

Co-formulation; Innovative Discourse in Insulin Therapy

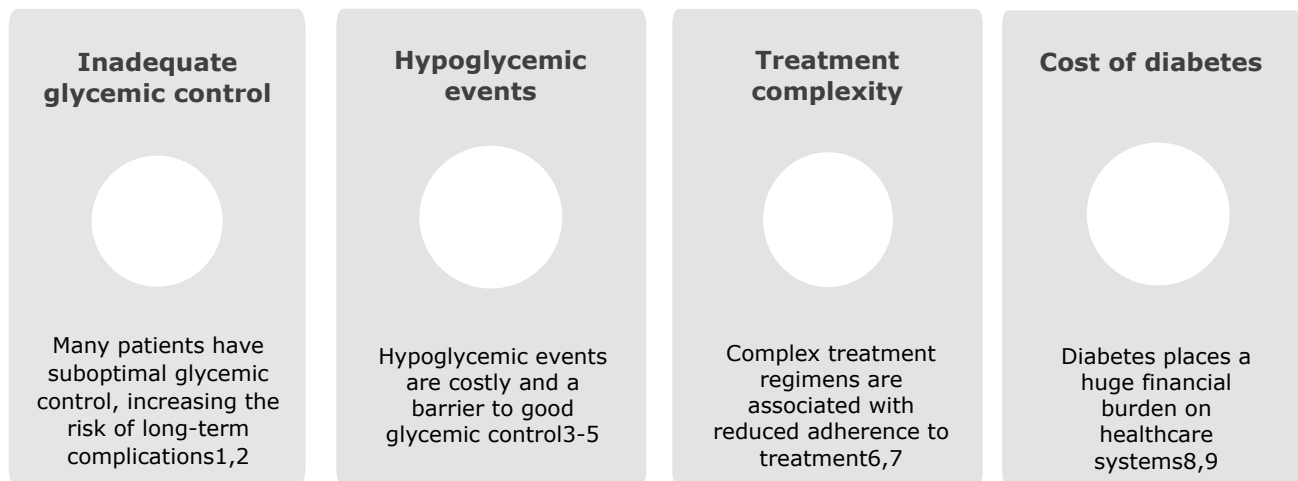
15 May 2025



This event is sponsored by Novo Nordisk Pars
Speaker disclosure:

Unmet needs in type 2 diabetes management

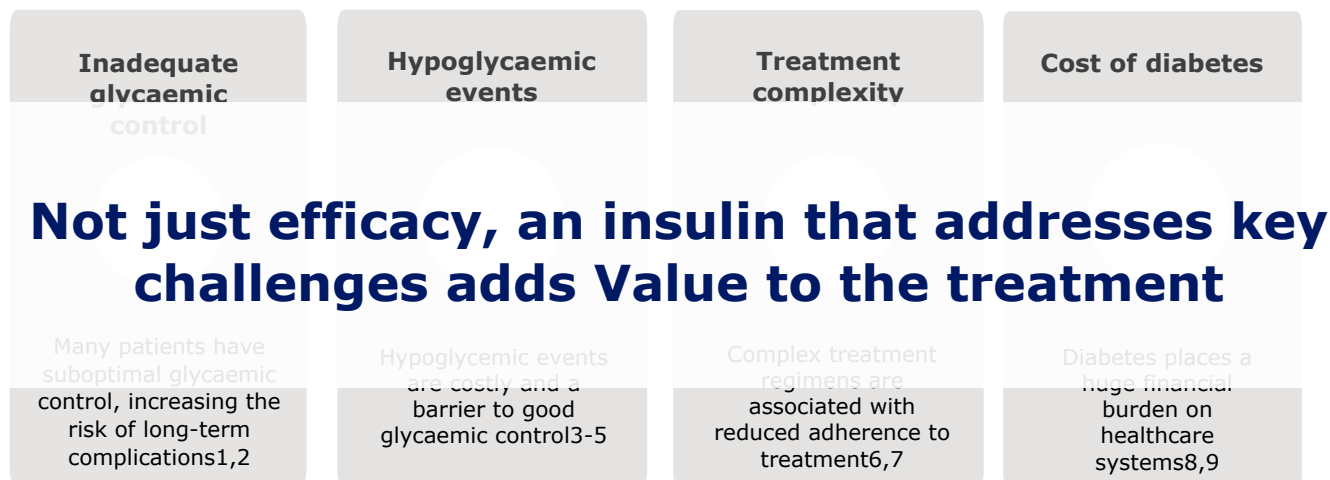
Key challenges in T2DM management



T2DM, type 2 diabetes mellitus.

1. Giugliano *et al. Diabetes Care*. 2011;34(2):510-7; 2. Stratton *et al. BMJ*. 2000;321(7258):405-12; 3. Leiter *et al. Can J Diabetes*. 2005;29(3):186-92; 4. Hammer *et al. JME*. 2009;12(4):281-90; 5. Brod *et al. Value Health*. 2011;14(5):665-671; 6. Peyrot *et al. Diabet Med*. 2012;29:682-9; 7. Jarab *et al. Int J Clin Pharm*. 2014;36(4):725-33; 8. IDF. Diabetes Atlas, 8th Edition. Available at: <http://www.diabetesatlas.org/>; 9. ADA. *Diabetes Care*. 2018;41(5):917-28.

Key challenges in T2DM management



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Insulin should have a simple regimen

Treatment complexity



Complex treatment regimens are associated with reduced adherence to treatment^{6,7}

**Complex insulin dosing:
Multiple injections + multiple Pens**

	Basal + Bolus						
	Mon	Tue	Wed	Thu	Fri	Sat	Sun
Breakfast							
Lunch							
Dinner							
BASAL*							
	28 SMBGs/week			28 needles/week			

2-4 injection per day

Up to 1460 injections in a year

More injections
More monitoring

*Once-daily SMBG testing is recommended with current basal insulin analogues.¹⁻³ Insulin degludec may be used with a simple monitoring and titration algorithm in patients with T2D: Once-weekly titration based on the average of 2 preceding FPG measurements^{4,5}

T2DM, type 2 diabetes mellitus.

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Innovation of Co-formulation

Co-formulation of insulin degludec with insulin aspart (IDegAsp)

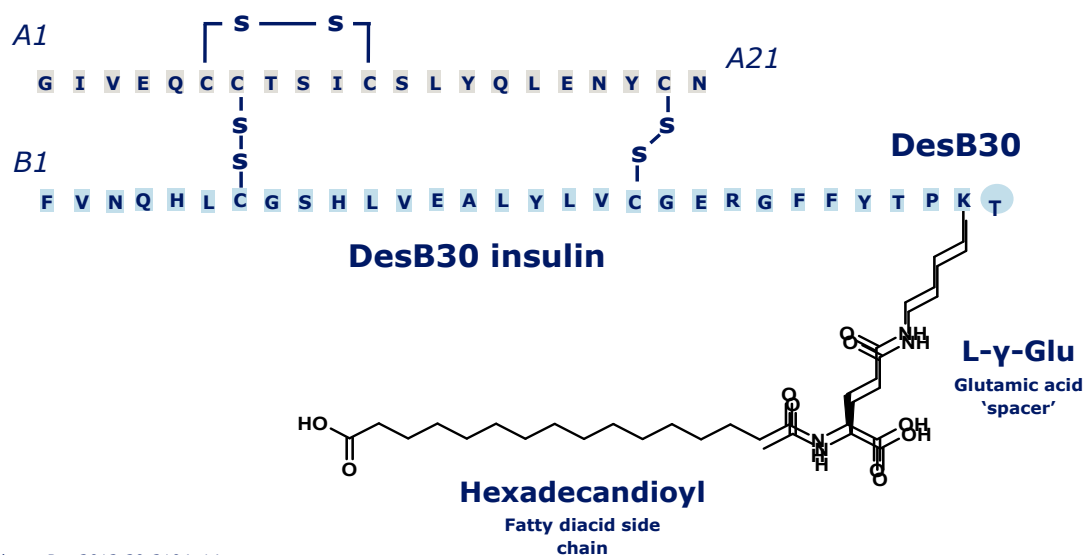


IAsp, insulin aspart; IDegAsp, insulin degludec/insulin aspart

Introduction to novel insulin degludec

Degludec: rationally designed, beyond sequence modification

Des(B30) LysB29(γ -Glu N ϵ -hexadecandioyl) human insulin

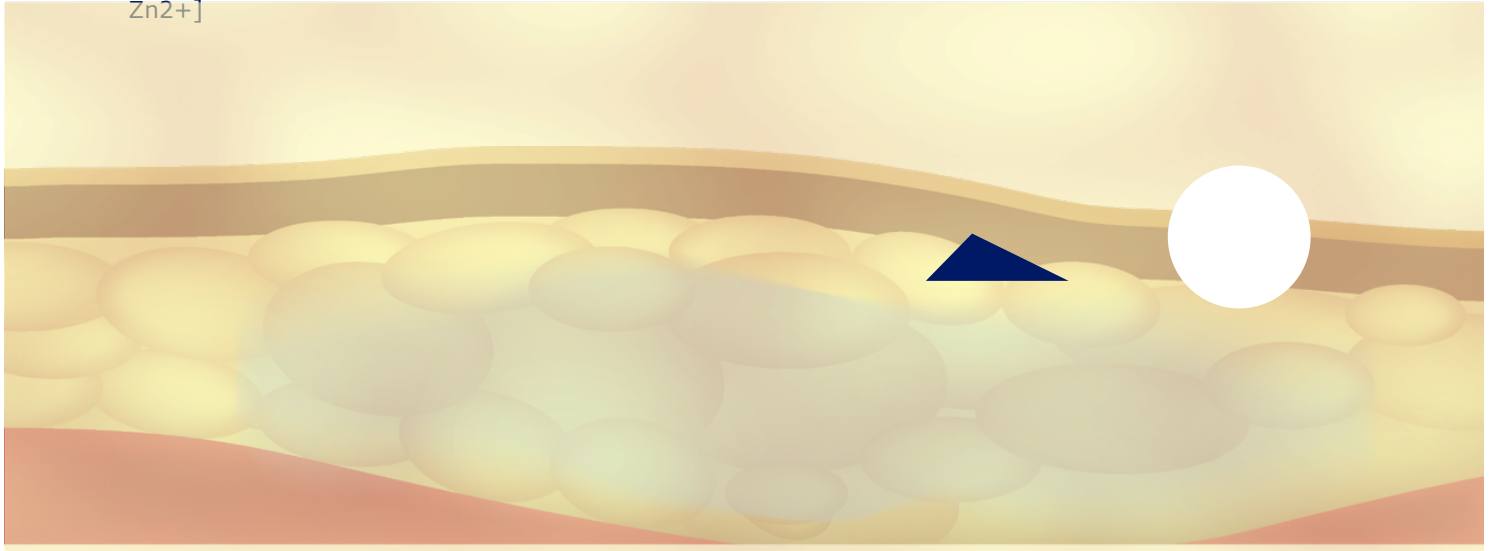


Insulin degludec

Mode of protraction

[Phenol;
Zn²⁺]

Insulin degludec is administered with a pen device into the subcutaneous tissue



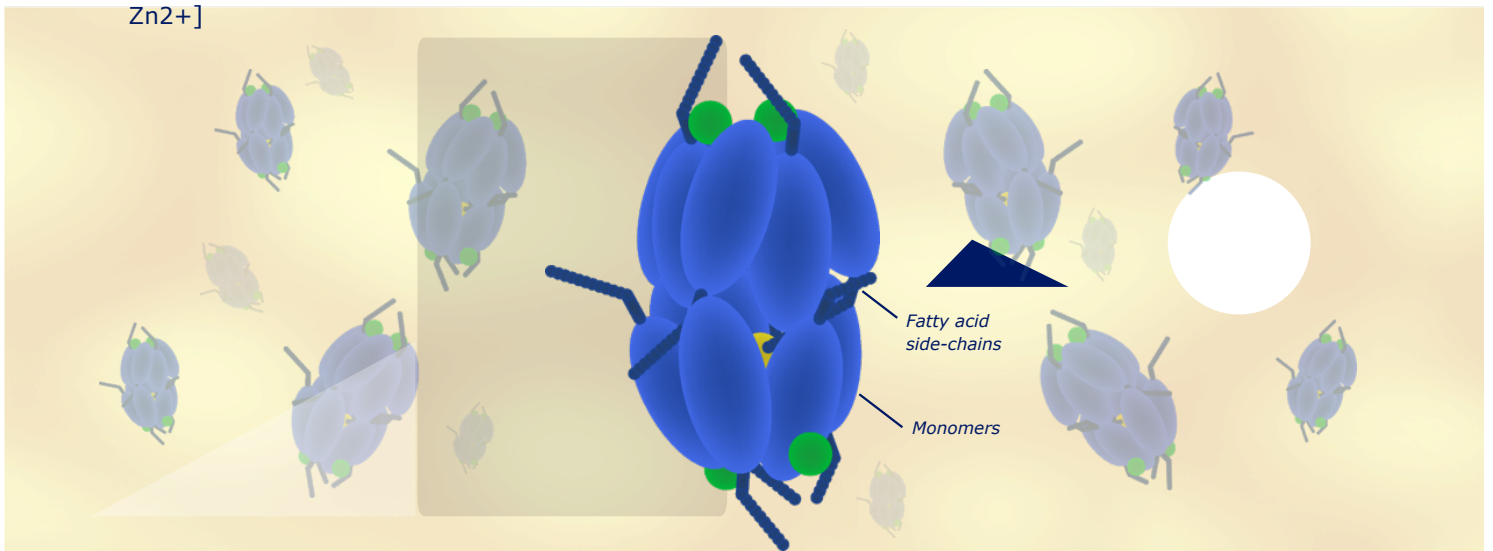
Jonassen et al. Pharm Res 2012;29:2104–14

Insulin degludec

Mode of protraction

[Phenol;
Zn²⁺]

The stable dihexamers formed in solution in the pen are injected into the subcutaneous space

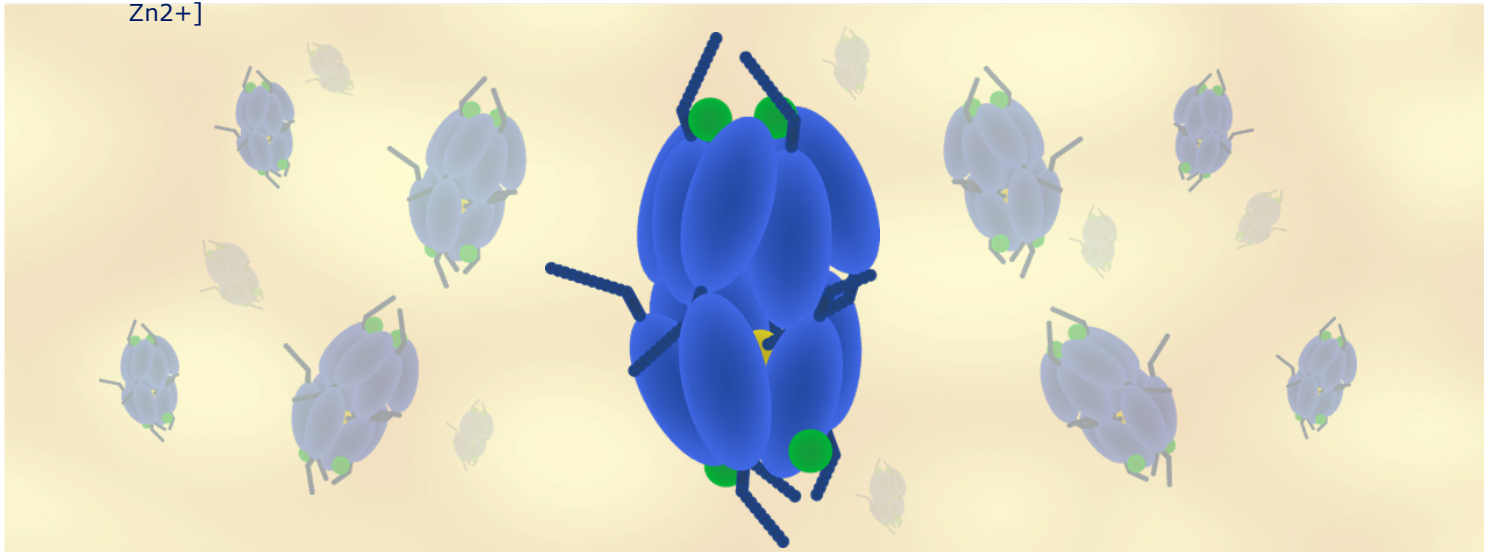


Jonassen et al. Pharm Res 2012;29:2104–14

Insulin degludec

Mode of protraction

● [Phenol; Zn²⁺]

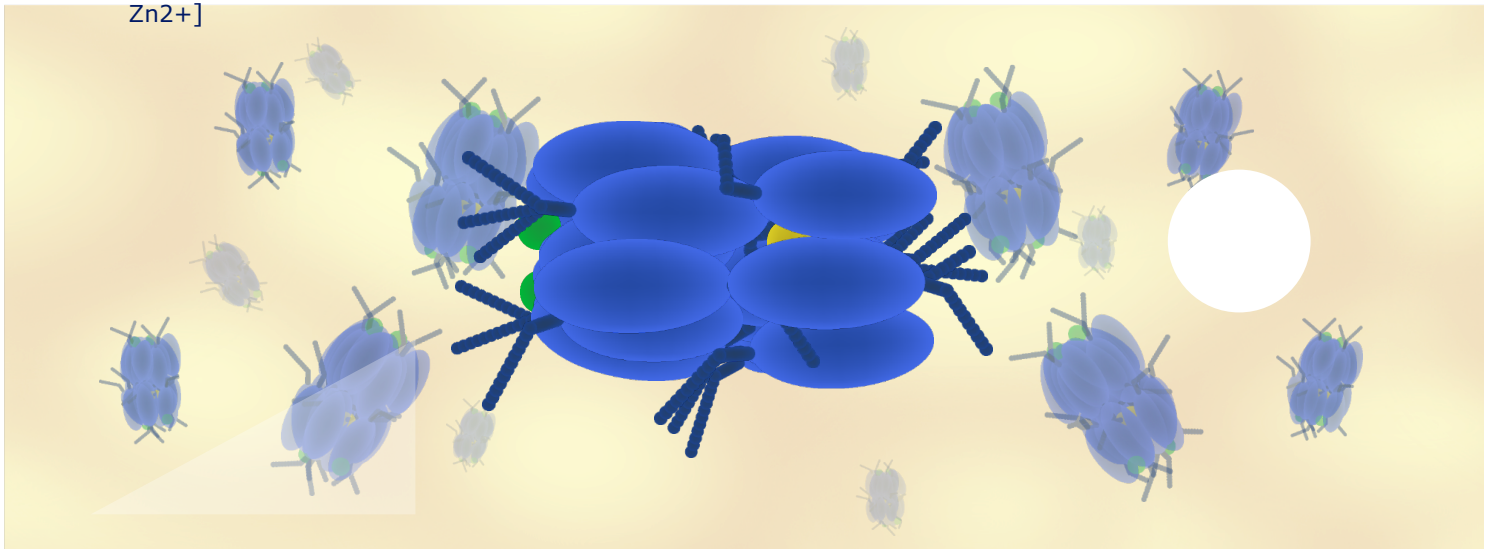


Jonassen et al. Pharm Res 2012;29:2104–14

Insulin degludec

Mode of protraction

● [Phenol; Zn²⁺]



After injection, the insulin degludec dihexamers adapt to an open conformation after phenol has rapidly diffused from the vehicle

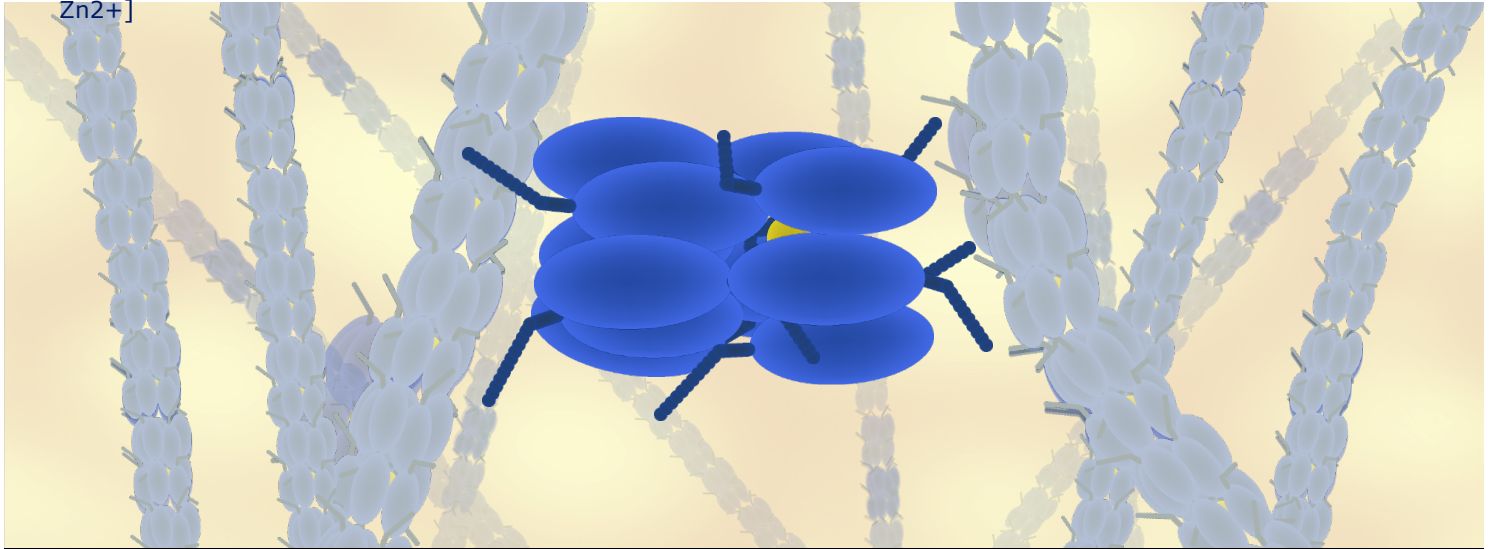
Jonassen et al. Pharm Res 2012;29:2104–14

Insulin degludec

Mode of protraction

[●
Zn²⁺]

After the diffusion of phenol and conformation change, the dihexamers link together via single side-chain contacts. Long multihexamer chains assemble

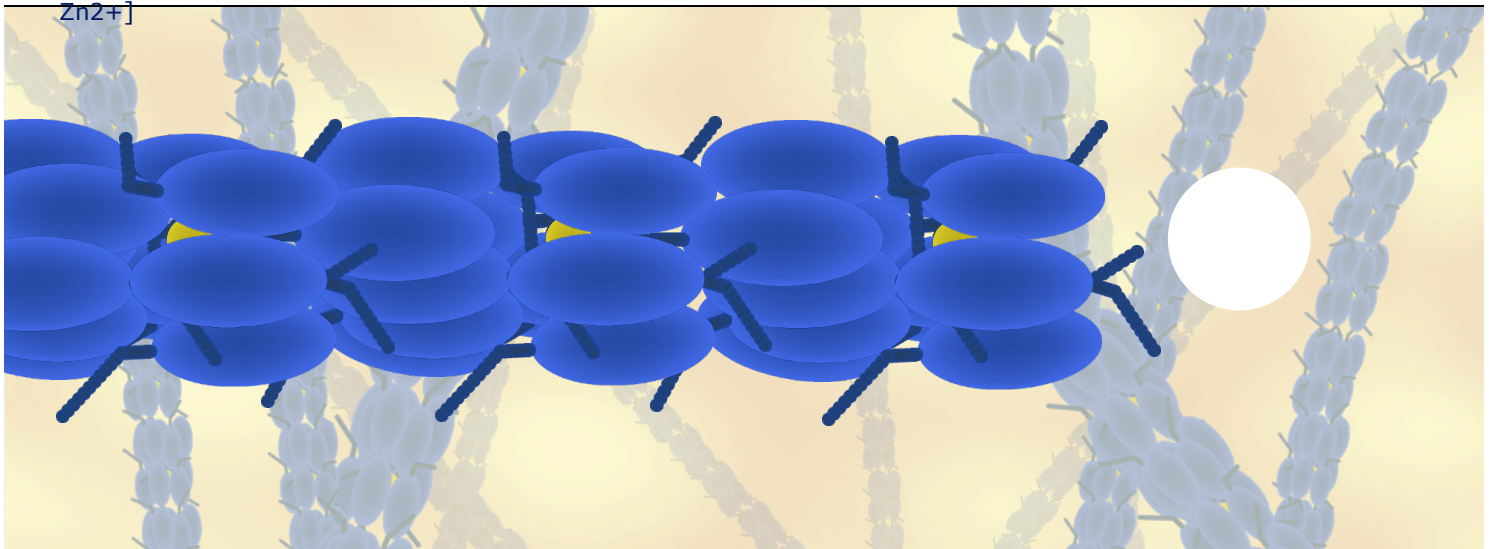


Jonassen et al. Pharm Res 2012;29:2104–14

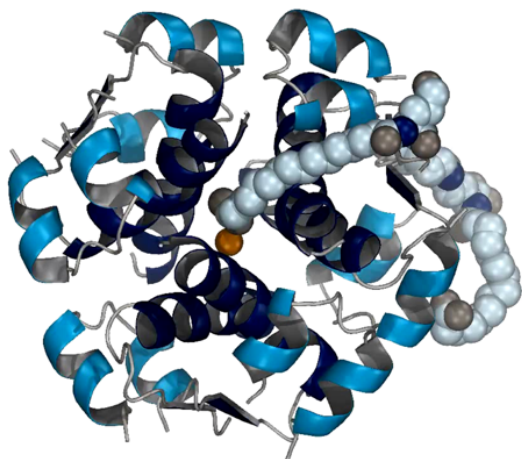
Insulin degludec

Mode of protraction

[●
Zn²⁺]



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



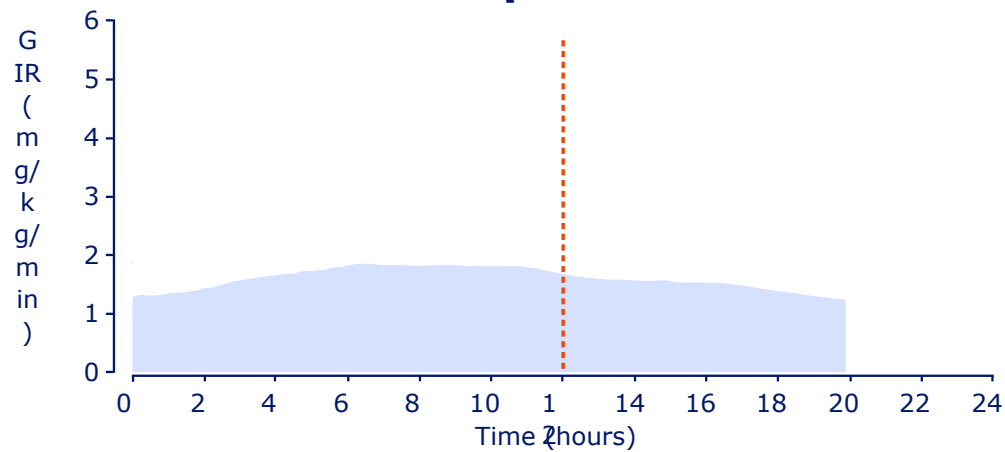
Pharmacokinetics/ pharmacodynamics (PK/PD) of Insulin Degludec

Degludec has a longer half-life than glargine U100 and U300

	U100 0.4 U/kg OD	U300 0.4 U/kg OD	Degludec 0.4 U/kg OD
Half-life	13.5 hours	19.0 hours	25.9 hours

Glargine U300, insulin glargine 300 units/mL
Dahmen *et al. Diabetes* 2013;62(Suppl. 2):A29; Becker *et al. Diabetes Care* 2015;38:637–43; Haahr H, Heise T. A review of the pharmacological properties of insulin degludec and their clinical relevance. *Clin Pharmacokinet.* 2014;53:787–800
Heise *et al. Diabetes* 2011;60(Suppl. 1):LB11; Heise *et al. Diabetologia* 2011;54(Suppl. 1):S425; Heise *et al. Expert Opin Drug Metab Toxicol* 2015;11:1193–201

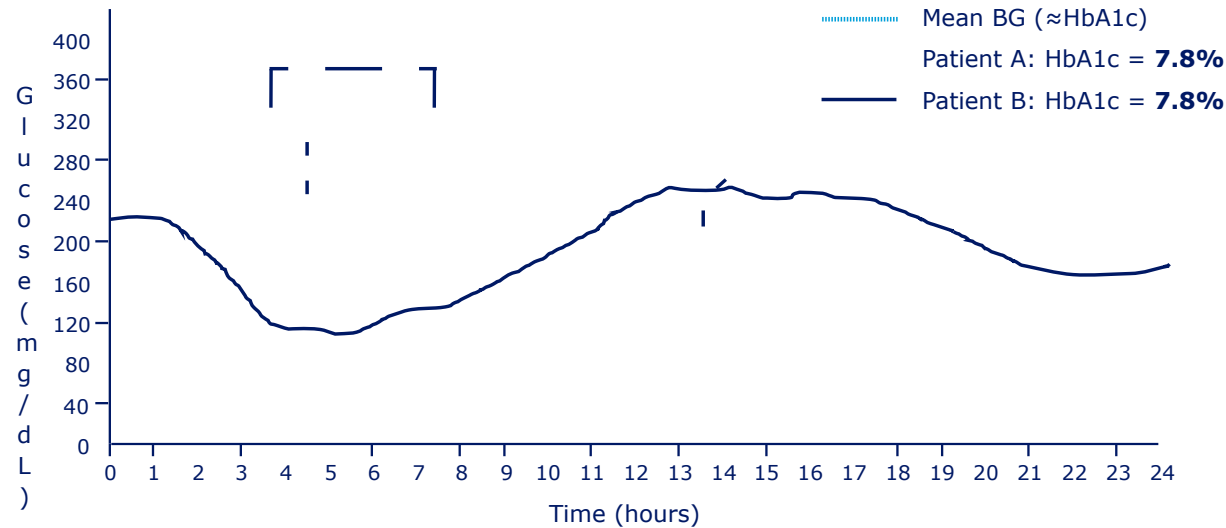
Degludec flat time-action profile in T1D at steady state



Degludec		
Dose level	AUCGIR,0-12h	AUCGIR,12-24h
0.4 U/kg	50%	50%

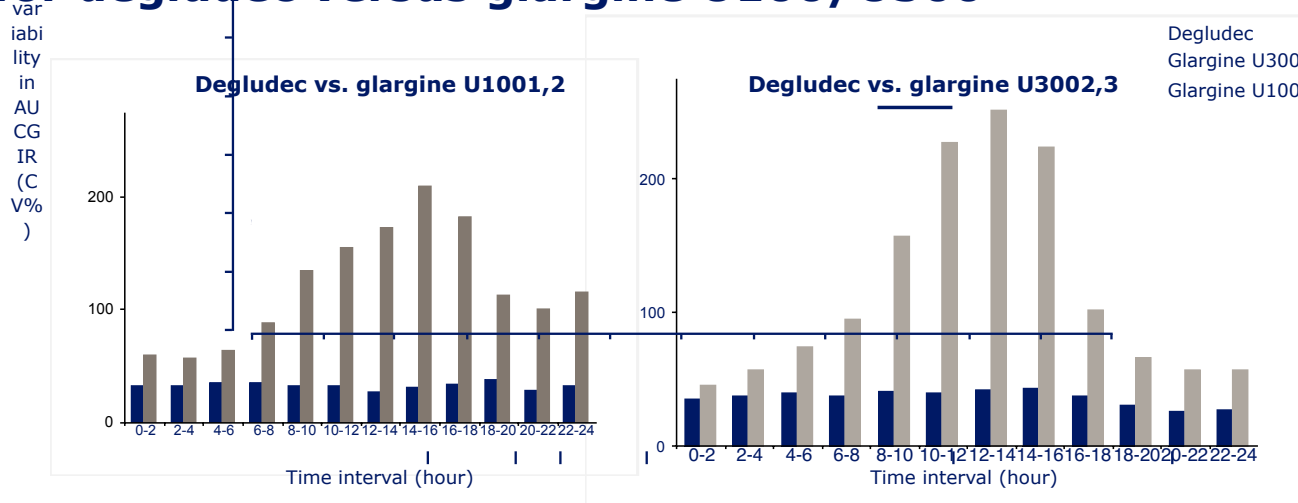
Degludec= 0.4 U/kg; n=66
AUC, area under the curve; GIR, glucose infusion rate
Heise et al. Expert Opin Drug Metab Toxicol. 2015;11:1193-201

Fluctuations in blood glucose occur despite stable HbA1c



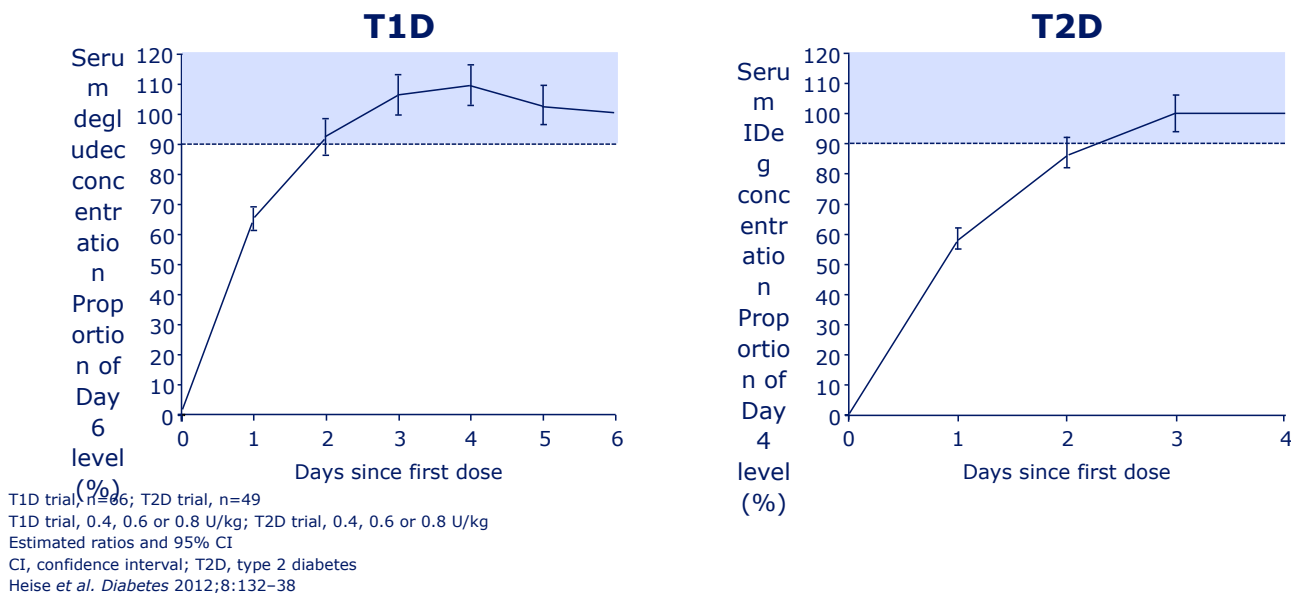
BG, blood glucose
Schematic representation

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



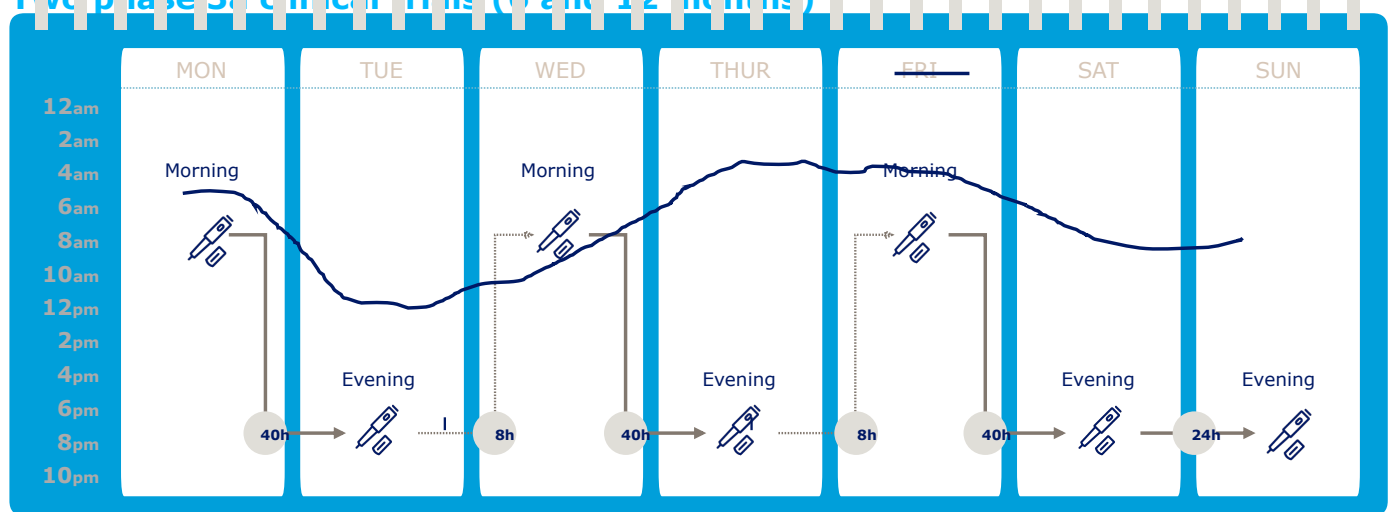
1. Heise et al. *Diabetes Obes Metab* 2012;14:859–64; 2. Heise et al. *J Diabetes Sci Technol* 2018;12:356–63; 3. Heise et al. *Diabetes Obes Metab* 2017;19:1032–9

Degludec concentration reaches steady state in 3 days



Flexible administration of IDeg was tested in both T1D and T2D

Two phase 3 clinical trials (6 and 12 months)

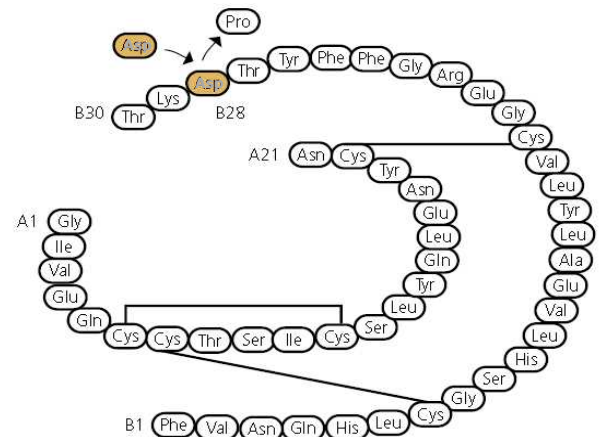


IDeg, insulin degludec; T1D, type 1 diabetes; T2D, type 2 diabetes
Meneghini *et al. Diabetes Care* 2013;36:858–64; Mathieu *et al. J Clin Endocrinol Metab* 2013;98:1154–62

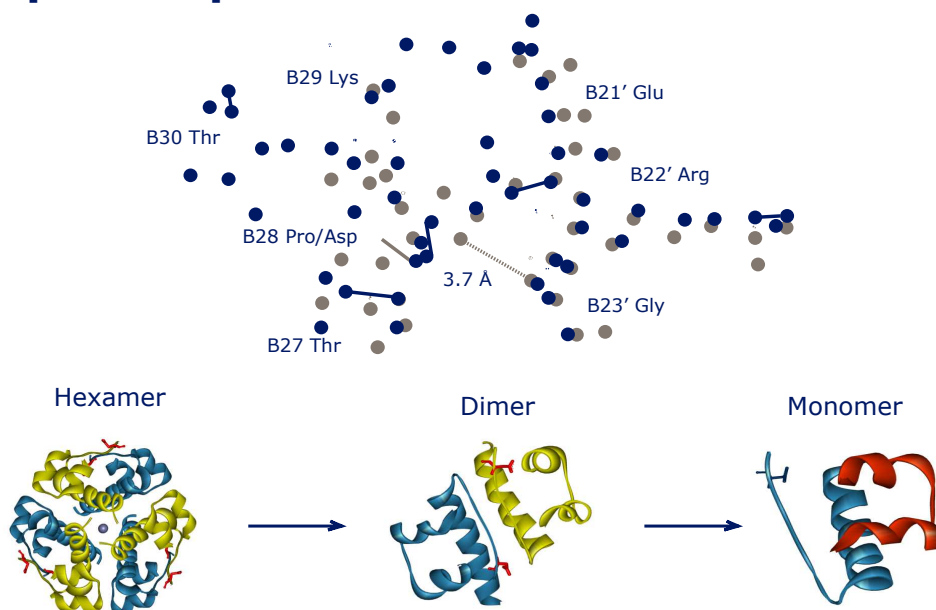
Introduction to insulin aspart

Structure of insulin aspart molecule

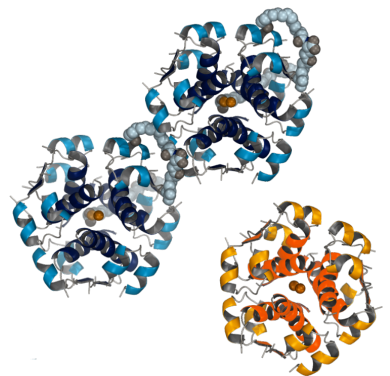
- Insulin aspart is a biosynthetically modified analogue of human insulin
- A single proline amino acid at position 28 of the insulin B-chain has been replaced with an aspartic acid residue
- In all other respects, insulin aspart and human insulin are structurally identical



Insulin aspart: rapid dissociation into monomers



Clinical profile of novel insulin co-formulation



Co-formulation of insulin degludec with rapid-acting insulin possible because of stable dihexamers in solution

In the formulation

IDegAsp = Insulin degludec (70%) + IAsp (30%) existing separately in one formulation

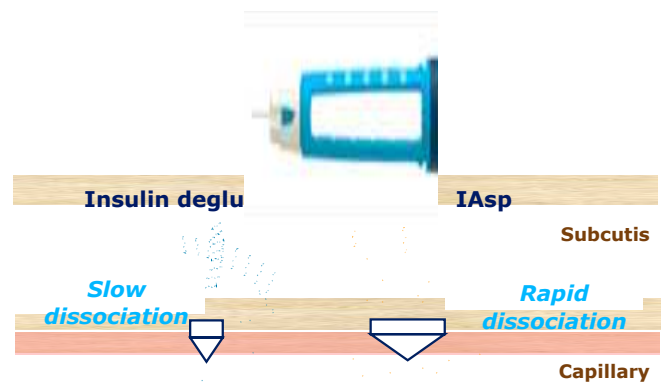


Insulin degludec dihexamers

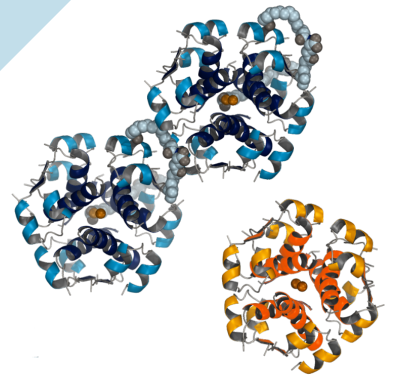
IAsp hexamers



In the subcutaneous depot

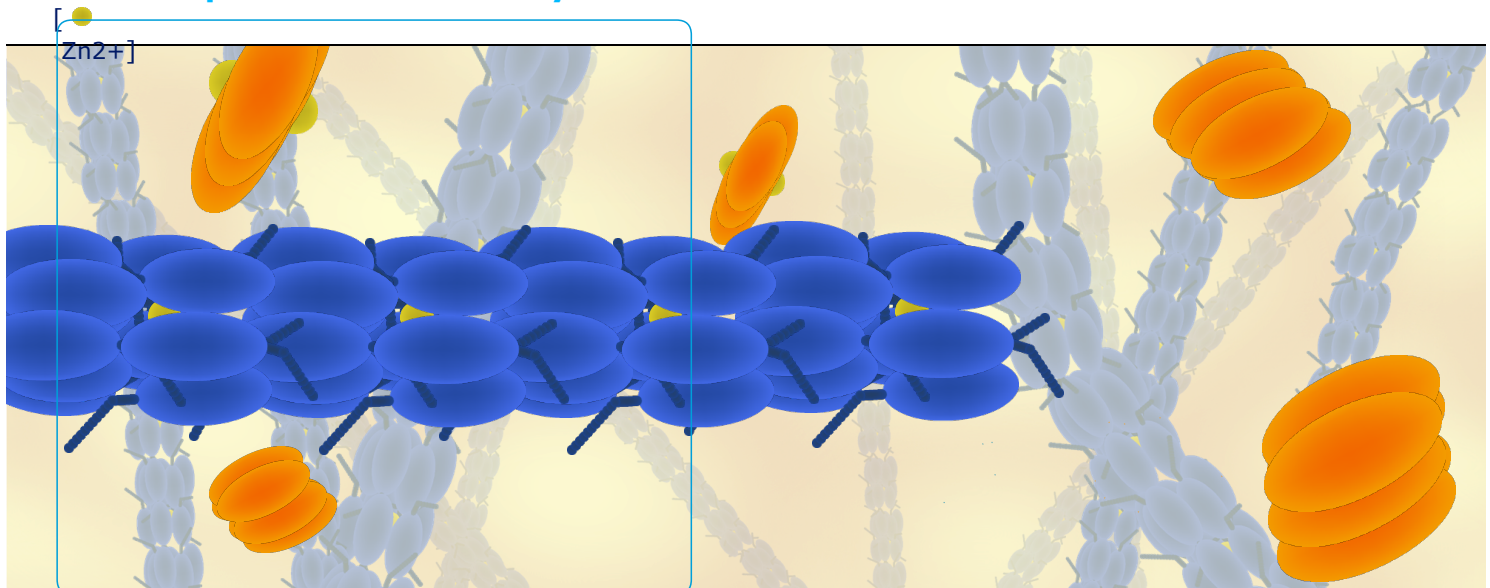


The pharmacokinetics and pharmacodynamics of IDegAsp



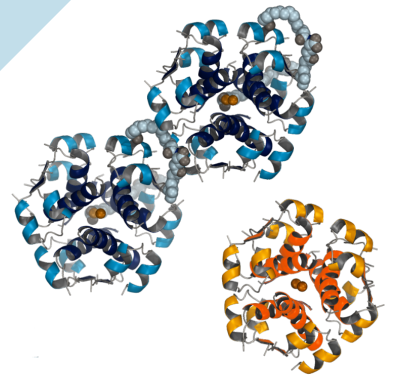
IDegAsp

Mode of protraction at steady state

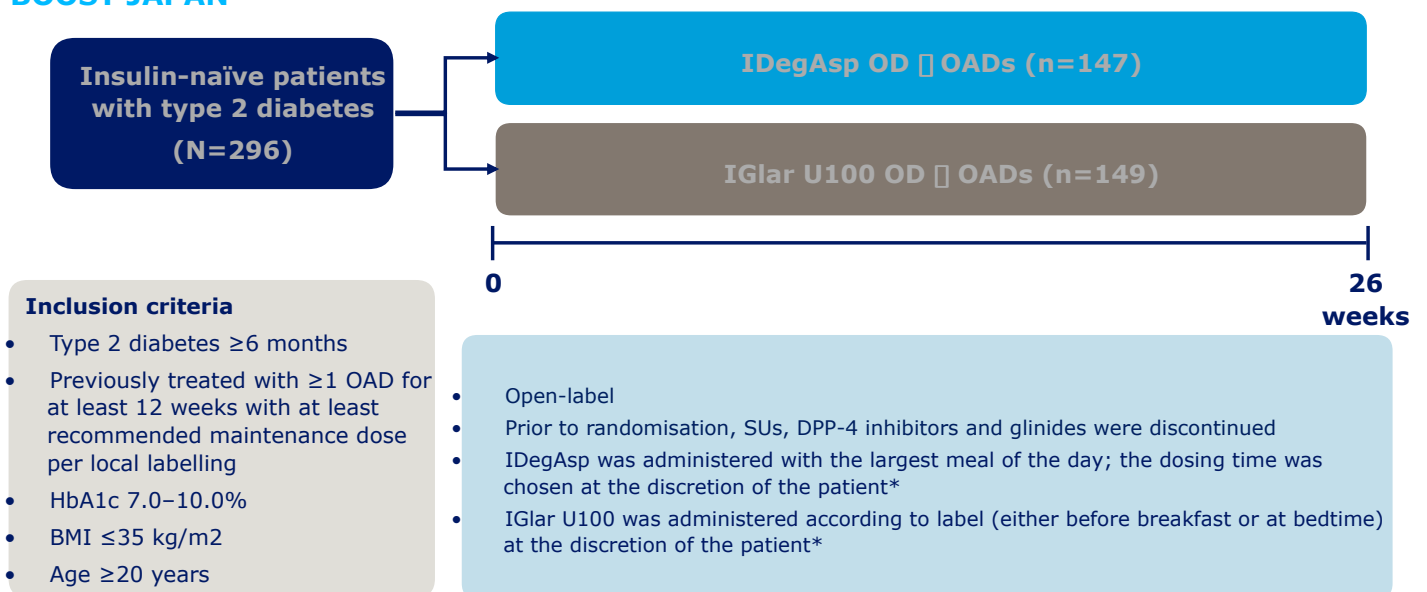


IDegAsp, insulin degludec/insulin aspart
Jonassen *et al. Pharm Res* 2012;29:2104–14

Insulin-naïve T2D OD BOOST JAPAN



Insulin-naïve T2D OD: study design BOOST JAPAN



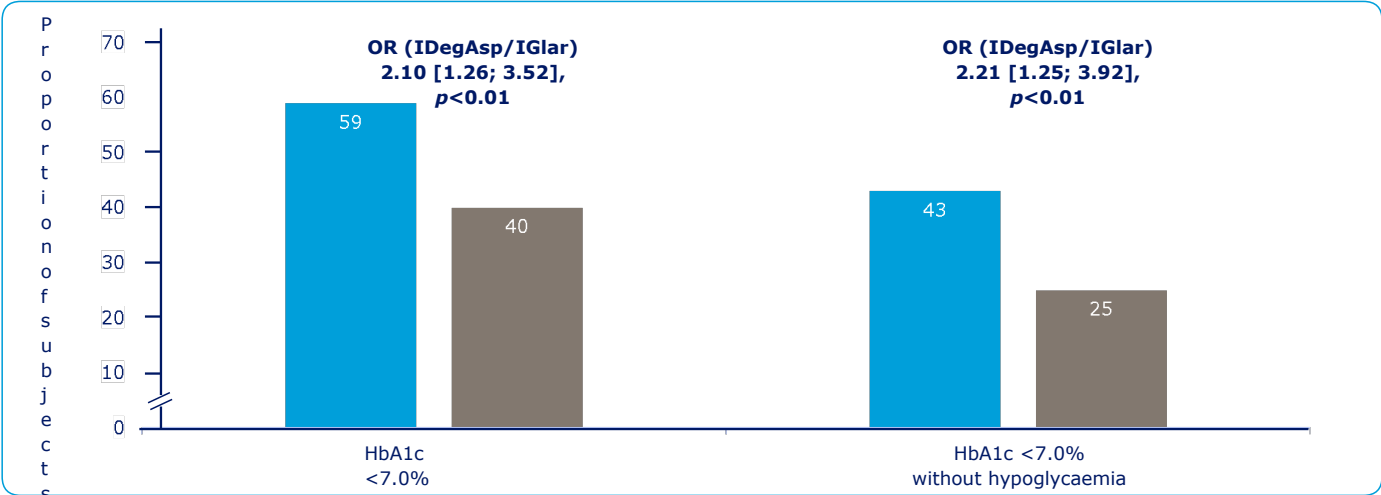
*Starting dose was 10U

BMI, body mass index; DPP-4, dipeptidyl peptidase 4; IDegAsp, insulin degludec/insulin aspart; IGLar U100, insulin glargine U100; OAD, oral antidiabetic drug; OD, once daily; SU, sulphonylurea; T2D, type 2 diabetes; U, units

Onishi et al. *Diabetes Obes Metab* 2013;15:826–32

Subjects achieving treatment targets

IDegAsp OD IGlar U100 OD



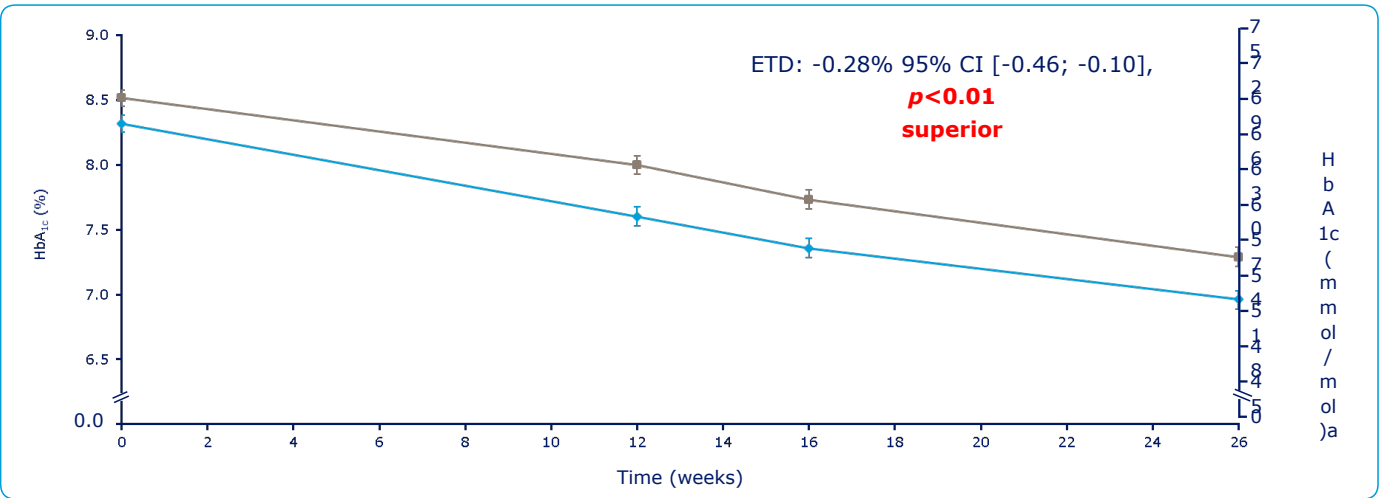
A significantly higher proportion of patients achieved a glycaemic target of HbA1c < 7% which is two times higher with IDegAsp than with IGlar U100

IDegAsp, insulin degludec/insulin aspart; IGlar U100, insulin glargine U100; OD, once daily; OR, odds ratio
Onishi et al. Diabetes Obes Metab 2013;15:826-32

HbA1c over time

BOOST JAPAN

IDegAsp OD (n=147) IGlar U100 OD (n=149)

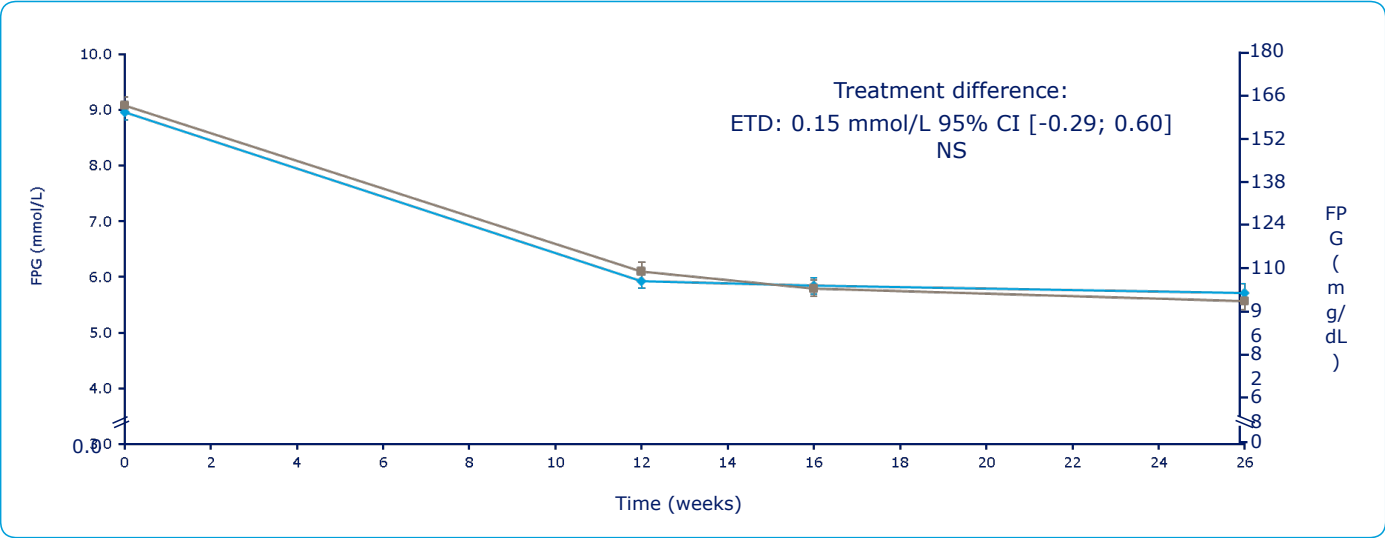


Mean±SEM; FAS; LOCF
aCalculated, not measured
Comparisons: Estimates adjusted for multiple covariates
CI, confidence interval; ETD, estimated treatment difference; FAS, full analysis set; IDegAsp, insulin degludec/insulin aspart; IGlar U100, insulin glargine U100; LOCF, last observation carried forward; OD, once daily; SEM, standard error of mean; T2D, type 2 diabetes
Onishi et al. Diabetes Obes Metab 2013;15:826-32

FPG over time

BOOST JAPAN

◆ IDegAsp OD (n=147)
■ IGlär U100 OD (n=149)

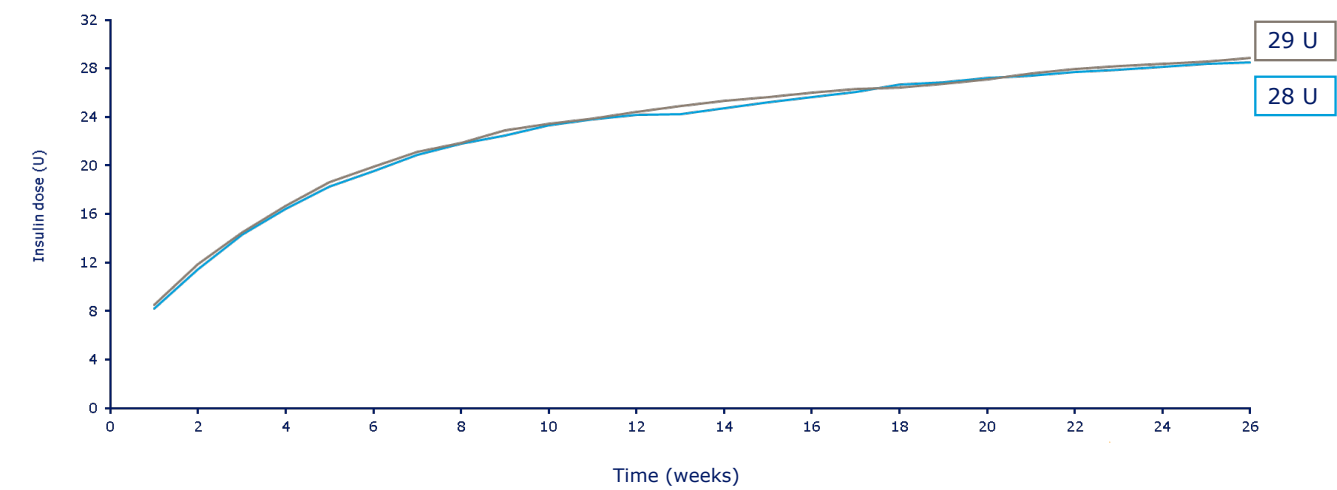


Mean±SEM; FAS; LOCF
Comparisons: Estimates adjusted for multiple covariates
CI, confidence interval; ETD, estimated treatment difference; FAS, full analysis set; FPG, fasting plasma glucose; IDegAsp, insulin degludec/insulin aspart; IGlär U100, insulin glargine U100; LOCF, last observation carried forward; NS, not significant; OD, once daily; SEM, standard error of mean; T2D, type 2 diabetes
Onishi et al. Diabetes Obes Metab 2013;15:826-32

Total insulin dose over time

BOOST JAPAN

— IDegAsp OD (n=147)
— IGlär U100 OD (n=149)

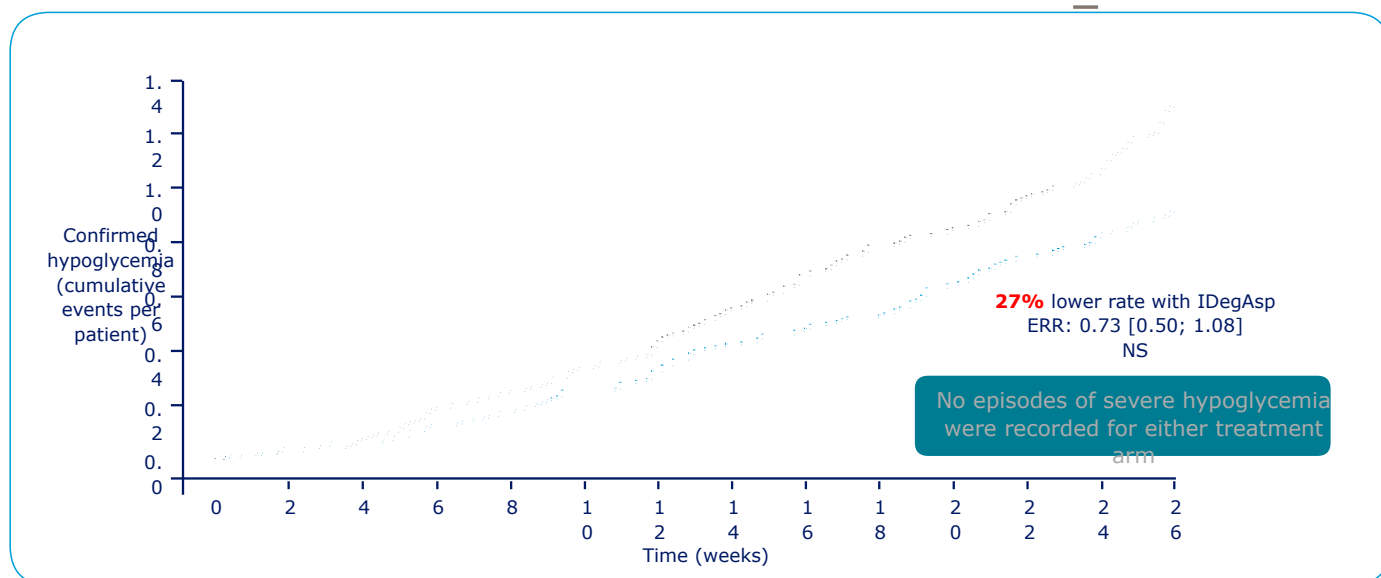


SAS; LOCF
IDegAsp, insulin degludec/insulin aspart; IGlär U100, insulin glargine U100; LOCF, last observation carried forward; OD, once daily; SAS, safety analysis set; T2D, type 2 diabetes
Onishi et al. Diabetes Obes Metab 2013;15:826-32;

Confirmed hypoglycemia

BOOST JAPAN

— IDegAsp OD (n=147)
— IGlAr U100 OD (n=149)

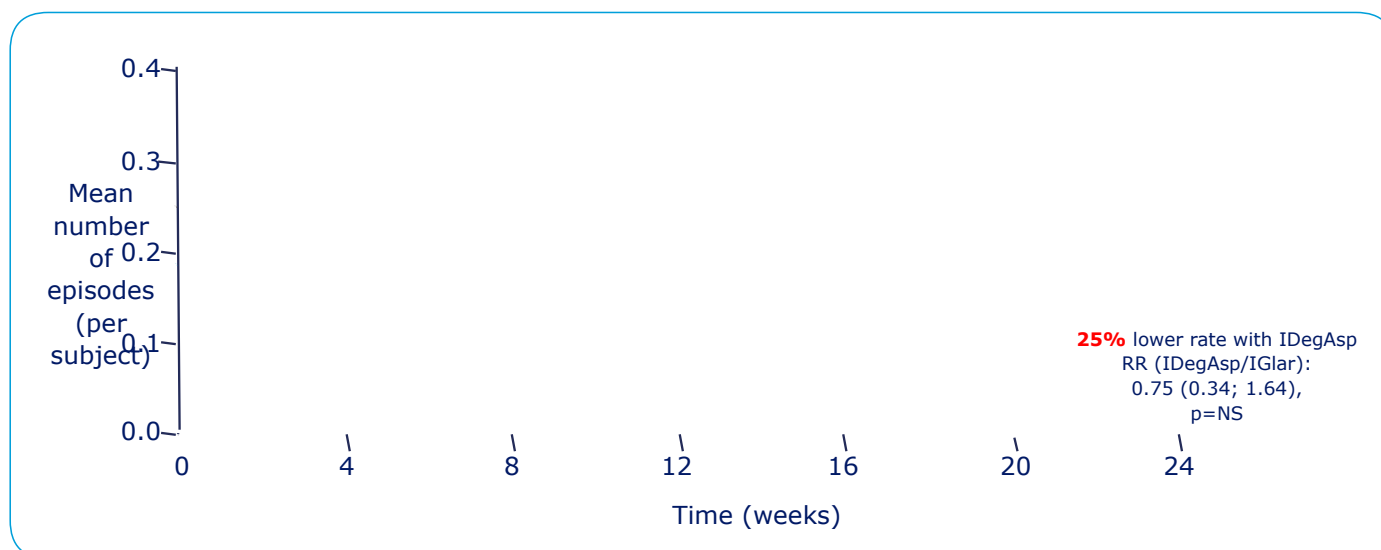


SAS
Comparisons: Estimates adjusted for multiple covariates
ERR, estimated rate ratio; IDegAsp, insulin degludec/insulin aspart; IGlAr U100, insulin glargine U100; NS, not significant; OD, once daily; SAS, safety analysis set; T2D, type 2 diabetes
Onishi et al. *Diabetes Obes Metab* 2013;15:826–32

Nocturnal confirmed hypoglycemia

BOOST JAPAN

— IDegAsp OD (n=147)
— IGlAr U100 OD (n=149)



SAS
Comparisons: Estimates adjusted for multiple covariates
ERR, estimated rate ratio; IDegAsp, insulin degludec/insulin aspart; IGlAr U100, insulin glargine U100; NS, not significant; OD, once daily; RR, rate ratio; SAS, safety analysis set; T2D, type 2 diabetes
Onishi et al. *Diabetes Obes Metab* 2013;15:826–32

Conclusions

BOOST JAPAN

Week 26		
IDegAsp VS IGlar U100	HbA1c	Superiority confirmed*
	Total daily insulin dose	Similar (NS)
	Confirmed hypoglycaemia	27% lower with IDegAsp (NS)
	Nocturnal-confirmed hypoglycaemia	25% lower with IDegAsp (NS)

* $p < 0.01$
 IDegAsp, insulin degludec/insulin aspart; IGlar U100, insulin glargine U100; NS, not significant
 Onishi et al. *Diabetes Obes Metab* 2013;15:826–32



Clinical Use of IDegAsp



Device-IDegAsp is delivered in the FlexPen®

Maximum dose/injection:
60 U

**70/30 –
3 ml
prefilled
pen**

Pen Capacity:
3ml=300 IU

Storage:

Opened pens 2–8°C or room temperature for 4 weeks
Unopened pens 2–8°C until expiry date (30 months)

Injection sites:

Rotate frequently within the chosen area

IDegAsp, insulin degludec/insulin aspart
Ryzodeg® FlexPen ® 100 U/ml Patient Leaflet STF-Dec-2020

Recommended starting dose for initiations

Starting dose

10 Unit/OD

With largest meals

Severe Hyperglycemia
HbA1c >10% *

> 10 Unit/OD

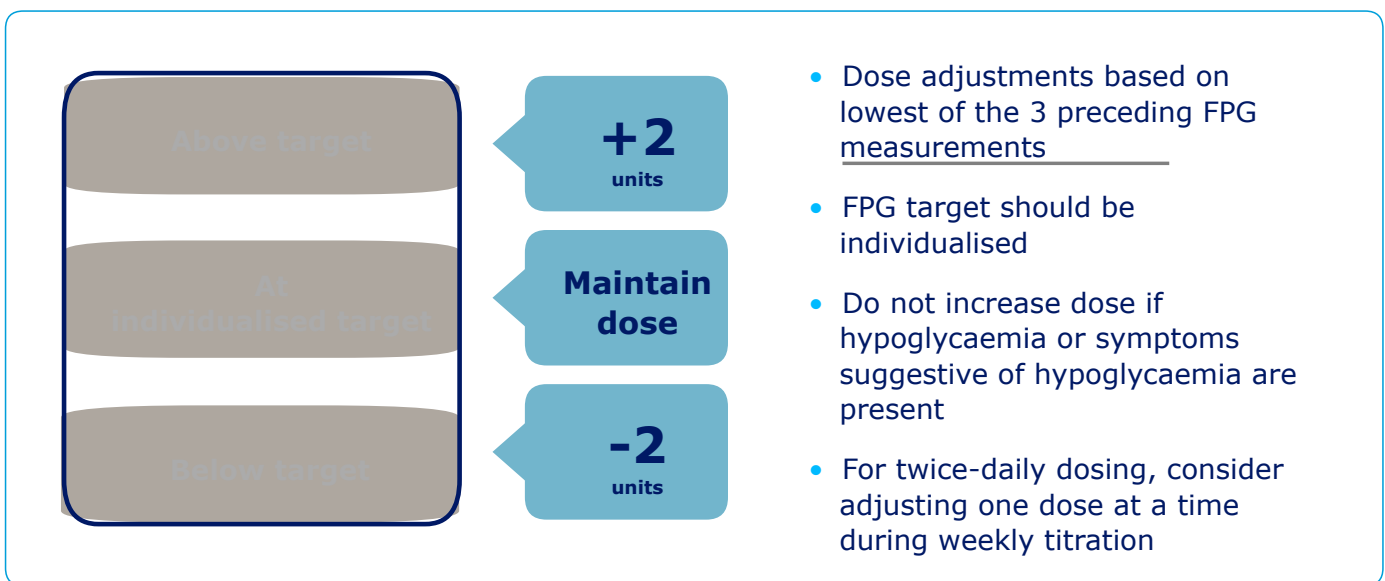
With largest meals

*This posology is based on expert recommendations from
Sarah G et al.

Followed by subsequent **INDIVIDUAL** dosage
weekly adjustment until the desired **FPG**
reached

References: 1. Sarah J Glastras et al. J Clin Med 2020 Apr; 9(4): 1091 2. Roopa Mehta et al. Diabetes Obes Metab. 2020 Nov;22(11):1961-1975

Suggested once-weekly titration schedule for IDegAsp in T2D



FPG, fasting plasma glucose; IDegAsp, insulin degludec/insulin aspart; T2D, type 2 diabetes

1. Gerety *et al.* *Endocr Pract* 2016;22:546–54; 2. Endocrinologic and Metabolic Drug Advisory Committee. Insulin degludec and insulin degludec/insulin aspart treatment to improve glycemic control in patients with diabetes mellitus: NDAs 203314 and 203313 briefing document. Published November 8, 2012

IDegAsp Split

-If there are post prandial glucose excursion after 2 meals

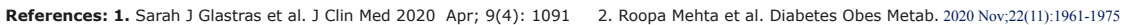
-Recommend a max OD dose 30-40 unit before splitting.

-The dose ratio: not necessarily (1:1) with a minimum dosing interval of 4 hours

Reference: Sarah J Glastras *et al.* *J Clin Med* 2020 Apr; 9(4): 1091



Switching to I



The diagram illustrates the concept of individualised care across different patient groups. It features a central white box labeled "Pregnancy" with a silhouette of a pregnant woman. To the left, a grey box labeled "Elderly" contains a silhouette of an elderly person. Above the "Elderly" box, a blue box labeled "Paediatrics" contains a silhouette of a child. To the right of the "Pregnancy" box, a blue box labeled "Renal and Hepatic impairment" contains a silhouette of a person. Arrows point from the "Paediatrics" and "Elderly" boxes towards the "Pregnancy" box, and from the "Pregnancy" box towards the "Renal and Hepatic impairment" box. The text "The IDe in p 200" is partially visible on the left, and "e be" is visible on the right. Below the "Elderly" box, the text "Can Glu inte individualised" is partially visible. Below the "Pregnancy" box, the text "ce nant" is partially visible.

Overall Summary

IDegAsp provides:


HbA1c

**Similar glycaemic control
among all the trials:**

- Lower insulin dose
- Reduction in nocturnal, overall & severe hypoglycaemia vs. comparators

**FPG and PPG control
achieved with flexible dosing
at the main meals**

**Simple intensification
with optimal flexibility in dose
timing vs. basal bolus**

Comparators: BIAsp 30 (start twice daily, Intensify Premix I and ALL, China, Ramadan); Insulin degludec OD + IAsp (twice daily vs. basal bolus); IDet (BOOST T1); IGlar U100 + IAsp (step-by-step trial)
BIAsp, biphasic insulin aspart; BID, twice daily; FPG, fasting plasma glucose; IDegAsp, insulin degludec/insulin aspart; IDet, insulin detemir; IGlar U100, insulin glargine U100; OD, once daily; PPG, post prandial glucose; T2D, type 2 diabetes

Real cases experience

- IDegAsp
- 125 patients
- 76 Males, 49 Females
- Mean Age: 52.5 ± 9.2
- 38 – 85 yrs
- Avg DM History: 11.2 ± 4.8



Criteria

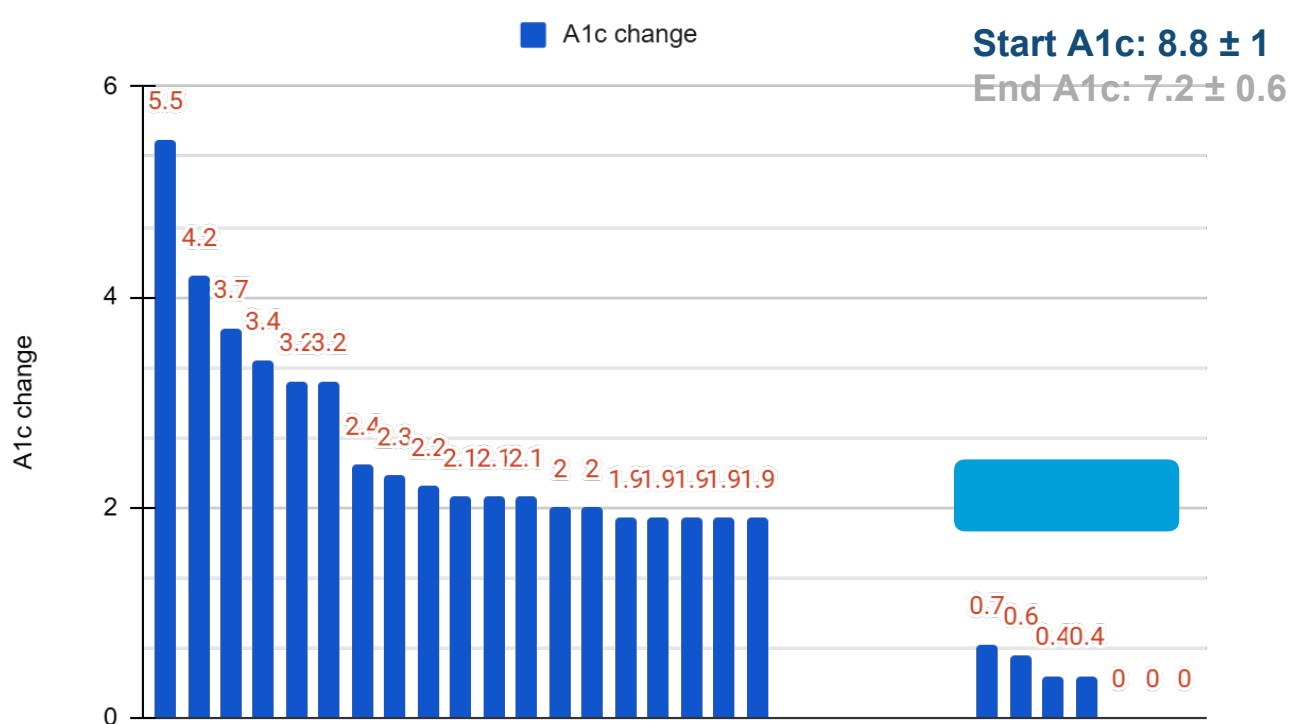
- Men and women with T2DM aged >18 years
- Who were on oral anti-diabetic drugs (OADs) only and initiated insulin therapy
- FBS, PPG and HbA1c values were measured at baseline and after 6 months



- A1c: 9.4 ± 1.7
- 62% Family History
- 14% Smoker
- 30% HTN
- 41% Dyslipidemia

• (IDegAsp)

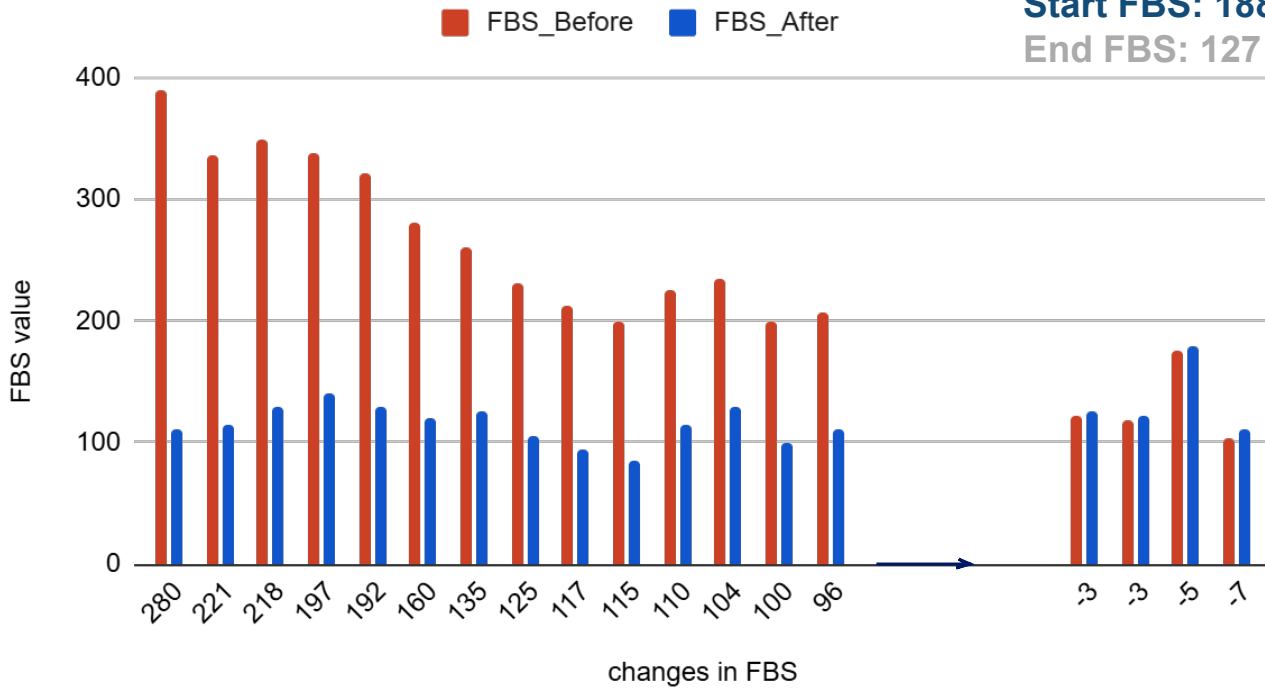
- 6 – 50 Units
- Avg 20 Units of insulin



FBS_Before and FBS_After

Start FBS: 188 ± 42

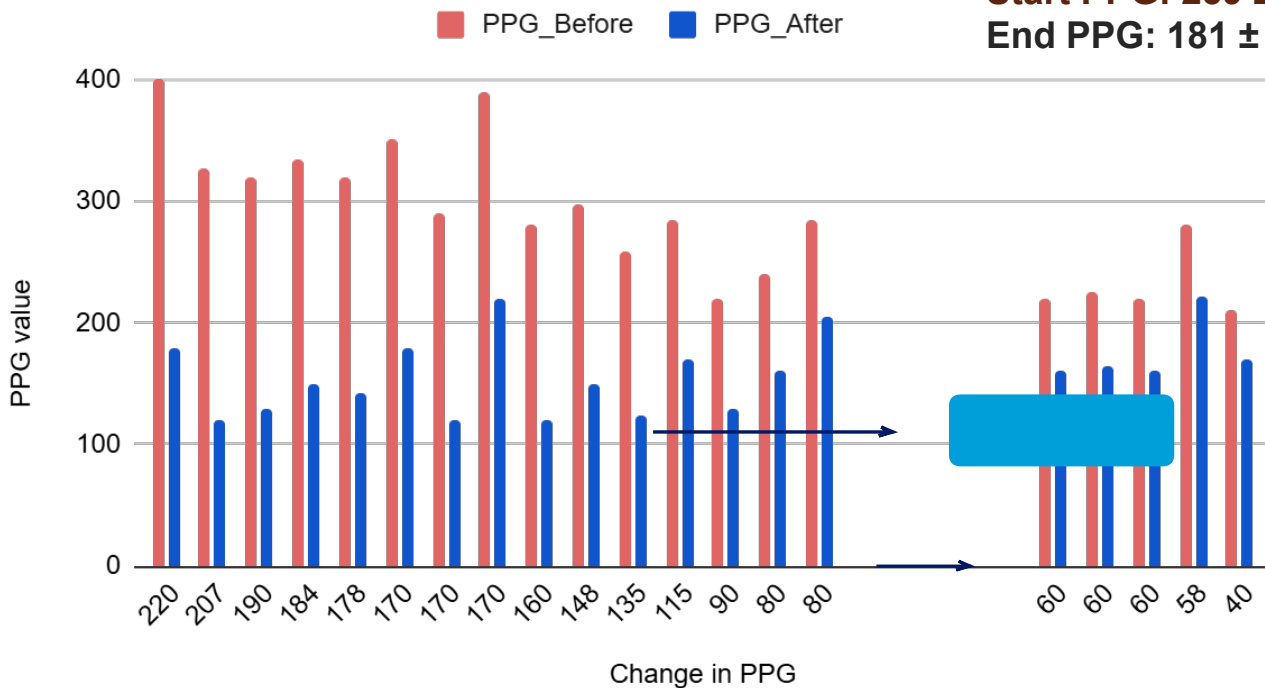
End FBS: 127 ± 17



PPG_Before and PPG_After

Start PPG: 259 ± 31

End PPG: 181 ± 25



Classification of hypoglycemia

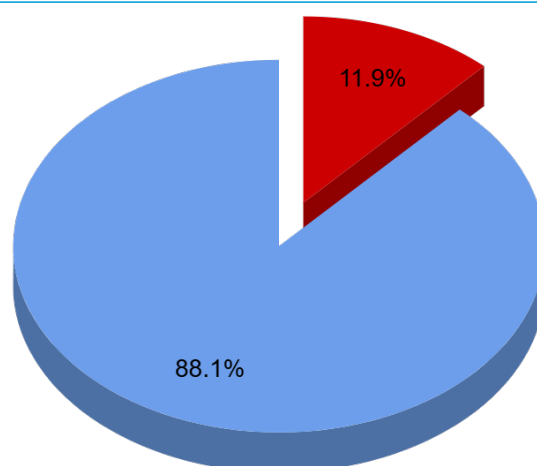
Classification of hypoglycemia

- Level 1 Glucose <70 mg/dL (<3.9 mmol/L) and ≥ 54 mg/dL (≥ 3.0 mmol/L)
- Level 2 Glucose <54 mg/dL (<3.0 mmol/L)
- Level 3 A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia, irrespective of glucose level

Hypoglycemia symptoms in 15 patients

Only Three reports of Confirmed Hypoglycemia

No adverse events or reports of severe hypoglycemia



Reported Hypoglycemia symptoms