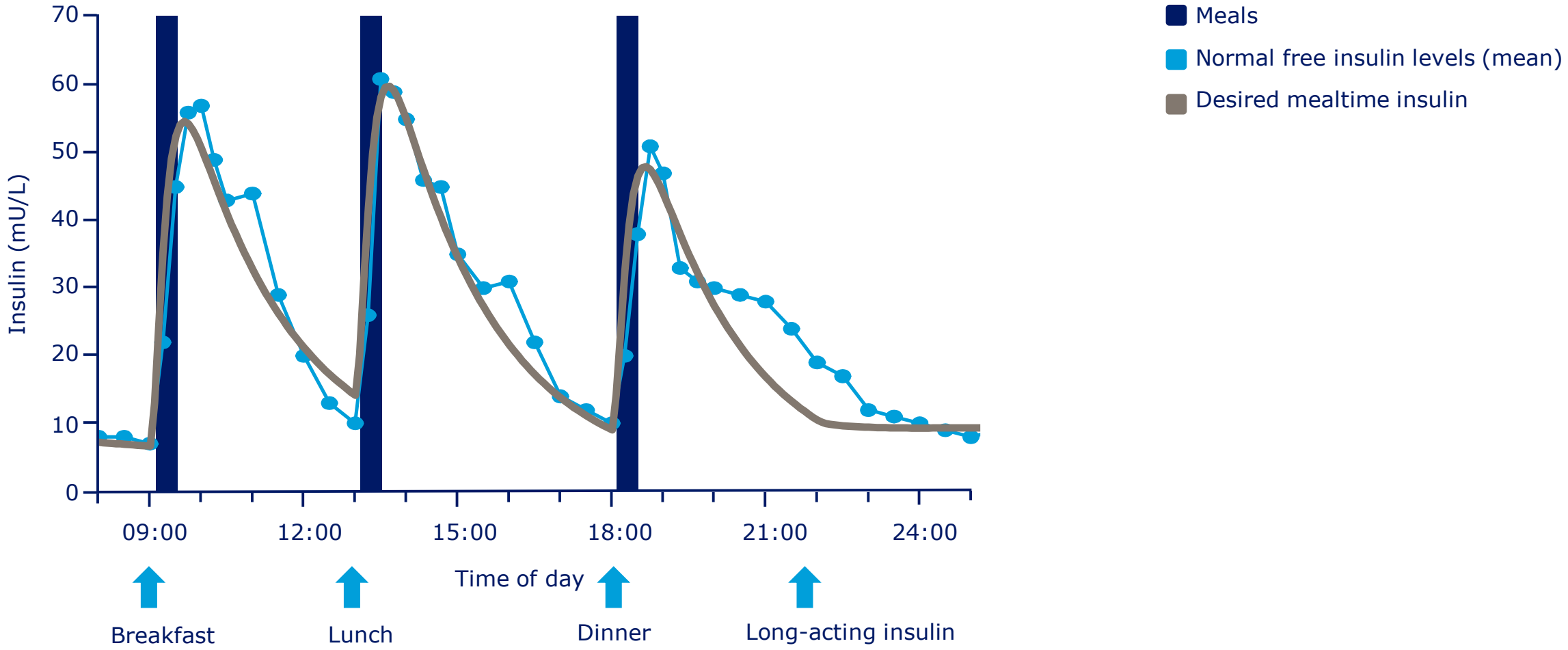



CSI, continuous subcutaneous insulin regimen; degludec, insulin degludec; OD, once daily; T1D, type 1 diabetes

Tresiba® September 2017 (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002498/WC500138940.pdf)

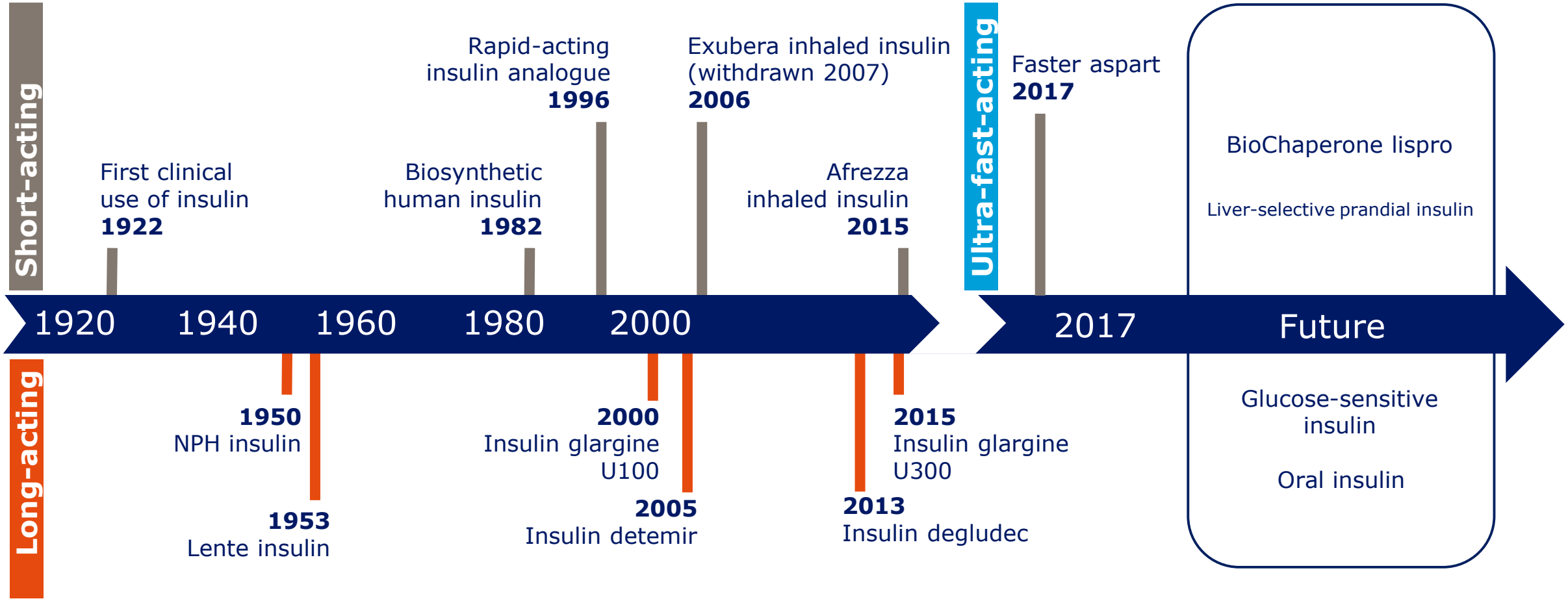
# New Generation of Bolus insulins

# Approaching physiological mealtime insulin therapy




Adapted from Polonsky *et al. N Engl J Med* 1988;318:1231–9

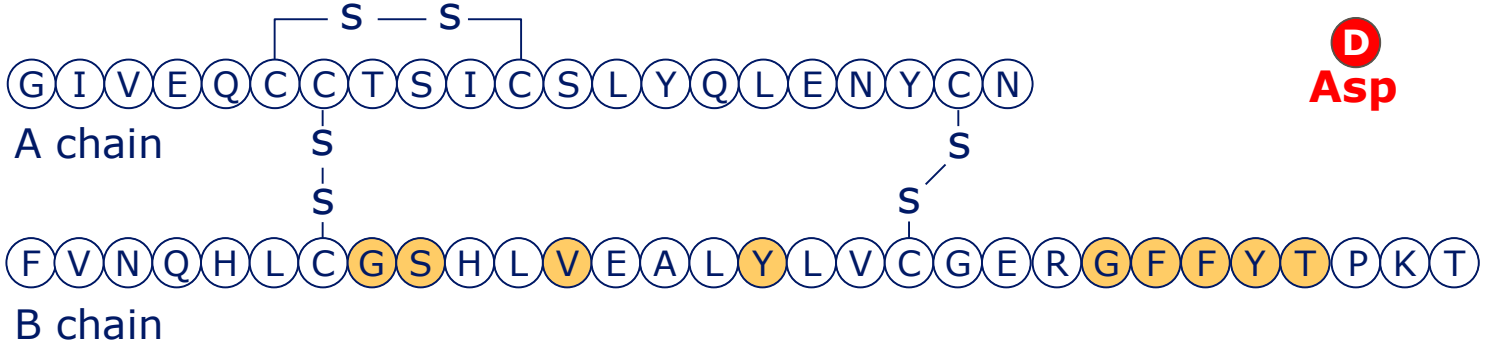
# Goal of insulin development: approach endogenous insulin secretion by healthy pancreatic beta-cells




Faster aspart, fast-acting insulin aspart; NPH, neutral protamine Hagedorn

Adapted from Cahn *et al. Lancet Diabetes Endocrinol* 2015;3:638–52; Eli Lilly. Patent application, 12 November 2015; Eli Lilly. Press release, 4 December 2015; Novo Nordisk. Capital Markets Day R&D update, 19 November 2015

# In insulin aspart, B28Pro is substituted with aspartic acid reducing the strength of the insulin dimer

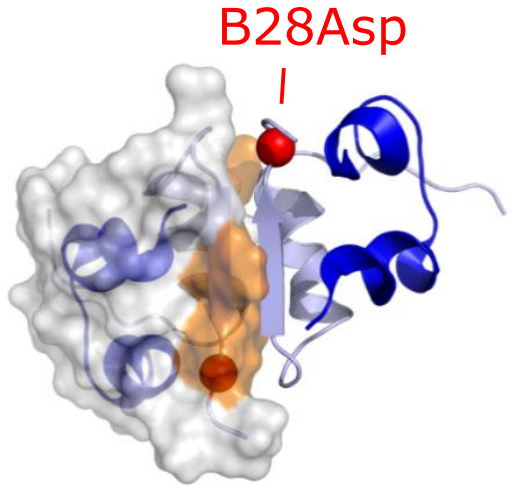






Dimer interface

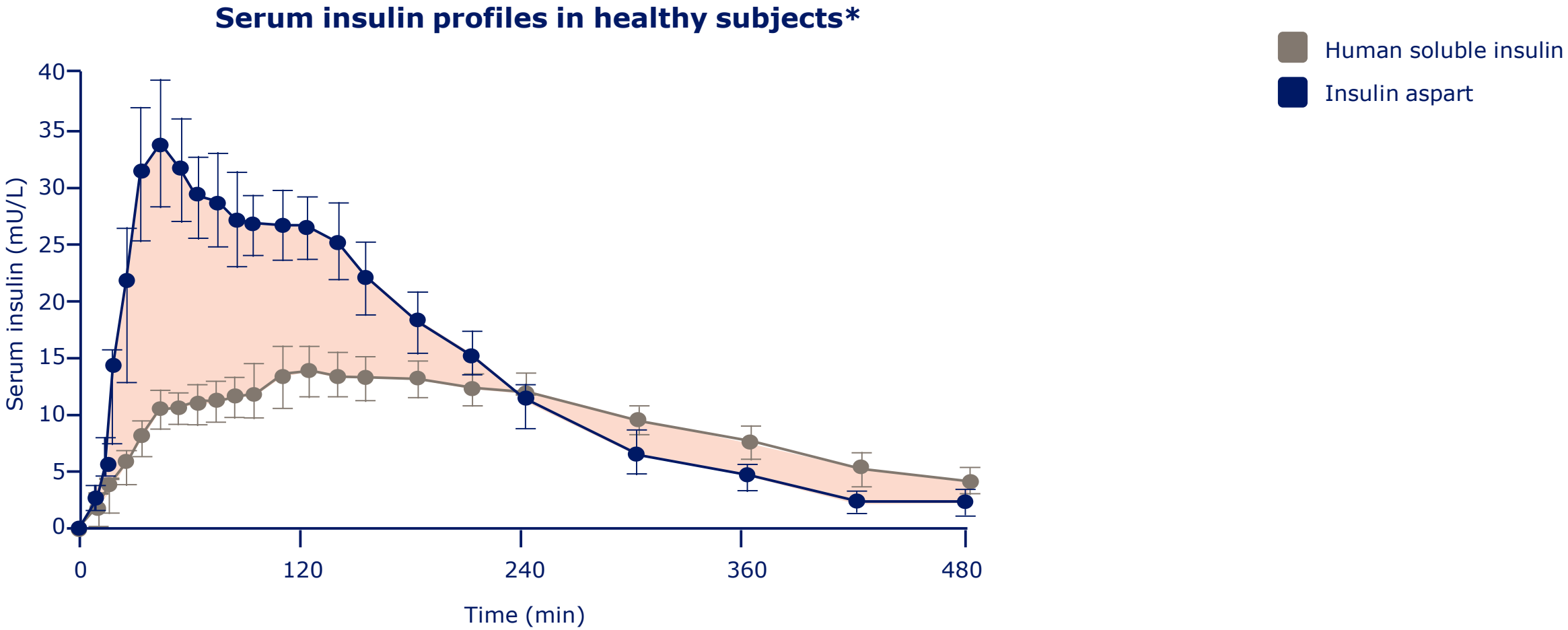
**Reduced monomer–monomer interaction in the dimer leads to fast monomer formation after injection**




Insulin aspart is currently marketed as NovoRapid and NovoLog
Asp, aspartic acid; faster aspart, fast-acting insulin aspart; pro, proline

Brange *et al*. *Diabetes Care* 1990;13:923–54

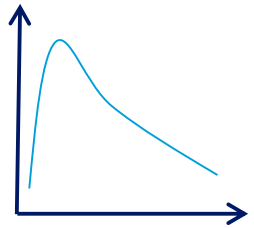
# Greater early insulin exposure with insulin aspart compared with human insulin




*Corrected for endogenous insulin

Home *et al. Eur J Clin Pharmacol* 1999;55:199–203

# Clinical and pharmacological improvements with insulin aspart compared with human insulin



Improved PPG control[1]

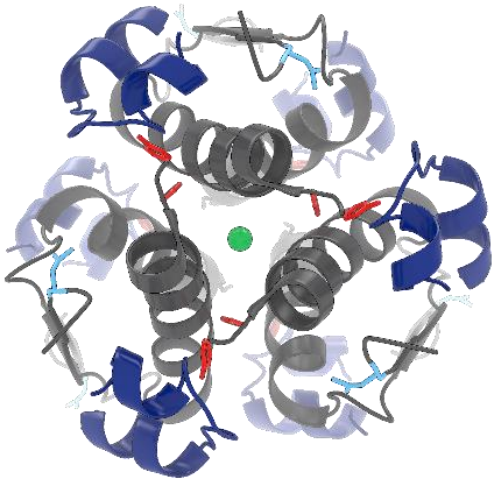
Can be dosed immediately before a meal or can be given soon after a meal when necessary*[1]

Low number of nocturnal hypoglycaemic events[2]

*Not in US label
PPG, postprandial plasma glucose

1. Novo Nordisk. Insulin aspart (NovoRapid) summary of product characteristics. 2015; 2. Heller *et al. J Diabetes* 2013;5:482–91

# Building on a strong foundation with insulin aspart

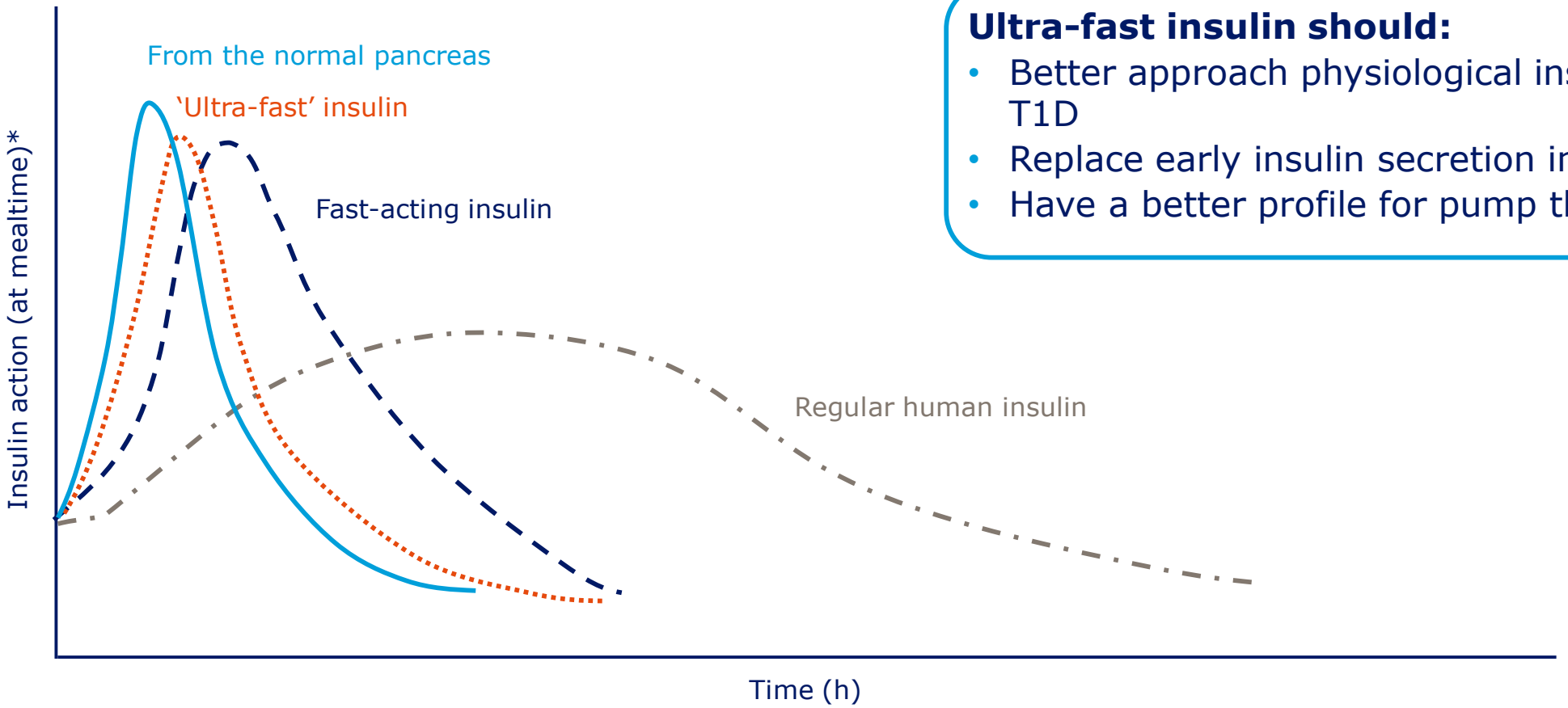


- Treatment of diabetes in adults, adolescents and children aged ≥1 years
- Continuous infusion in a pump system
- In iv use
- Pregnancy and breastfeeding
- Elderly patients

iv, intravenous

Novo Nordisk. Insulin aspart (NovoRapid) summary of product characteristics. 2016

# Ultra-fast insulin: approaching a physiological insulin profile even further



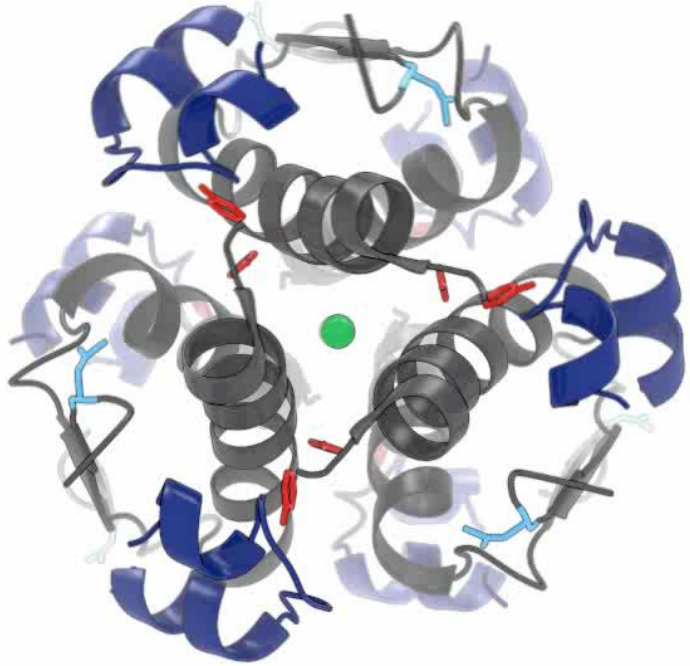

**Ultra-fast insulin should:**

- Better approach physiological insulin secretion in T1D
- Replace early insulin secretion in T2D
- Have a better profile for pump therapy

*Schematic representation
T1D, type 1 diabetes; T2D, type 2 diabetes

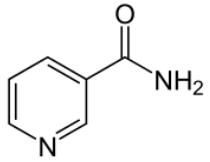
Adapted from Home. *Diabetes Obes Metab* 2015;17:1011–20

# Changing the formulation: faster aspart is insulin aspart in a new formulation



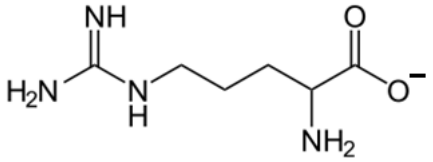
**Insulin aspart**

**Niacinamide:** absorption modifier




Vitamin B3

**L-Arginine:** added for stability




Naturally occurring amino acid

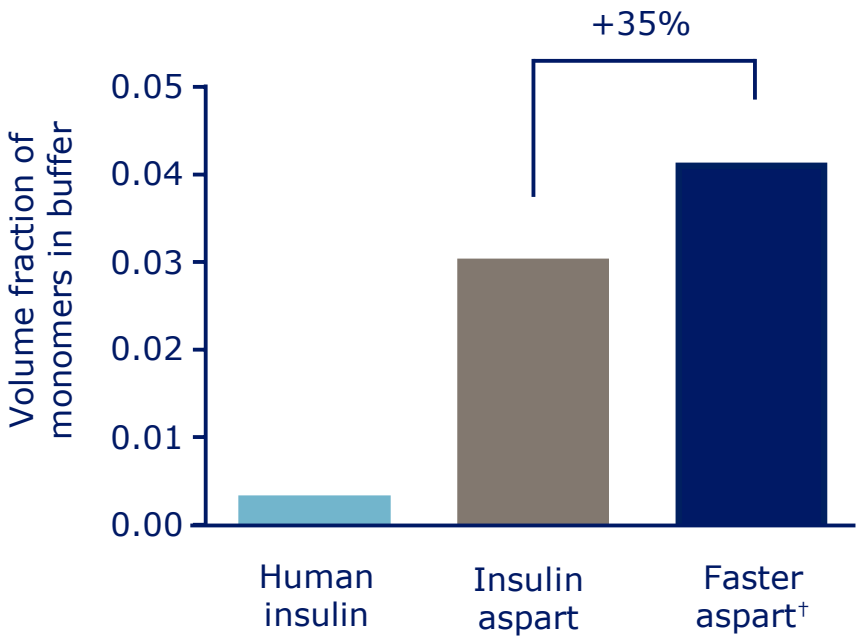
EDTA, ethylenediamine tetra-acetic acid

FDA. Inactive ingredient search for approved drug products database. www.accessdata.fda.gov/scripts/cder/iig/index.cfm

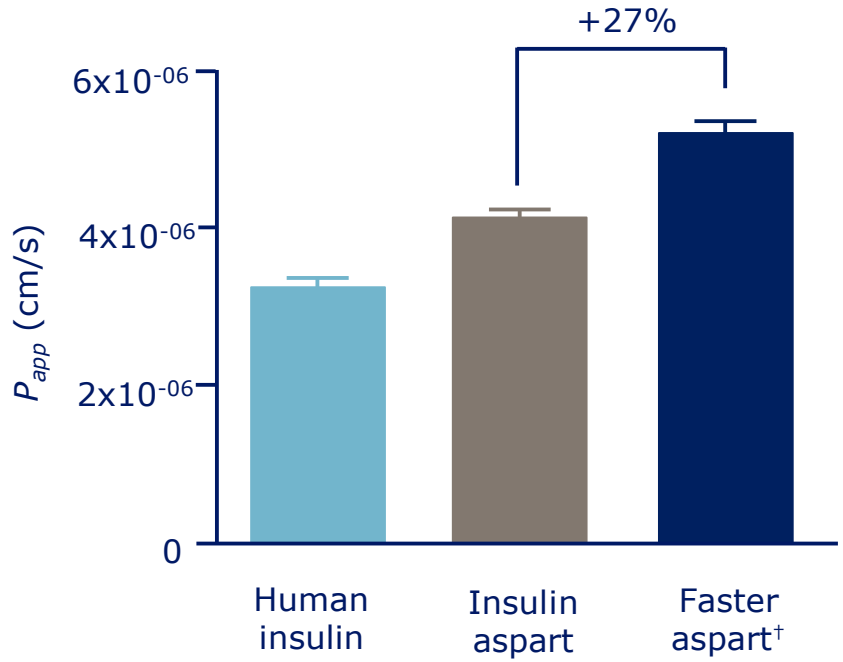
# Niacinamide increases monomer fraction and permeation rate of insulin aspart

## Rate of increase similar as improvement from human insulin to insulin aspart

### Monomer fraction




### Permeation rate across HDMEC cell monolayers




†Concentration of niacinamide simulating subcutaneous environment after injection
HDMEC, human dermal microvascular endothelial cells

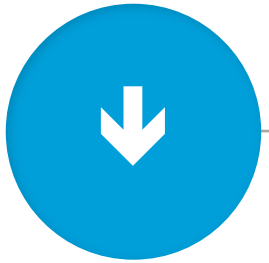
Buckley *et al.* ATTD 2016 (ATTD-0083); Novo Nordisk. Data on file

# Summary

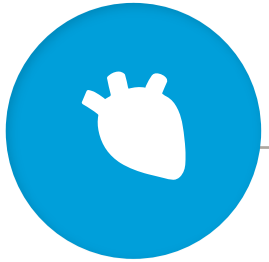
# Summary

## Degludec


**shows non-inferiority in $HbA_{1c}$ versus glargine U100**



**shows significant reductions in the rates of overall confirmed symptomatic, nocturnal confirmed symptomatic, and severe hypoglycaemia in T1D and T2D versus glargine U100**



**Confirm the CV safety in patients at high risk of cardiovascular disease, versus glargine U100**

Degludec, insulin degludec; FPG, fasting plasma glucose; glargine U100, insulin glargine 100 units/mL; T1D, type 1 diabetes; T2D, type 2 diabetes

# Summary

## Degludec

| | |
|---|---|
| 24 h | provides a flat and stable glucose-lowering effect, over 24 hours |
| ↓ $HbA_{1c}$ | shows non-inferiority in $HbA_{1c}$ versus glargine U100 |
| ↓ FPG | has greater FPG reductions in insulin-naïve patients with T2D versus glargine U100 |
| ↓ | shows significant reductions in the rates of overall confirmed symptomatic, nocturnal confirmed symptomatic, and severe hypoglycaemia in T1D and T2D versus glargine U100 |
| ↓ dose | Has significantly lower or clinically relevant equal insulin dose versus glargine U100 in T1D and in T2D |

Degludec, insulin degludec; FPG, fasting plasma glucose; glargine U100, insulin glargine 100 units/mL; T1D, type 1 diabetes; T2D, type 2 diabetes

# Summary

## Degludec

- **U300** — has lower day-to-day variability in glucose-lowering effect, and higher potency versus glargine U300
- has a simple titration schedule that has the potential for up to 5 fewer SMBG test strips/week versus glargine U100
- allows for flexibility in the timing of insulin administration when needed, without compromising the risk of hypoglycaemia
- improves QoL for patients initiating insulin therapy
- does not increase the risk of adverse cardiovascular outcomes in patients at high risk, versus glargine U100
- is well tolerated

Degludec, insulin degludec; glargine U100, insulin glargine 100 units/mL; glargine U300, insulin glargine 300 units/mL; SMBG, self-measured blood glucose; QoL, quality of life