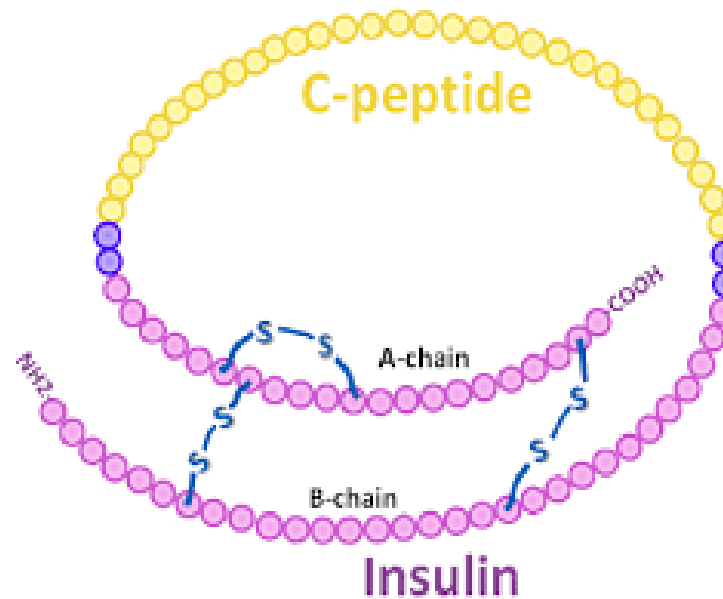


The Use of Insulin Degludec in Management of Pediatric Diabetes



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Overview

- Introduction on high rate of diabetes globally.
- History of insulin industry.
- Prevalence of diabetes worldwide.
- Ultra-long acting basal insulin Degludec.
- Review of benefits of insulin Degludec.
- Conclusion.

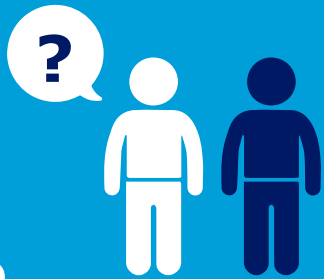


TODAY, more than **425 MILLION** people have diabetes¹

BY 2045, it's estimated that

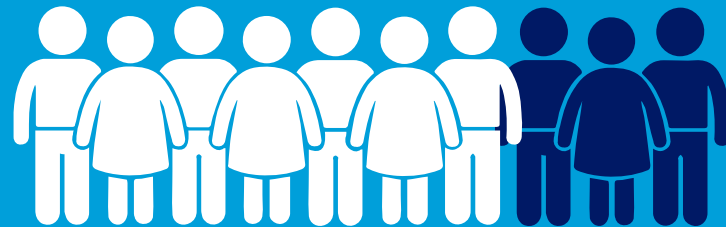
736 MILLION

people will have diabetes globally¹



1 in 2

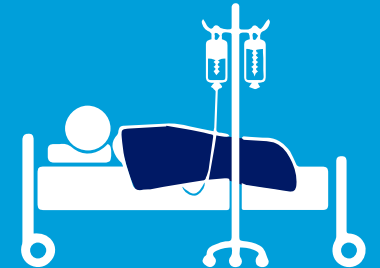
People with type 2 diabetes **do not know** they have it¹



7 in 10

People with diabetes **do not achieve desired treatment**

outcomes?



4 MILLION

Deaths were caused by diabetes in 2017¹

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.

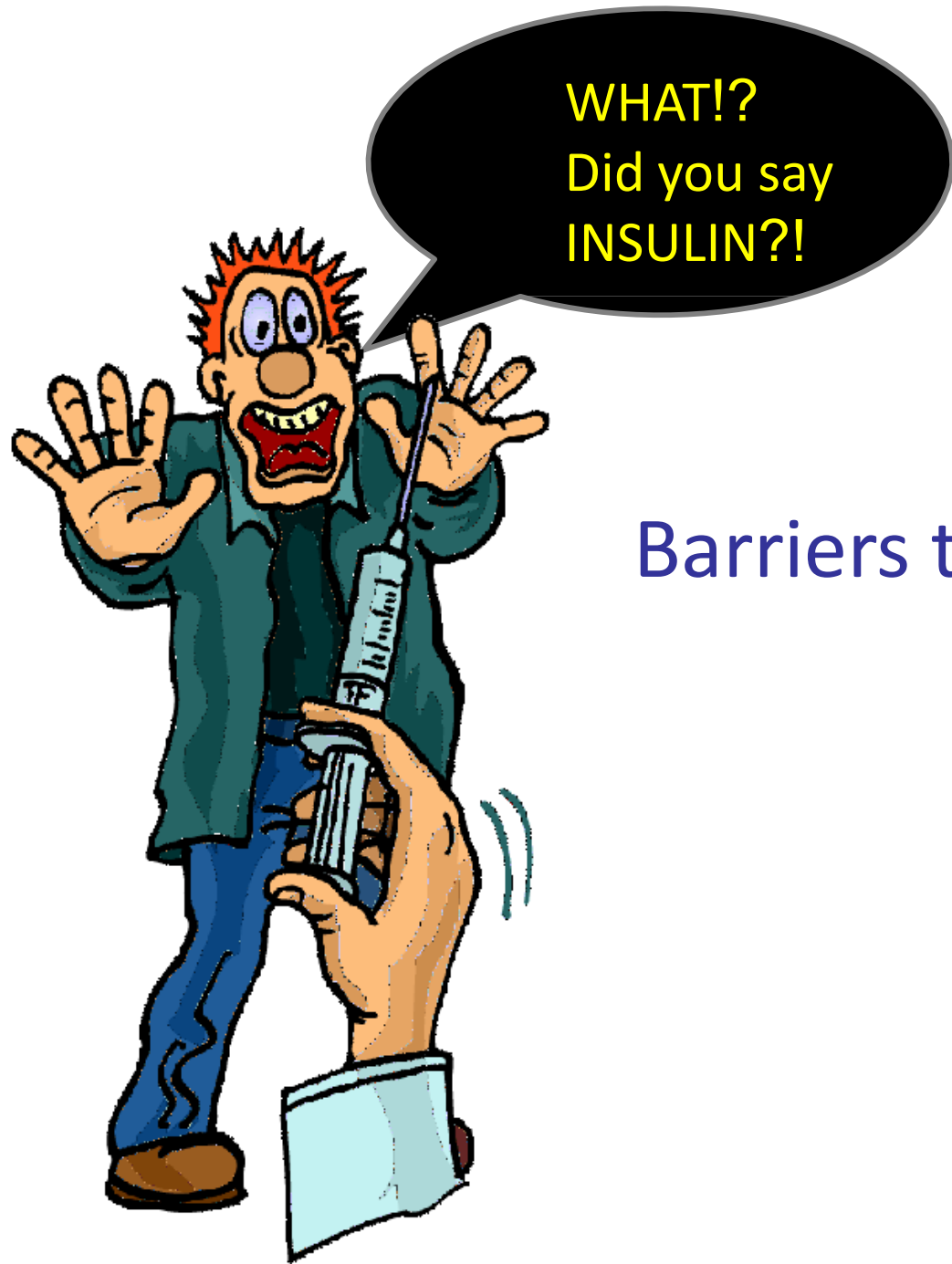
Prevalence of Type 1 Diabetes

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

Managing pediatric patients with type 1 DM is challenging!!





Barriers to the use insulin in children

Discovery of Insulin

1921



Banting



Best

Insulin was first discovered (late 1920's) which won the doctor and medical student who discovered it the Nobel Prize (Banting and Best)



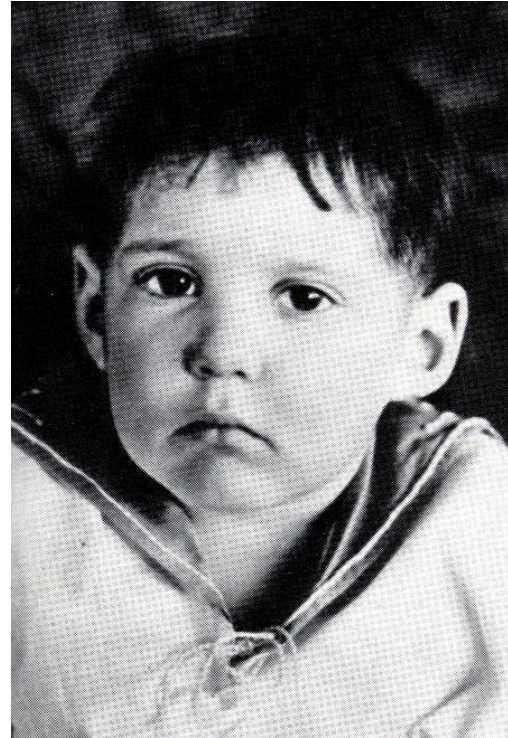


Banting & Best

The Miracle of Insulin



Patient J.L., December 1922 ,15

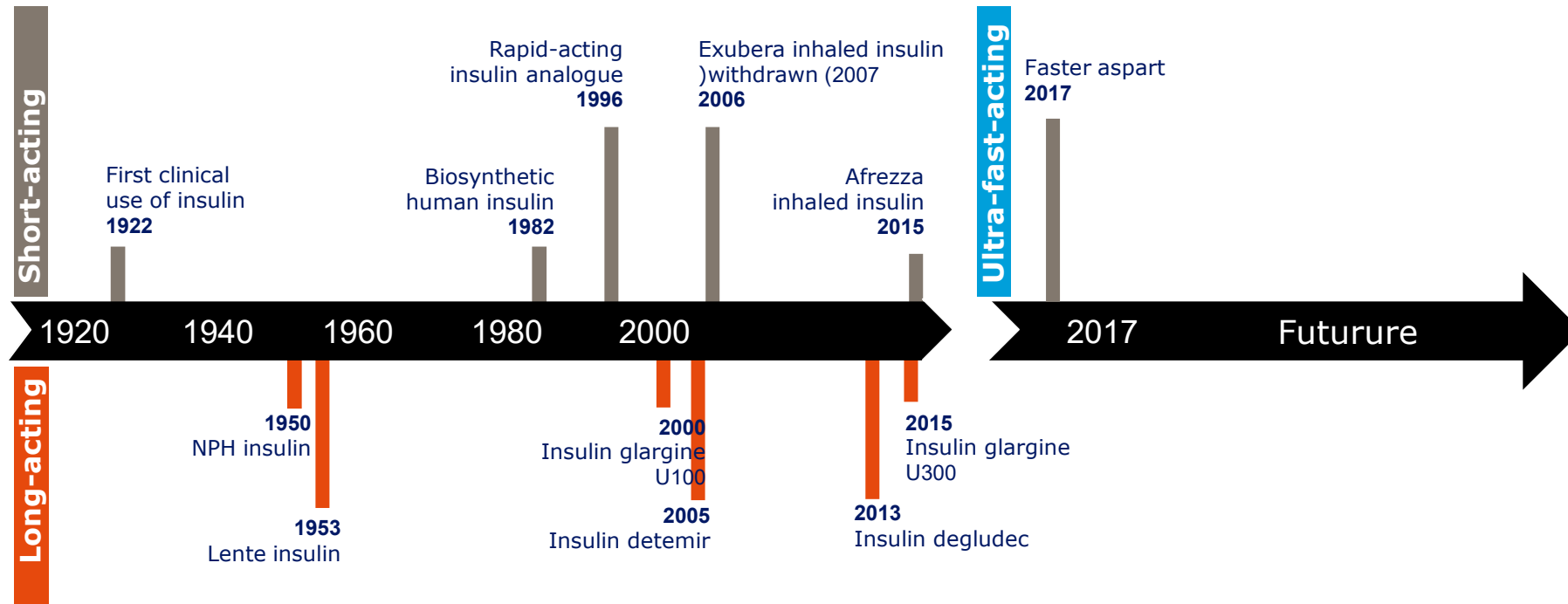


February 15, 1923

Human insulin

- The human insulin protein is composed of 51 amino acids, and has a molecular size of 5808 Da.
- It is a heterodimer of an A-chain and a B-chain, which are linked together by disulphide bonds.
- Insulin's structure varies slightly between species of animals.
- Porcine insulin is especially close to the human version, and was widely used to treat type 1 diabetics before human insulin could be produced in large quantities by recombinant DNA technologies

Evolution of insulin therapy since 1922

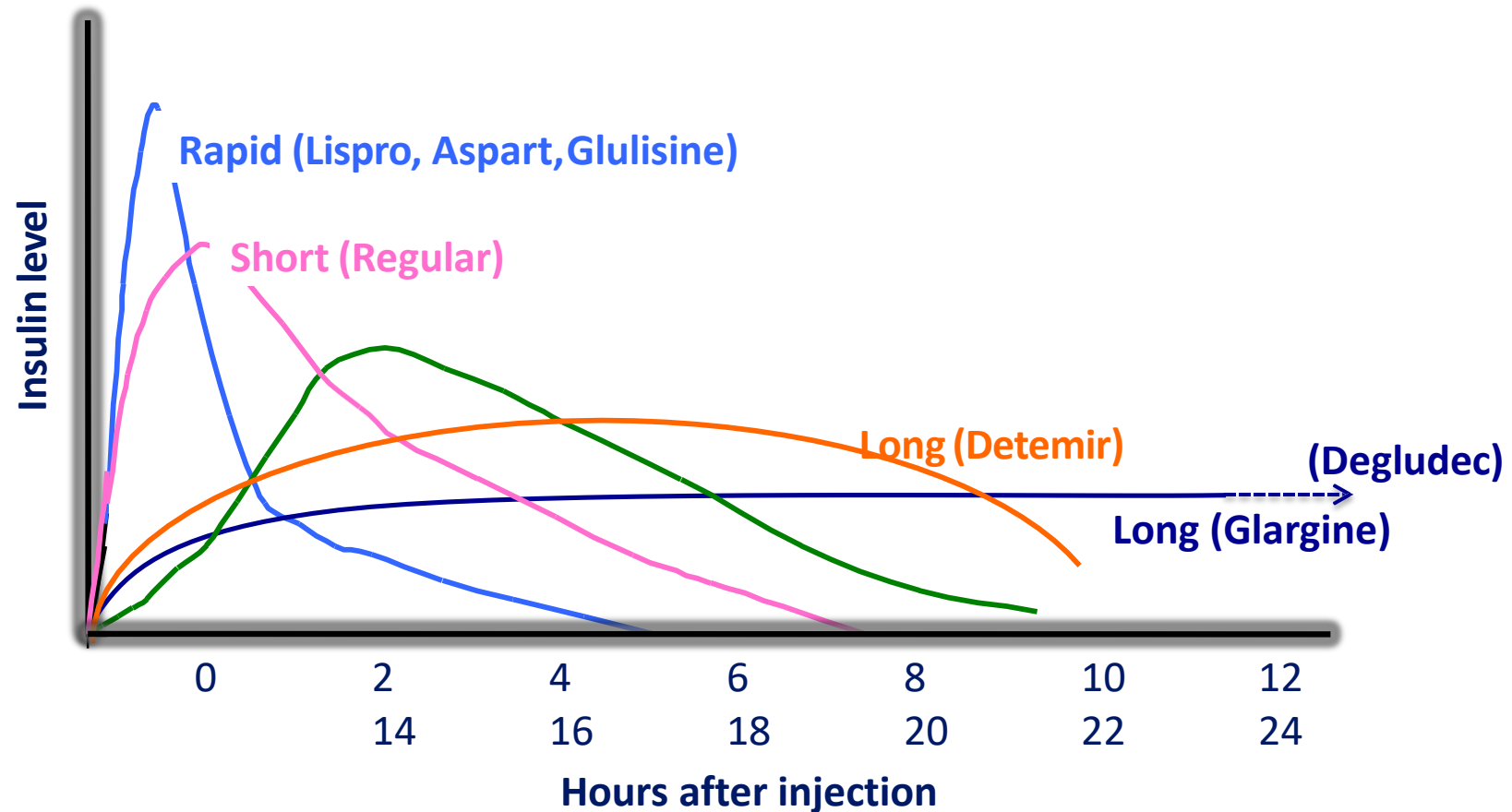


Adapted from Cahn *et al. Lancet Diabetes Endocrinol* 12 ,notiacilppa tnetap .yllil iIE;52–3:638;2015November 4 ,esaeler sserP .yllil iIE;2015December D&R yaD stekraM latipaC .ksidroN ovoN;2015 19 ,etadpuNovember 2015

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



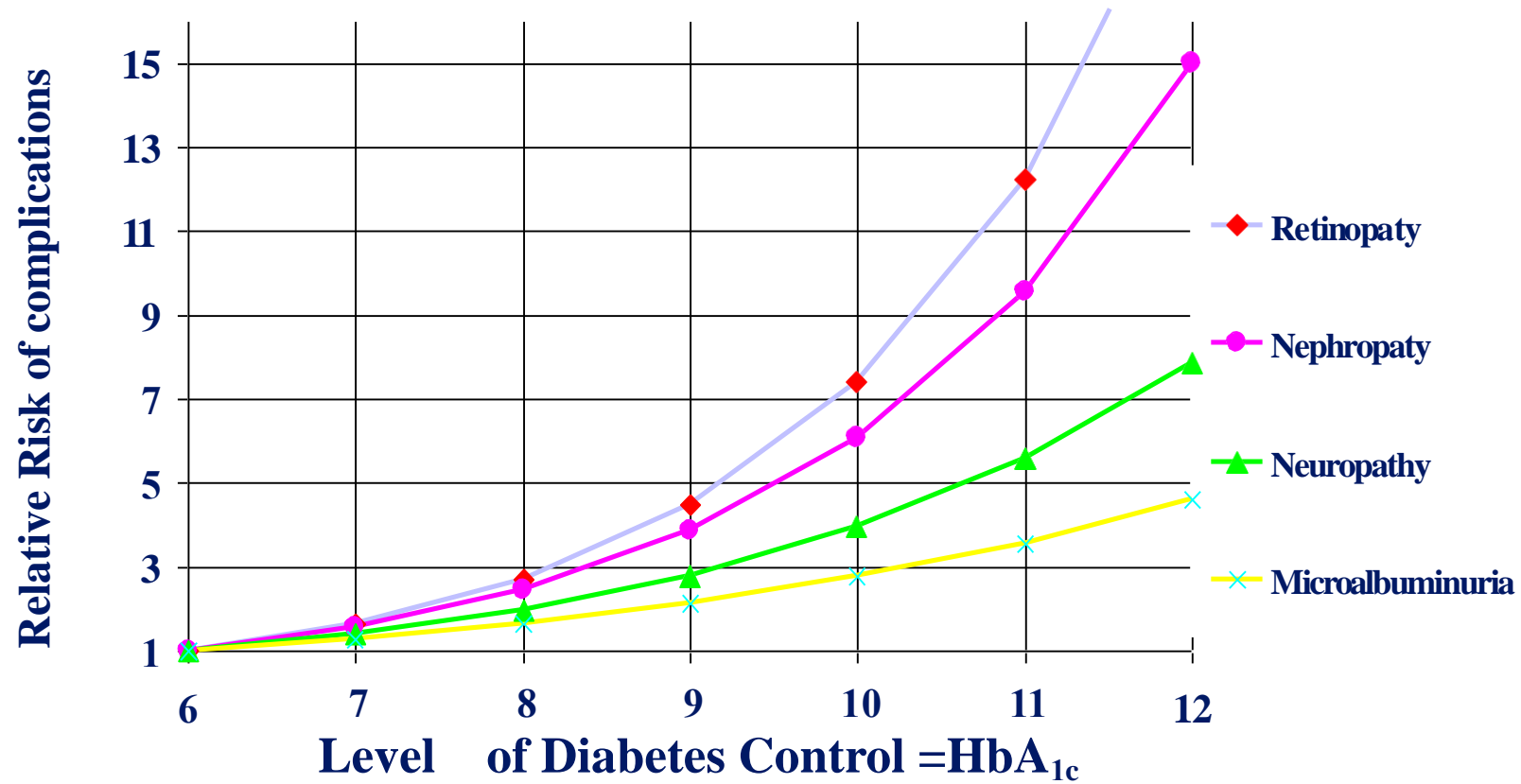
Various insulin preparations available so far as basal – bolus insulin therapy



The most important fact is Everyone has different needs!



Good glycemic control will lead to low risk of complications (DCCT)



Ultra-long acting basal insulin Degludec.



Tresiba[®] (insulin degludec injection) 100 U/mL, 200 U/mL



Objectives of developing a new basal insulin

Longer duration of action

- Control fasting BG with one injection per day for all individuals
- Flexible dosing time

Flat time-action profile

Lower risk of hypoglycaemia

Less day-to-day variability

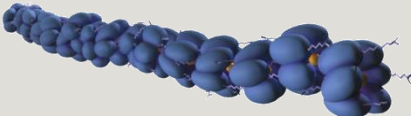
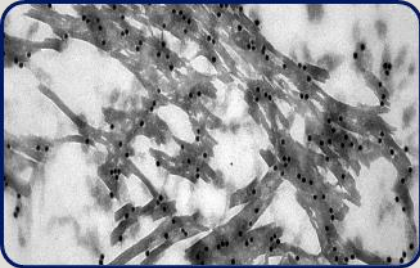
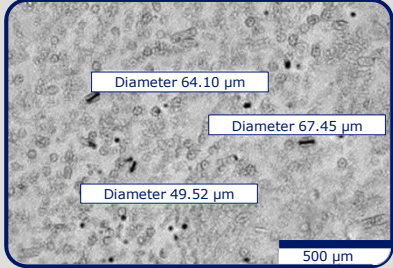
Potential for titration to lower FPG target without hypoglycaemia
(More predictable action)

BG, blood glucose; FPG, fasting plasma glucose

Insulin Degludec

- Novel ultra long-acting insulin analogue.
- Insulin Degludec provides basal insulin coverage for more than 42 hours, and achieves similar glycaemic control with less overnight hypoglycemia than glargine.
- Half life is about 25 hours.
- FDA approved (September, 2015).
- Degludec is approved for use in Europe, Saudi Arabia & Gulf countries.

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

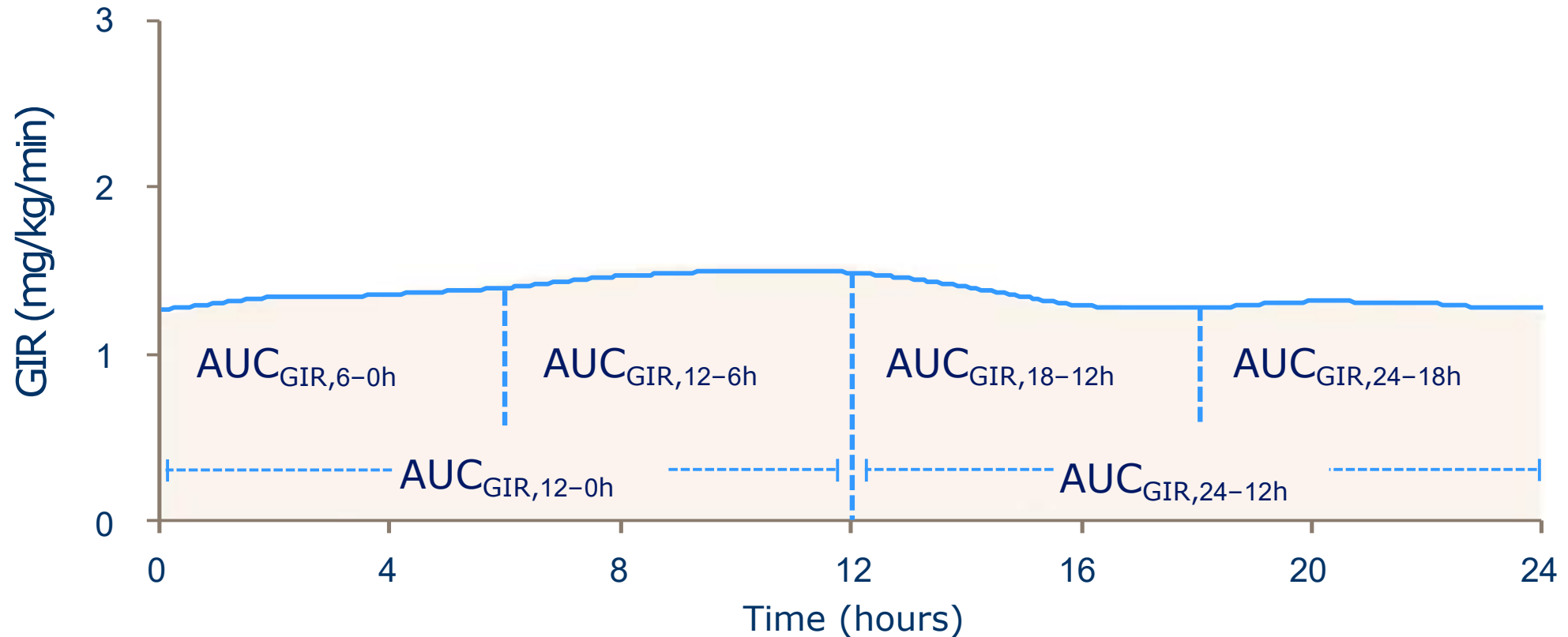
Jonassen *et al. Pharm Res* 2012;29:2104–14; Heise *et al. Expert Opin Drug Metab Toxicol* 2015;11:1193–201; Heise *et al. Diabetes Obes Metab* 2012;14:859–

Half-life of insulin degludec is double that of insulin glargine

	Insulin degludec			Insulin glargine		
	0.4U/kg	0.6U/kg	0.8U/kg	0.4U/kg	0.6U/kg	0.8U/kg
Half-life (sruoh)	25.9	27.0	23.6	11.5	12.9	11.9
Mean half-life	25.4			12.1		

*Insulin glargine was undetectable after 48 hours Results from 66 patients with type 1 diabetes (T1D)
IDeg, insulin degludec; IGlarg, insulin glargine
Heise *et al. Diabetes* ;11BL:(1 .lppuS)60;2011 *et al. Diabetologia* 425S:(1 .lppuS)54;2011

Flat time-action profile of insulin Degludec

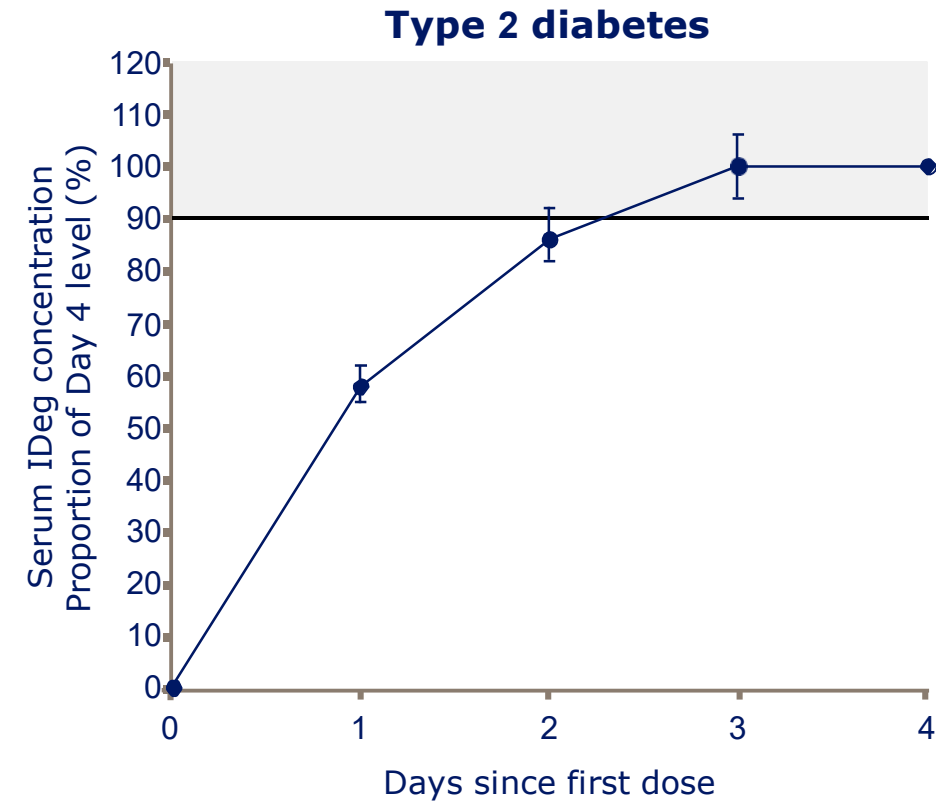
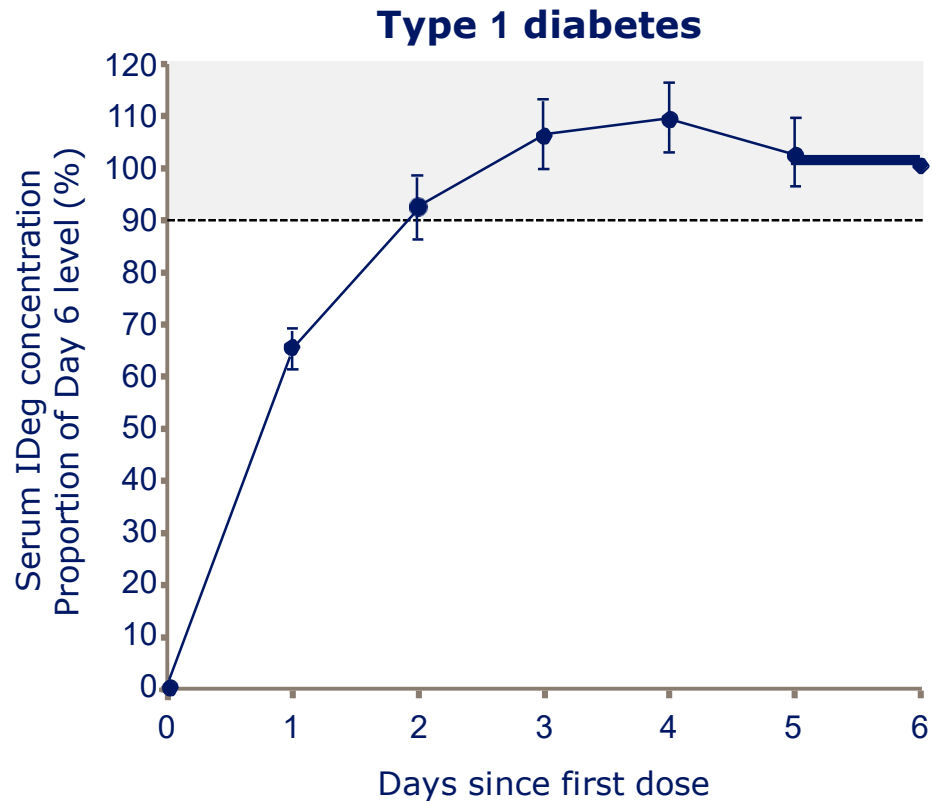


AUC_{x-y} , area under the curve for a specified time interval after injection

GIR, glucose infusion rate

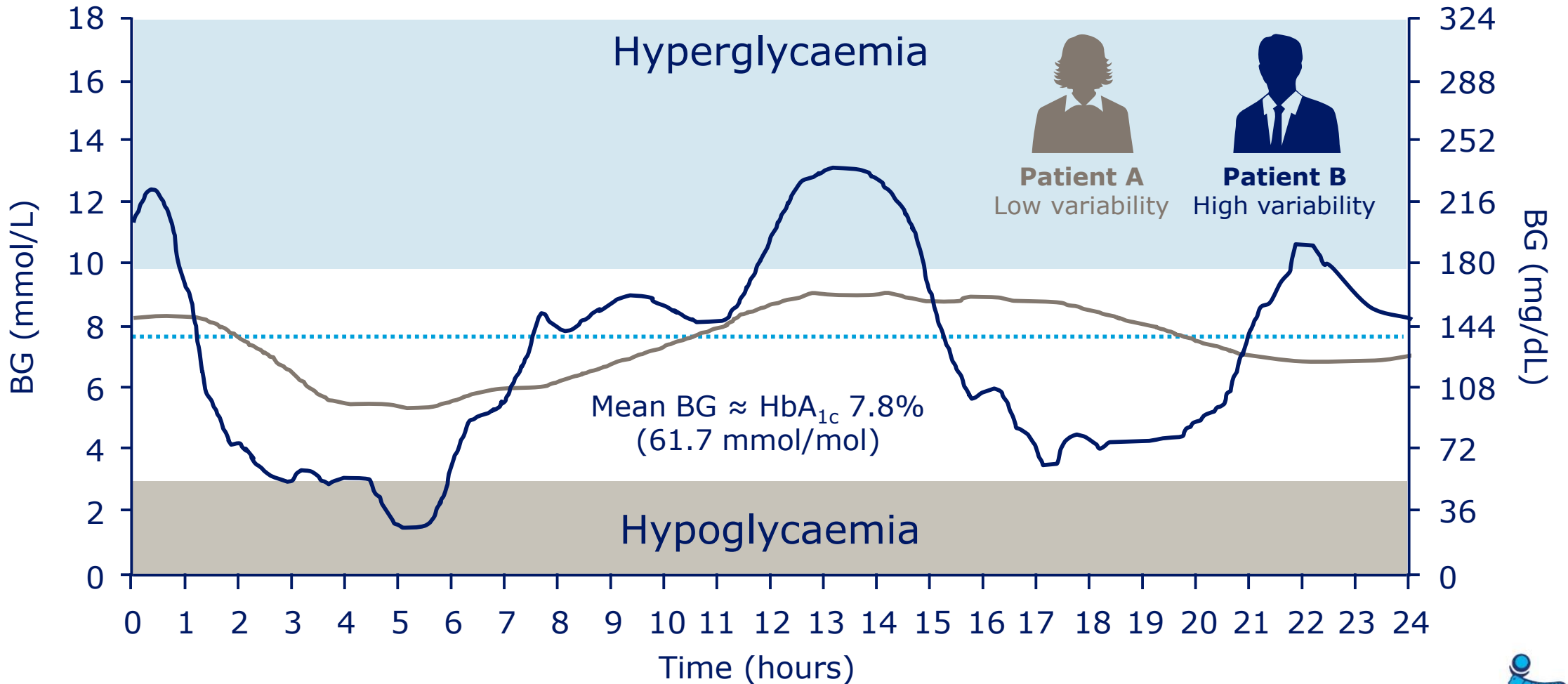
Type 2 diabetes, 49 patients, randomised, ta dessessa saw ytilibairaV lairt yad-12 ,doirep-2
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Insulin degludec concentration reaches steady state in 3 days



Type 1 diabetes trial, n=2 epyT ;66diabetes trial, n=49
T1D trial, 0.6 ,0.4or 0.8 U/kg; T2D trial, 0.6 ,0.4or 0.8 U/ kg
Estimated ratios and 95% CI
Heise et al. *Diabetes* 259A:(1 .lppuS)61;2012

Glycaemic control: variability

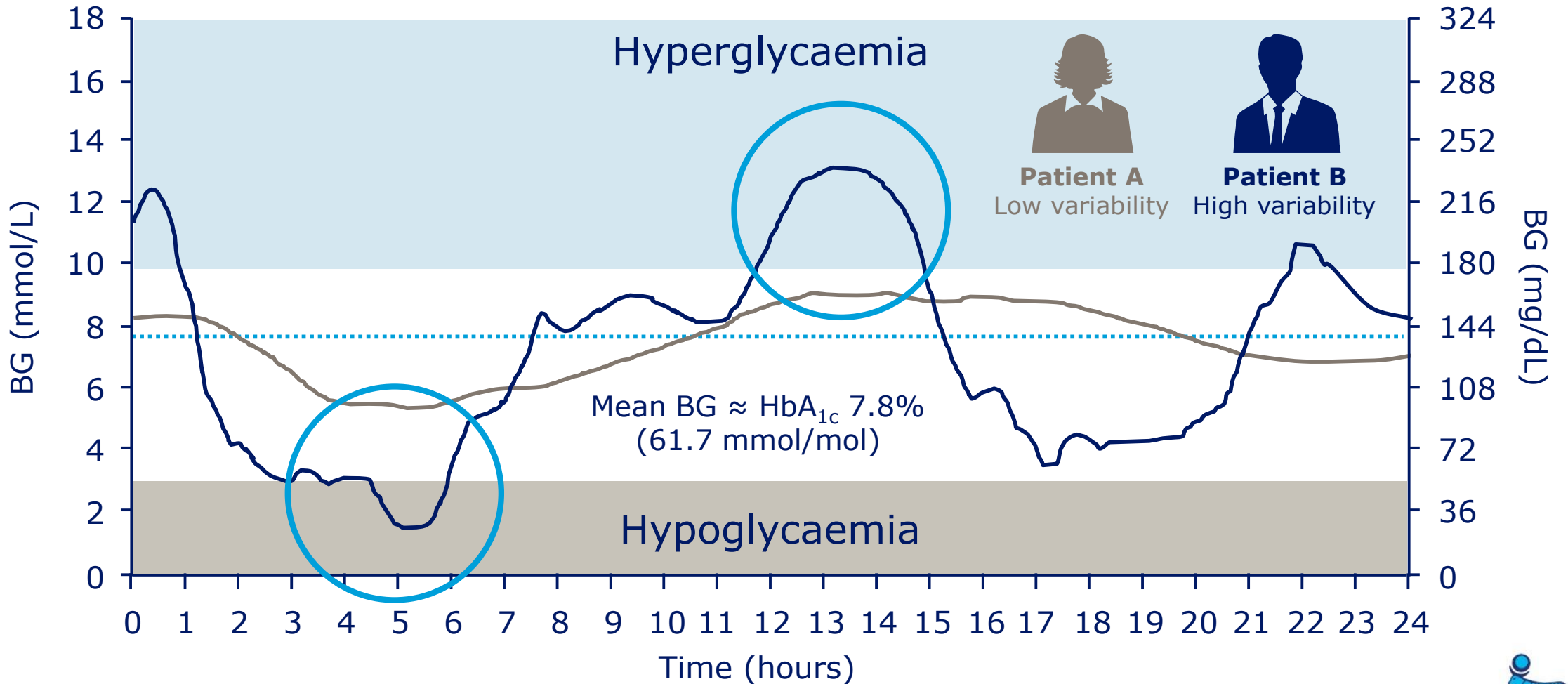


BG, blood glucose; HbA_{1c}, glycated haemoglobin.

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.

For internal Medical Affairs training only

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



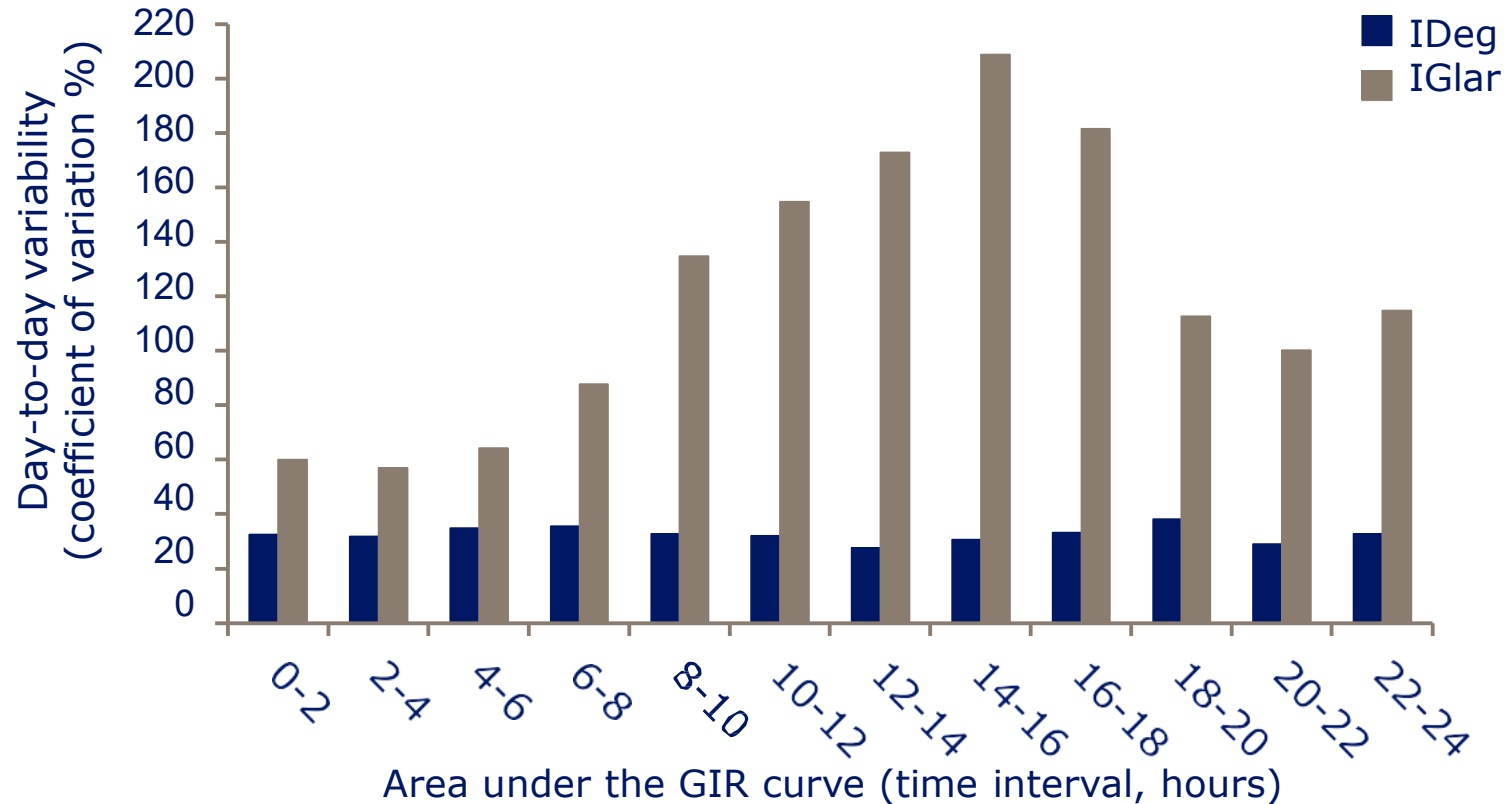
BG, blood glucose; HbA_{1c}, glycated haemoglobin.

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.

For internal Medical Affairs training only



Insulin Degludec has 4 times lower variability than insulin Glargine



Endpoint	IDeg CV(%)	IGlar CV(%)	p value
AUC _{GIR,24-0h}	20	82	p0.0001>

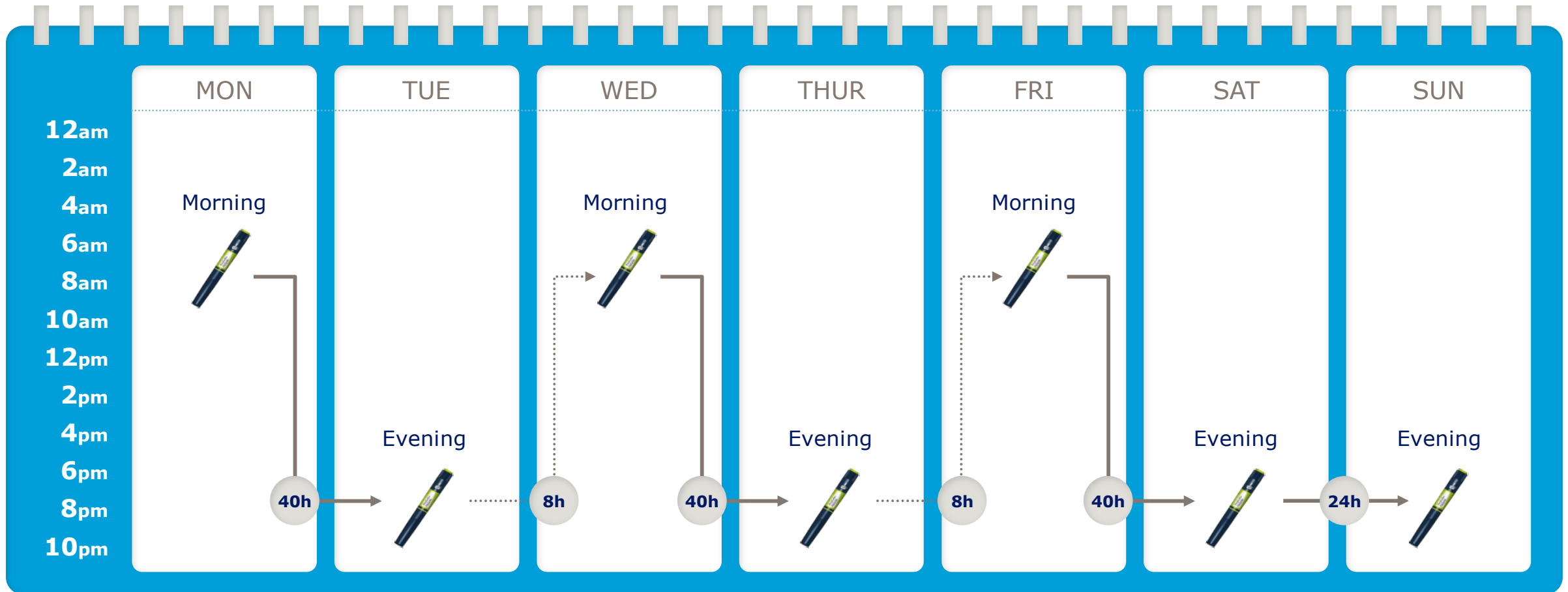
Flexibility

Possible flexible administration

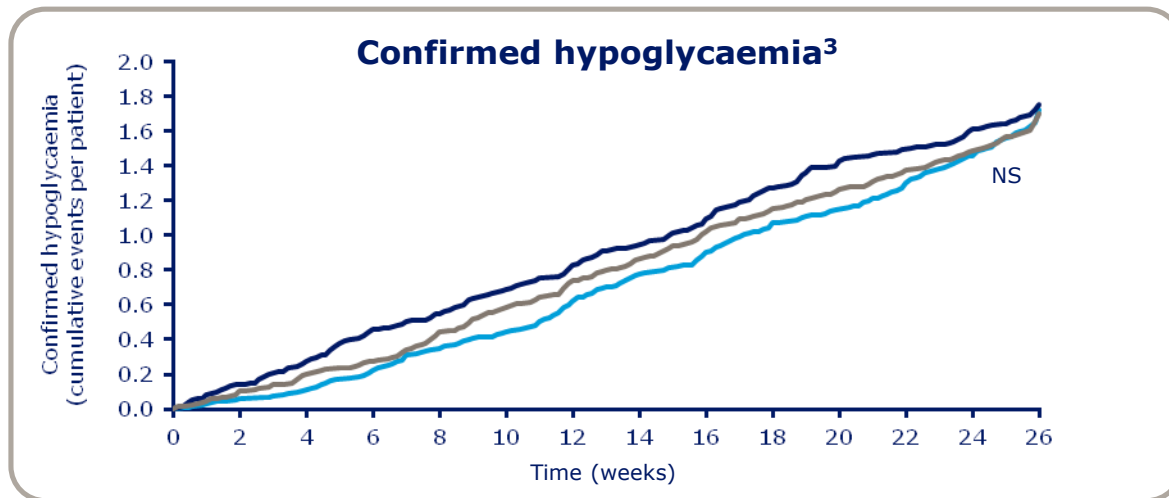
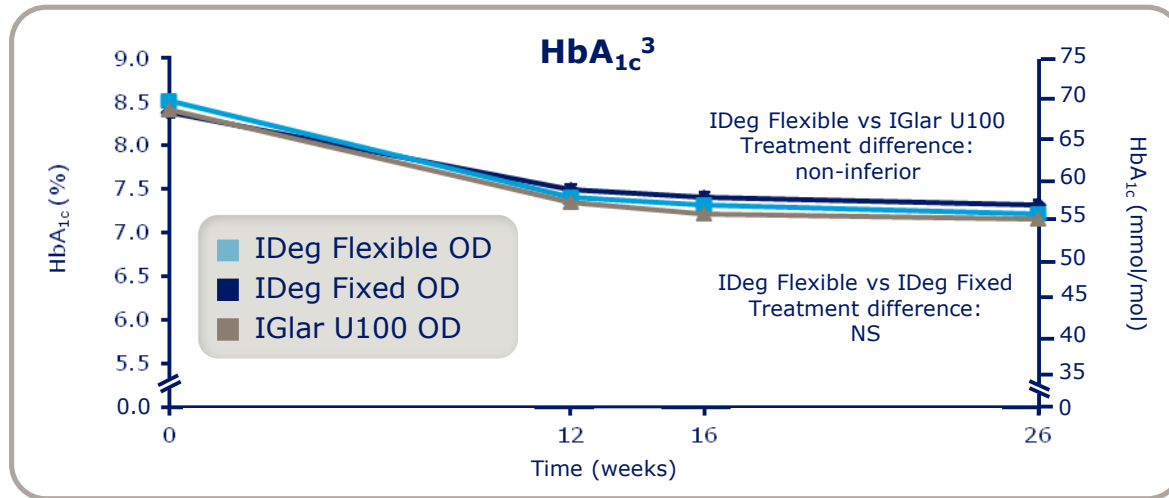


Flexible administration of IDeg was tested in both T1D and T2D

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



Flexibility can benefit patients who find it challenging to inject at the same time each day^{1,2}



Drug Profile

For reprint orders, please contact reprints@expert-reviews.com

EXPERT REVIEWS

Insulin degludec: a novel ultra-long-acting basal insulin for use in Type 1 and 2 diabetes

"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

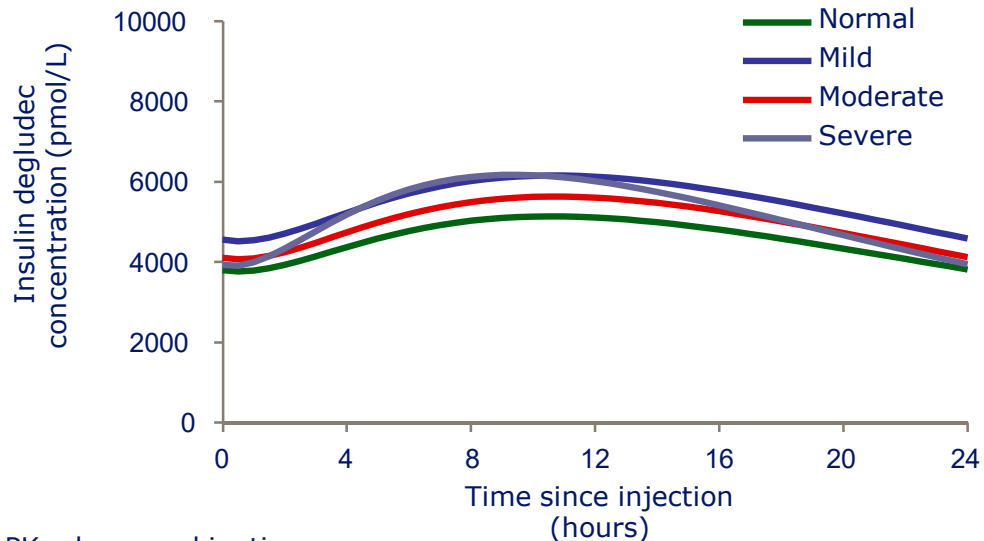
IDeg, insulin degludec; IGlargin U100, insulin glargine U100; NS, not significant; OD, once daily

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

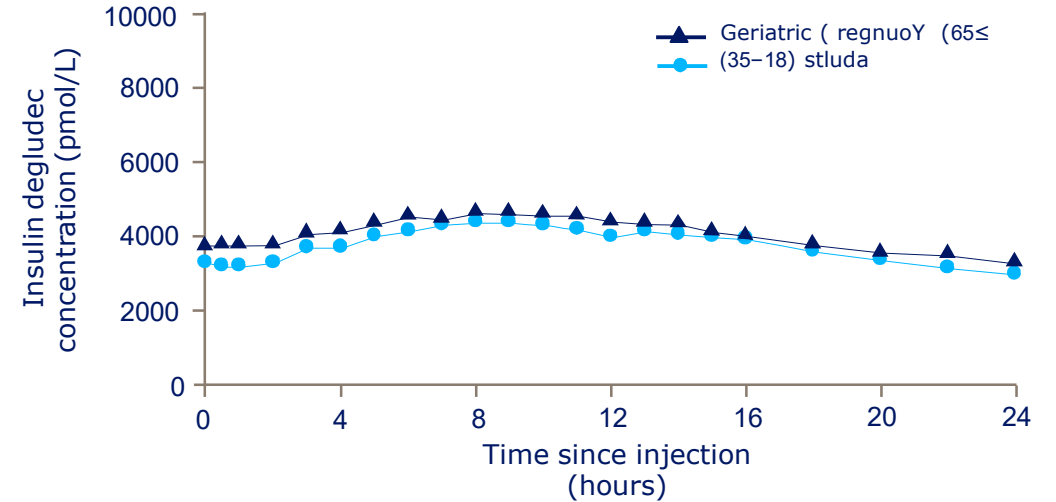
Pharmacokinetics of insulin degludec in special populations

The PK properties of insulin degludec are not affected by increasing age, renal impairment or hepatic impairment

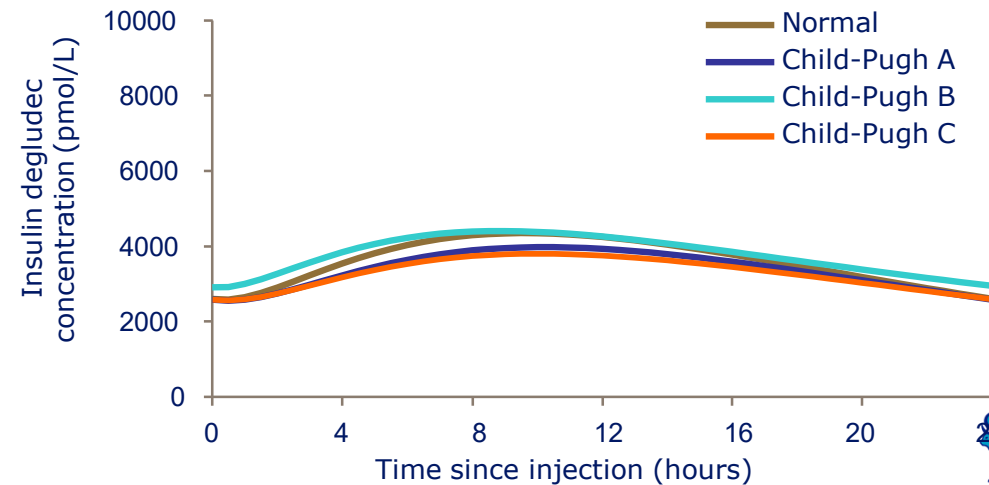
Renal function



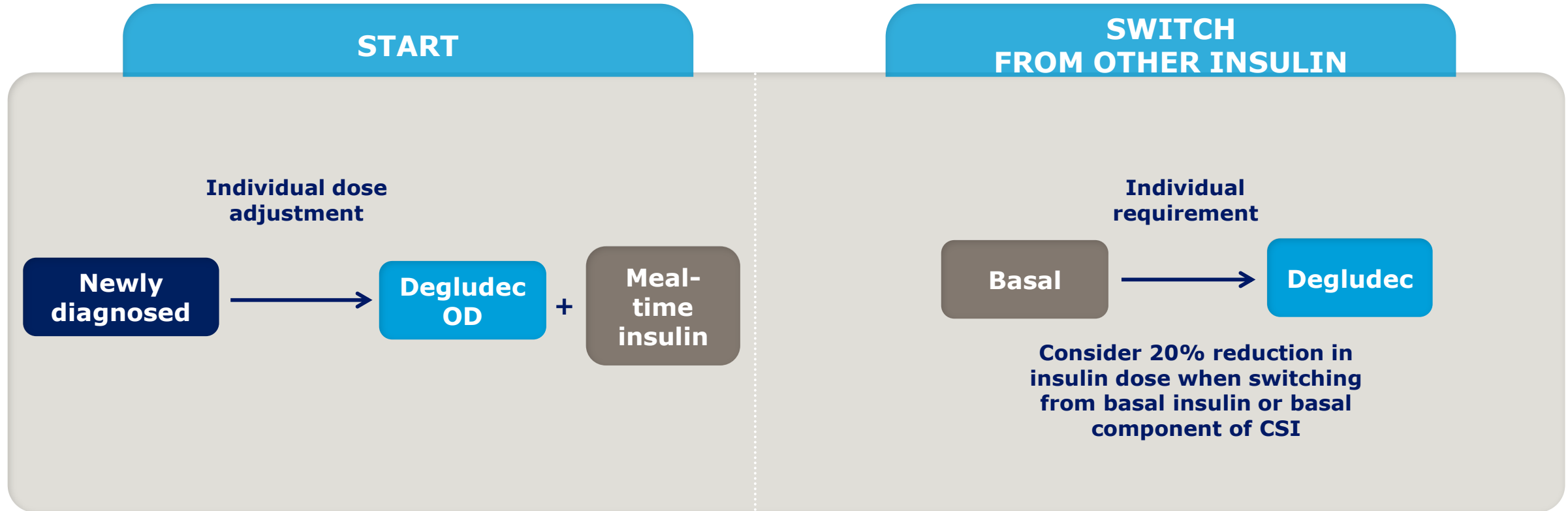
Age



Hepatic function



Initiation of Degludec in T1D



Summary

Degludec



HbA_{1c}

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

