Prof(Surg Capt) Abhay Ahluwalia
MD(AFMC) DNB DM (Endo)(AIIMS)
Columbia Asia Palam Vihar Gurgaon

- *Practicing Endocrinologist for the past 22 years with Distinguished Service of 29 years in Indian Armed Forces*
- *Achieved the following during medical carrier spanning three decades*
- *AWARDS*
- *Gold medal first Position MD (Medicine) AFMC*
- *DP Basu Young Scientist award API 2004*
- *DSL award Endocrine Society India*
- *Vice Chief Of Army medal & GOC –IN –C Medal*
- *Publication 28 in indexed journal*
- *Invited faculty RSSDI ,API , ESI ,BMC , Indonesian Endocrine Society*
- *Examiner MD , DM DNB Endo*
- *Post Graduate Teacher with 23 years teaching experience*
- ***Previous Appointments***
- *HOD Medicine & Endocrinology ACMS & Base Hospital Delhi , HOD Endocrinology AFMC Pune , INHS Asvini Mumbai*

The Promise of Novel Co-formulation & Glycemic Outcome: Clinical use and Practical Guidance

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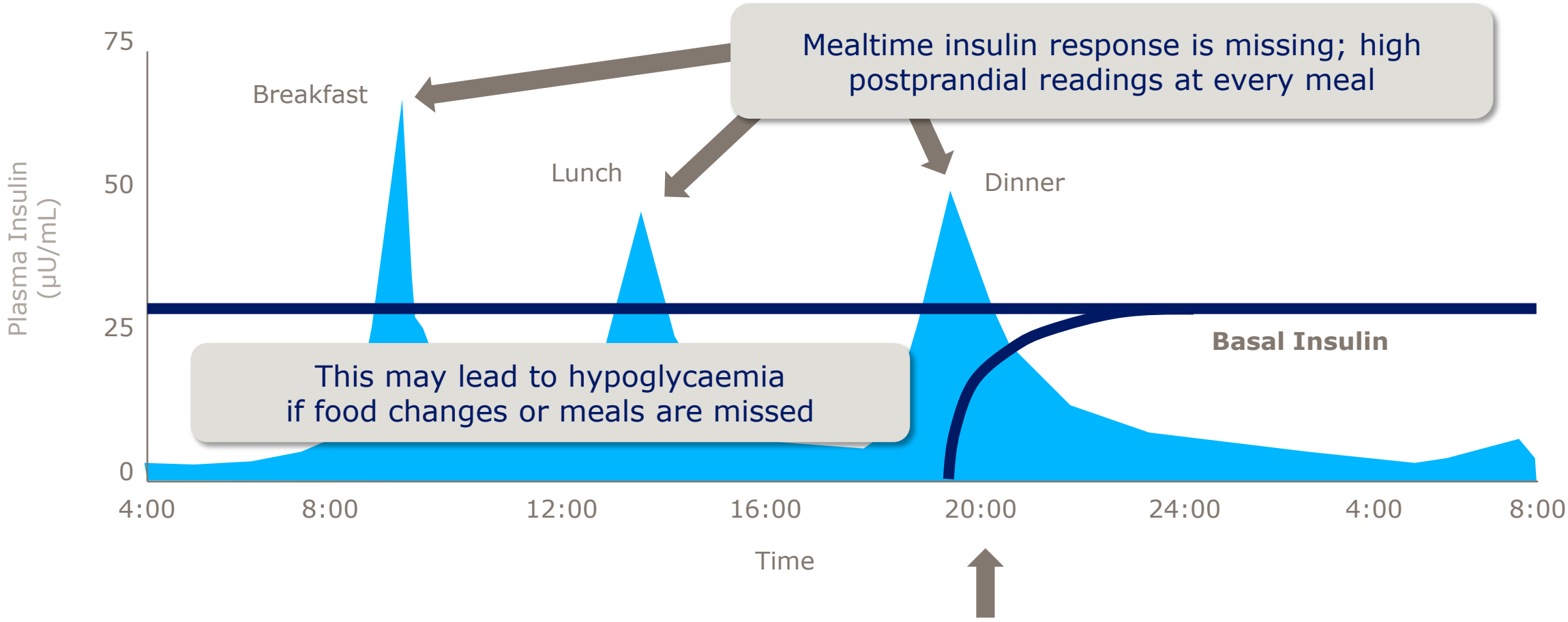
GURGAON INDIA

The addition of mealtime coverage is needed when basal insulin is no longer enough



Garber *et al. DOM* 2009;11(Suppl. 5):14-8

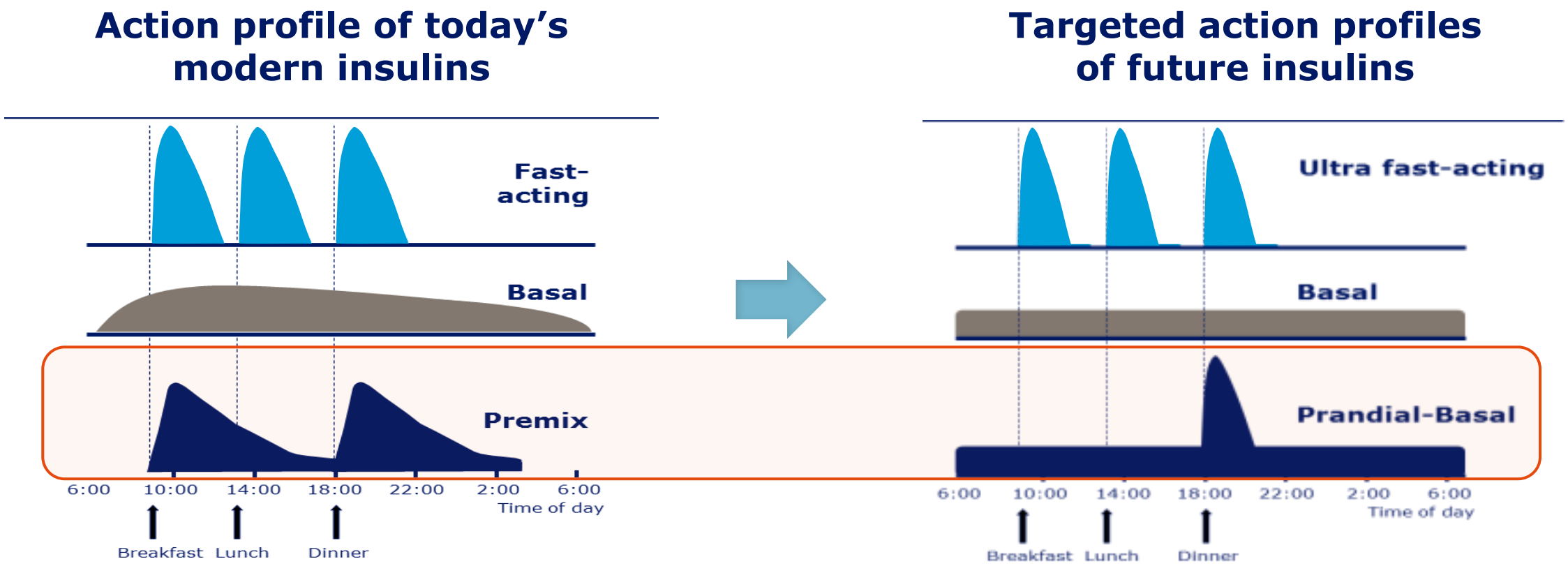
Rationale for combining basal and bolus insulin in a single injection

- Type 2 diabetes is a progressive disease
- The addition of insulin to provide mealtime coverage is needed when basal insulin is no longer enough[1]
- Existing basal and bolus regimens offer basal and precise postprandial glucose control but as separate injections[2,3]
- A combination of basal and bolus insulin could allow for a simple regimen with fewer injections[2]

1. Garber et al. Diabetes Obes Metab 2009;11(suppl 5):14–18; 2. Inzucchi et al. Diabetes Care 2012;35:1364–1379;
3. Nathan et al. Diabetes Care 2009;32:193–203

The insulin co-formulation concept

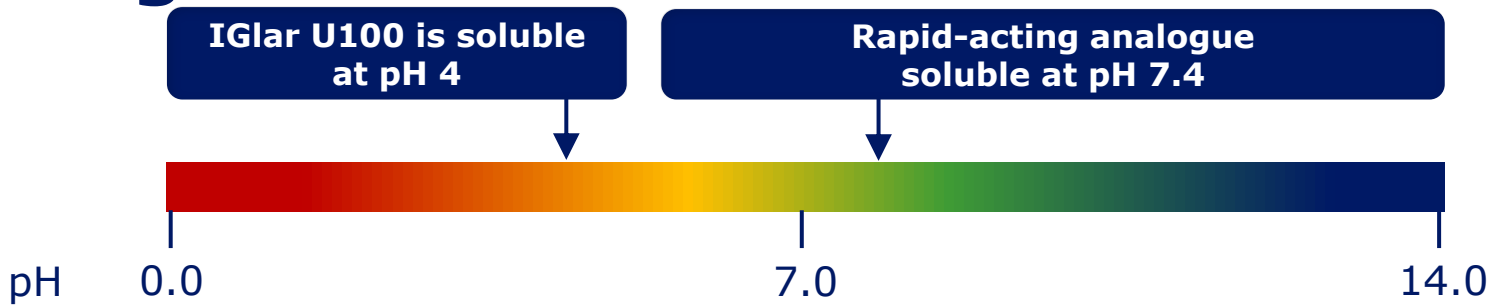
Mimicking physiological responses



For illustrative purposes only

Challenges with co-formulating IDet or IGlar U100 with rapid-acting analogues

IGlar U100



IGlar U100 is soluble at pH 4 and designed to microprecipitate at neutral pH (7.4) in subcutaneous tissue, whereas commercially available rapid-acting analogues are soluble at pH 7.4[1]

IDet

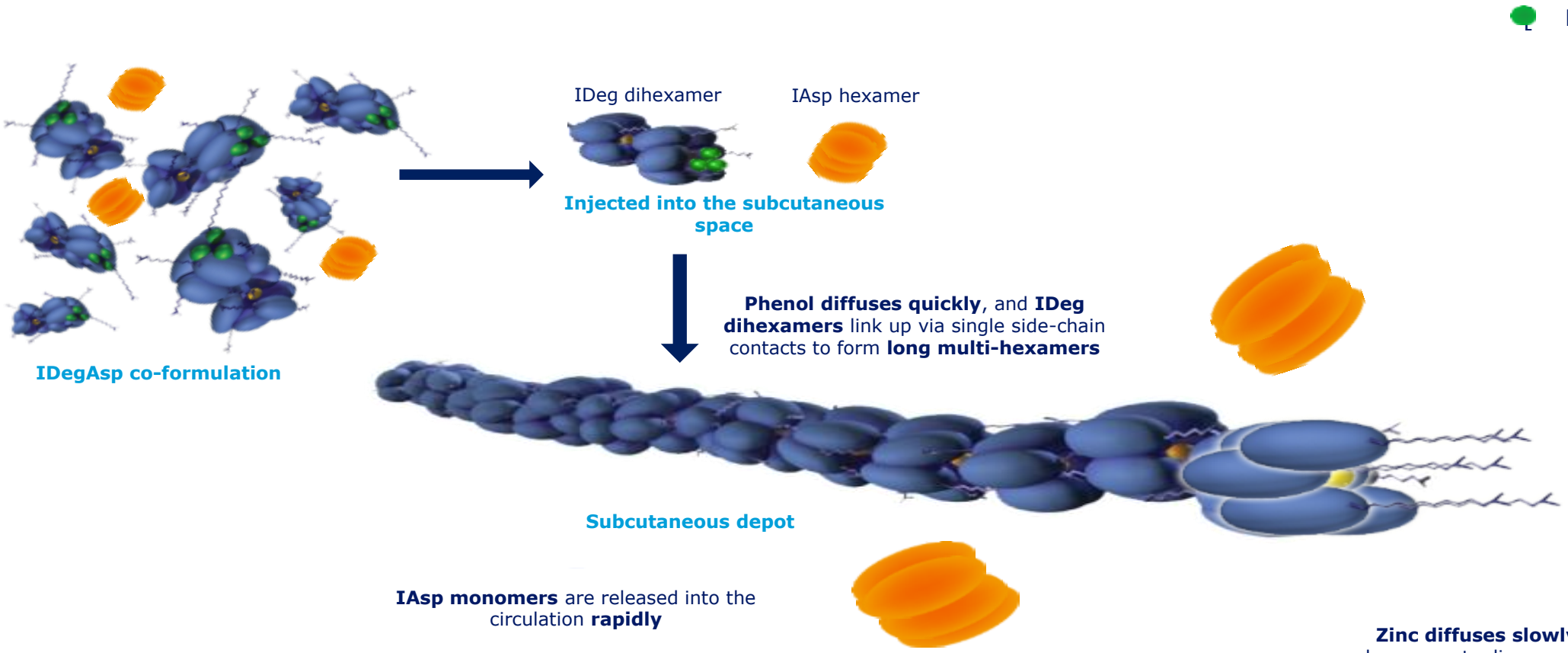
When IDet is co-formulated with commercially available rapid-acting analogues under standard conditions, mixed hexamers form with unsuitable PK/PD profiles[2]

IAsp, insulin aspart; IDet, insulin detemir; IGlar U100, insulin glargine U100; PD, pharmacodynamic; PK, pharmacokinetic

1. Lantus® US Prescribing Information. Sanofi April 2010; 2. Jonassen *et al. Pharm Res* 2012;29:2104–14

IDegAsp

Mode of protraction at steady state



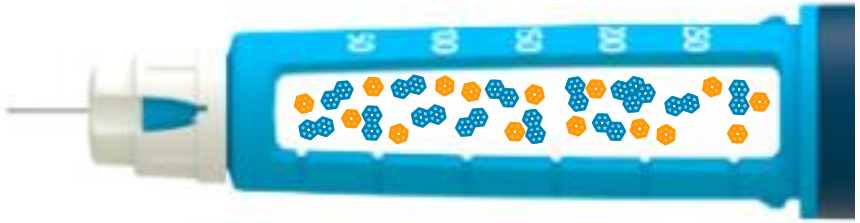
IAsp, insulin aspart; IDeg, insulin degludec; IDegAsp, insulin degludec/insulin aspart; Zn, zinc

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

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

In the formulation

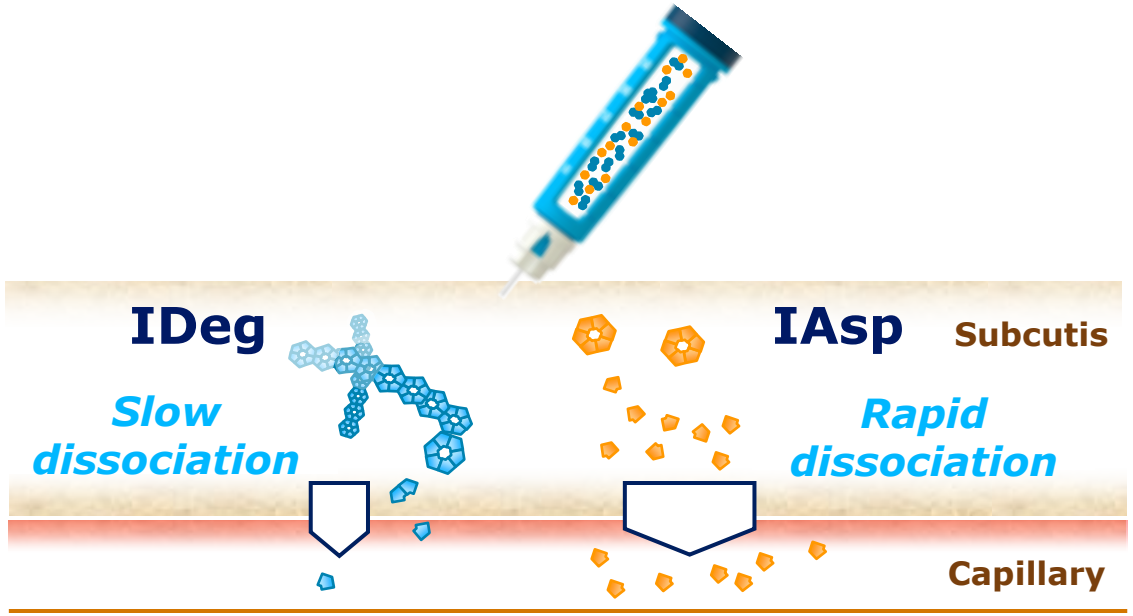
IDegAsp = IDeg (70%) + IAsp (30%)
existing separately in one formulation



IDeg dihexamers

IAsp hexamers

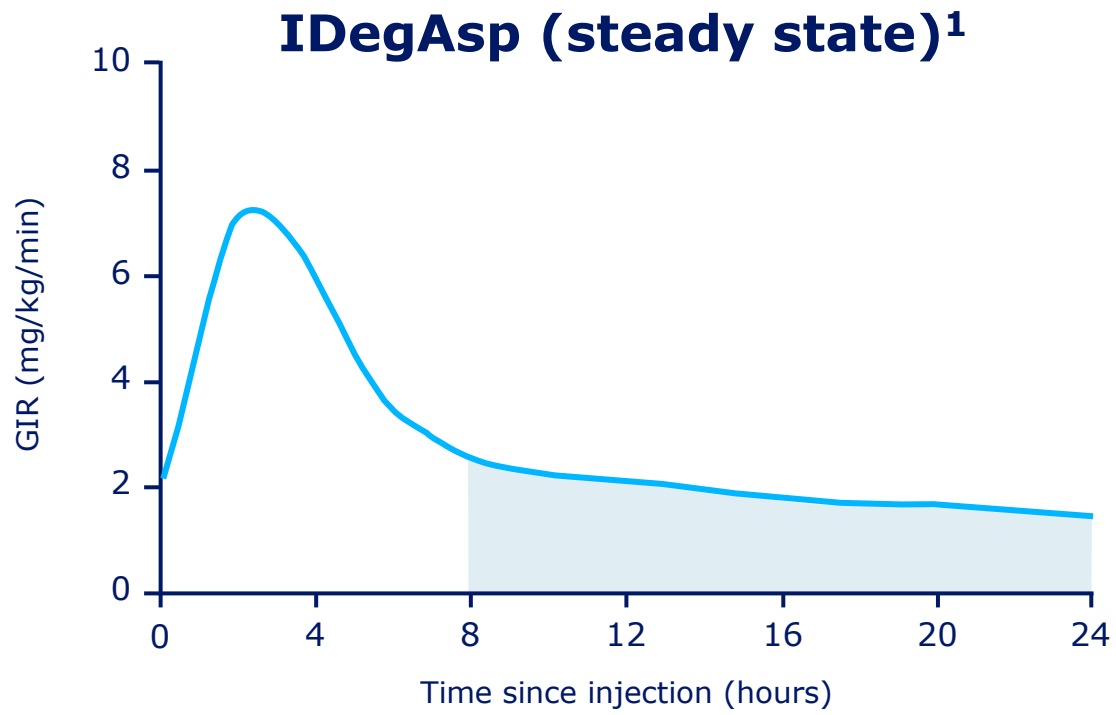
In the subcutaneous depot

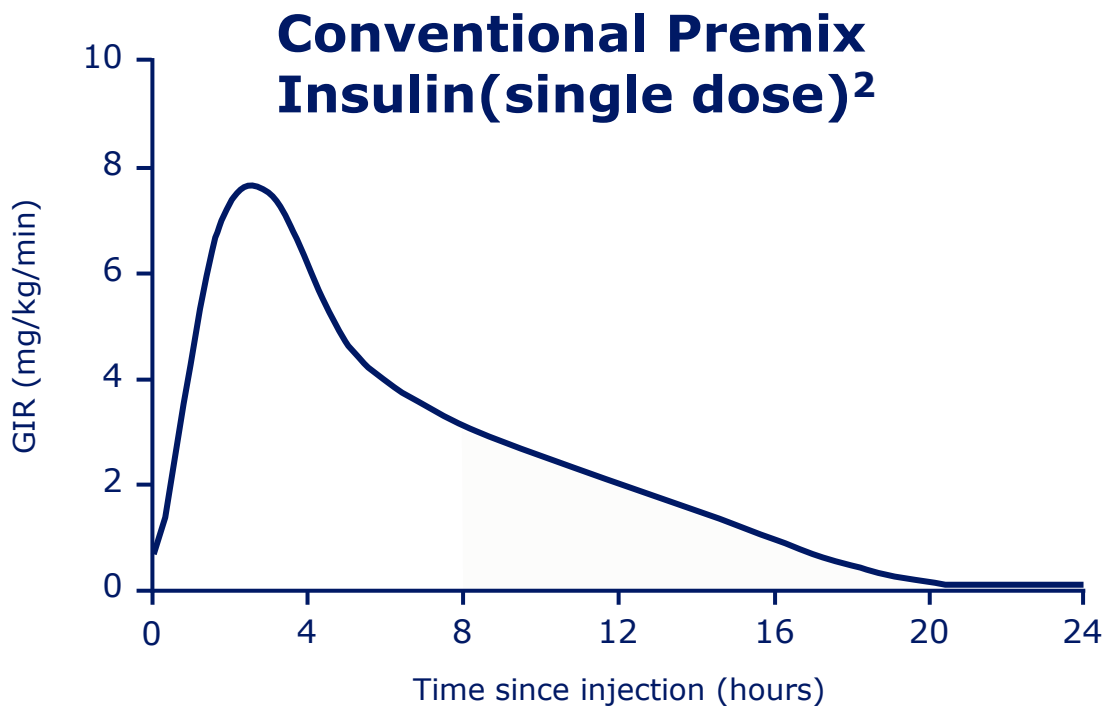


IAsp, insulin aspart; IDeg, insulin degludec; IDegAsp, insulin degludec/insulin aspart
Havelund *et al. Pharm Res* 2015;32:2250–8

IDegAsp shows distinct prandial and basal glucose-lowering effects compared with Conventional Premix Insulin

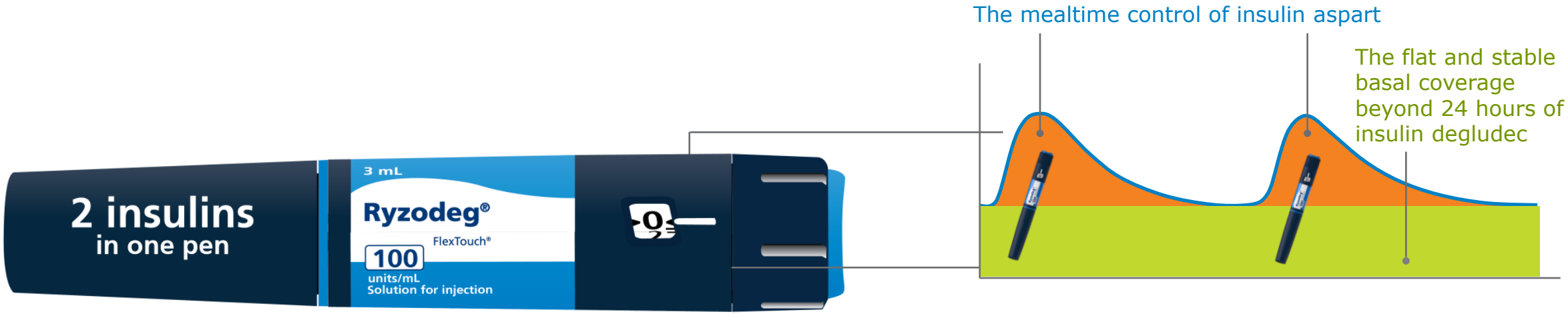
Mean GIRs for IDegAsp and BIAsp 30 in patients with T1D





IDegAsp: n=22; BIAsp 30: n=24; 0.6 U/kg
BIAsp 30, biphasic insulin aspart 30; GIR, glucose infusion rate; IDegAsp, insulin degludec/insulin aspart; T1D, type 1 diabetes
1. Heise *et al. Diabetes Ther* 2014;5:255–65; 2. Heise *et al. Diabetes* 2013;62(Suppl. 1):A241:947-P

2 insulins in 1 pen provides basal & meal-time coverage1



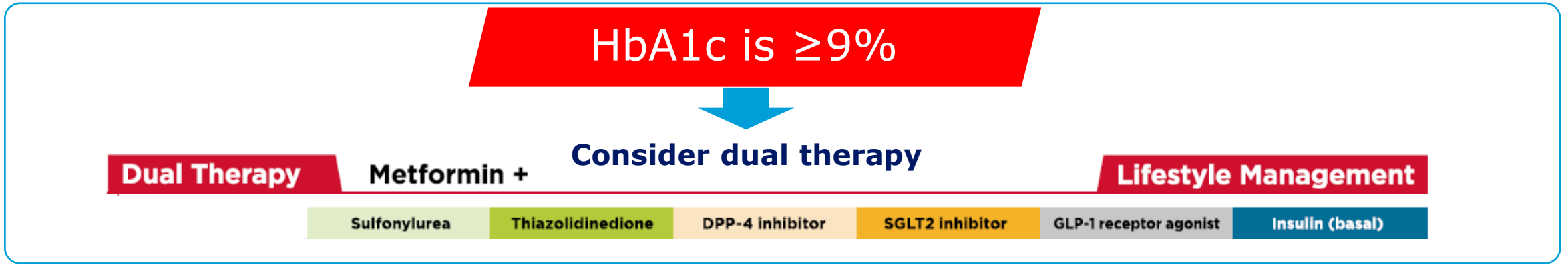
Ref.: 1. *Heise T, Nosek L, Roepstorff C, et al. Distinct prandial and basal glucose-lowering effects of insulin degludec/insulin aspart (IDegAsp) at steady state in subjects with type 1 diabetes mellitus. Diabetes Ther. 2014;5(1):255–265.*

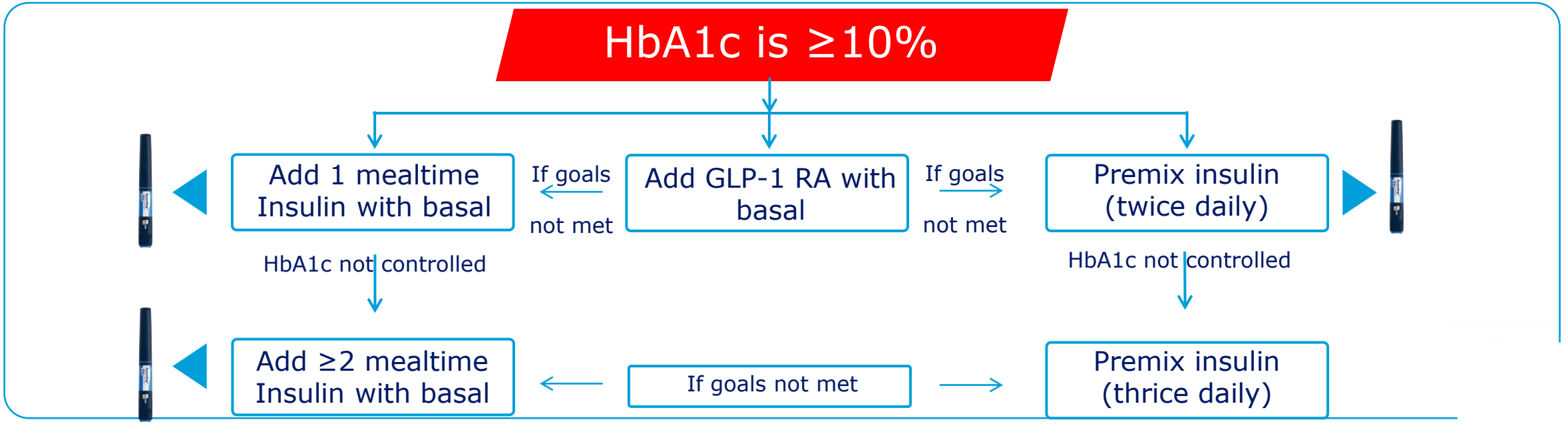
Summary of guidelines on insulin initiation and intensification

Origin	HbA_{1c} Targets	FPG Targets	PPG Targets	Insulin Initiation	Insulin Intensification
ADA/ EASD[1]	<7.0%	<7.2 mmol/L (<130 mg/dL)	<10 mmol/L (<180 mg/dL)	IA or LA basal	Basal,-bolus, Sequential addition of rapid acting analogue or premix
IDF[2]	< 7.0% (<53 mmol/mol)	<6.5 mmol/L (<115 mg/dL)	<9.0 mmol/L (<160 mg/dL)	LA basal or NPH or BID pre-mix	Multiple daily injections (meal time and basal)
AACE/ ACE[3]	<6.5%	<110 mg/dL	<140mg/dL	Basal, premix or basal-bolus. Add Insulin to OADs A1c≥8.5- to 9%	No clear guidance on intensification. T2DMs
NICE[4]	<6.5%	n/a	n/a	IA/NPH or premix OD or BID	From basal to BID premix or basal-bolus; or from BID premix to basal-bolus
CDA[5]	≤7.0%	4.0–7.0 mmol/L	5.0–10.0 mmol/L	IA or LA basal	To basal bolus

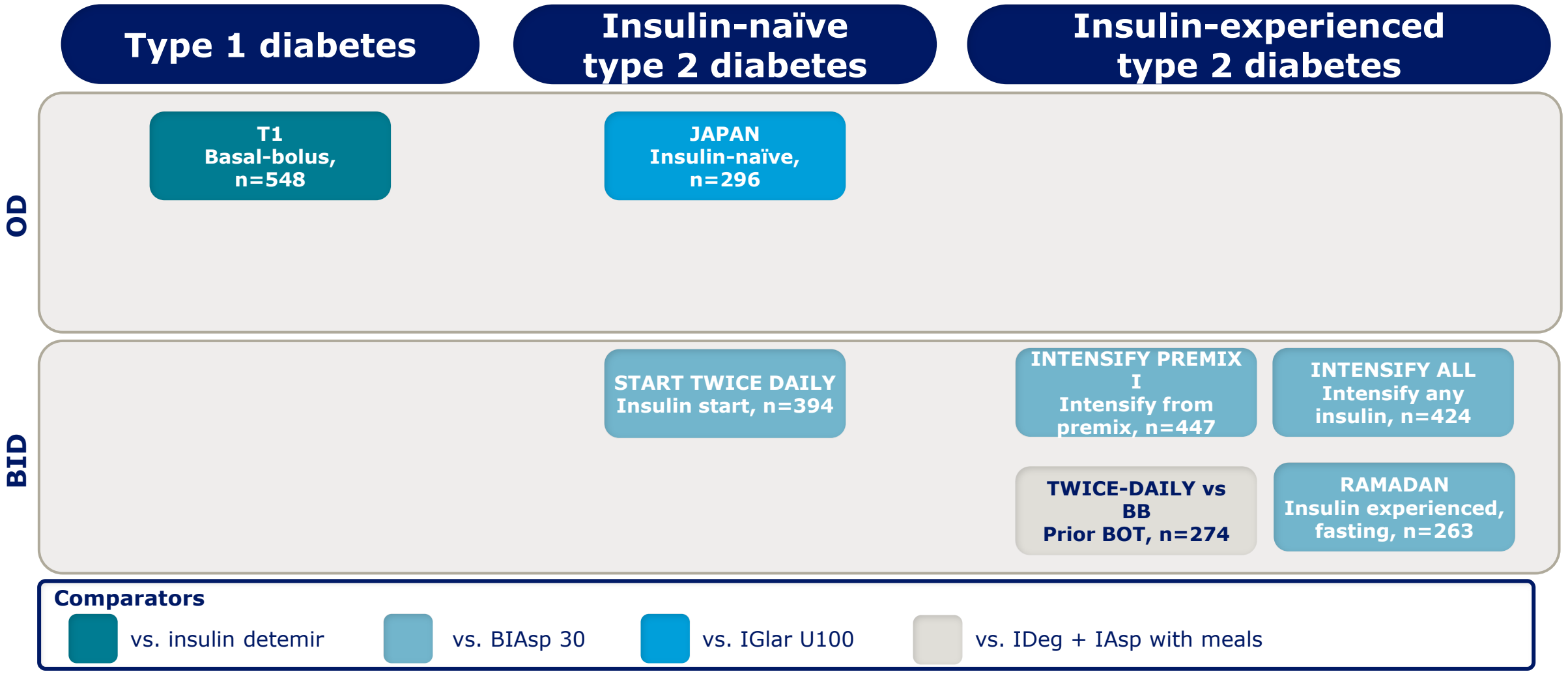
Vaag, A., *Eur Journal of Endocrinology* 2012;166: 159-170

IDegAsp is the smartest way of intensification which aligns with ADA 2017 guideline





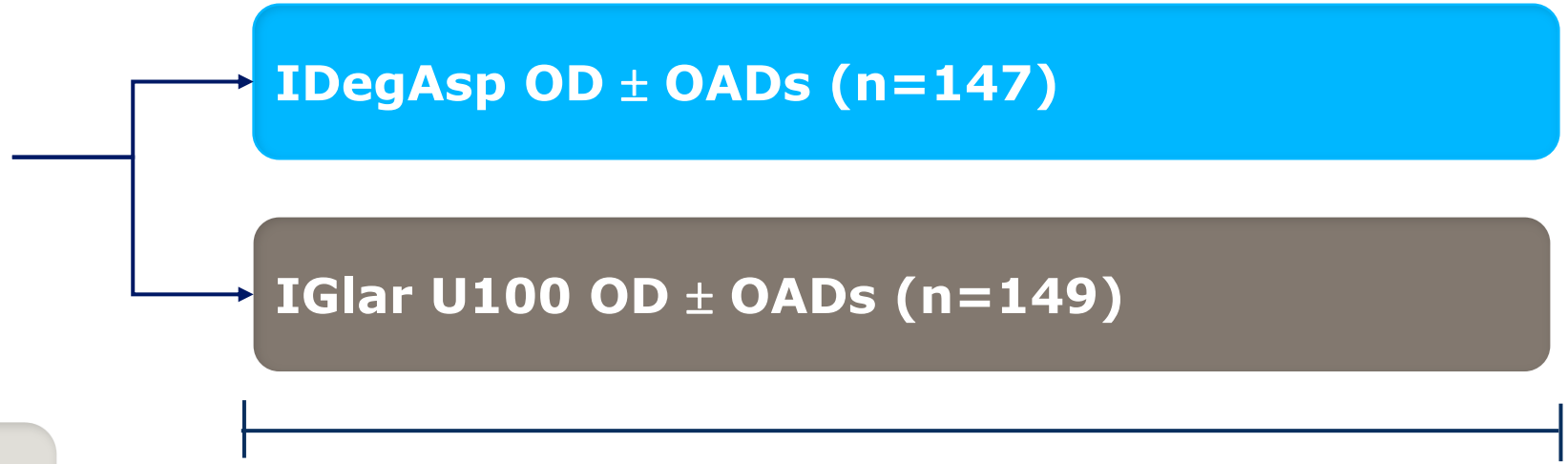
IDegAsp phase 3 clinical trial programme overview



BB, basal–bolus; BIAsp 30, biphasic insulin aspart 30; BID, twice daily; IAsp, insulin aspart; IDegAsp, insulin degludec/insulin aspart; IDeg, insulin degludec; IGlar U100, insulin glargine U100; OD, once daily

Insulin-naïve T2D OD: study design

BOOST JAPAN



Inclusion criteria

- Type 2 diabetes ≥6 months
- Previously treated with ≥1 OAD for at least 12 weeks with at least recommended maintenance dose per local labelling
- HbA_{1c} 7.0–10.0%
- BMI ≤35 kg/m^2
- Age ≥20 years

Open-label

Prior to randomisation, SUs, DPP-4 inhibitors and glinides were discontinued

Starting dose was 10 U for both treatment arms

IDegAsp was administered with the largest meal of the day; the dosing time was chosen at the discretion of the patient

IGlar U100 was administered according to label (either before breakfast or at bedtime at the discretion of the patient

The timing of the dosing was not to be changed during the trial

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

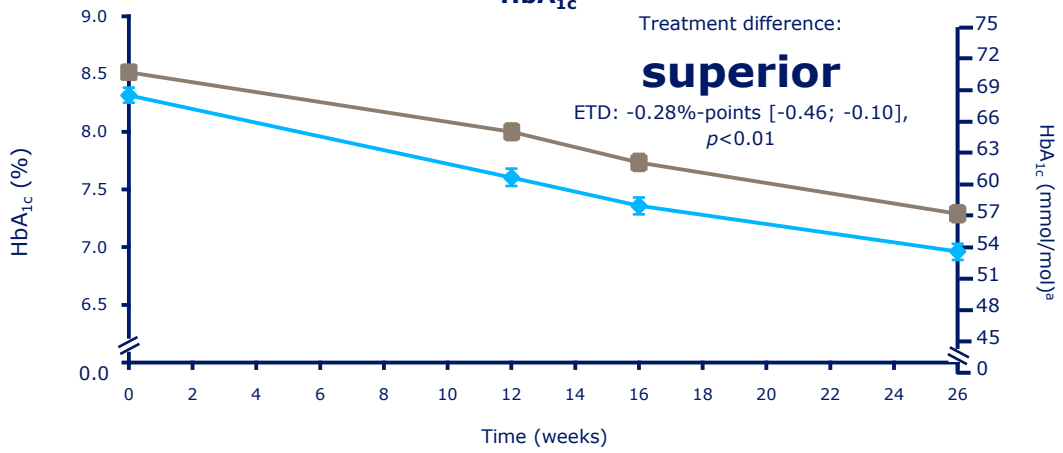
Onishi *et al. Diabetes Obes Metab* 2013;15:826–32

Insulin-naïve T2D OD: results

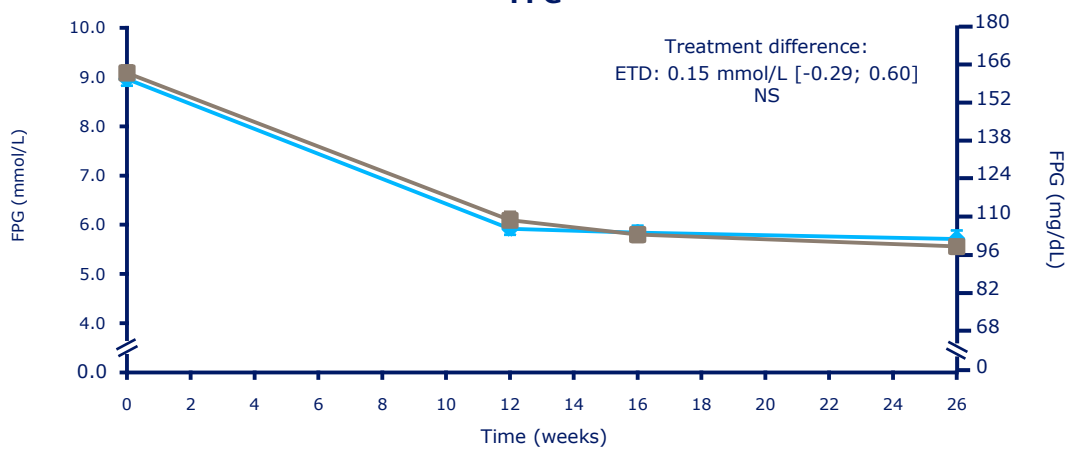
BOOST JAPAN

IDegAsp OD IGlar U100

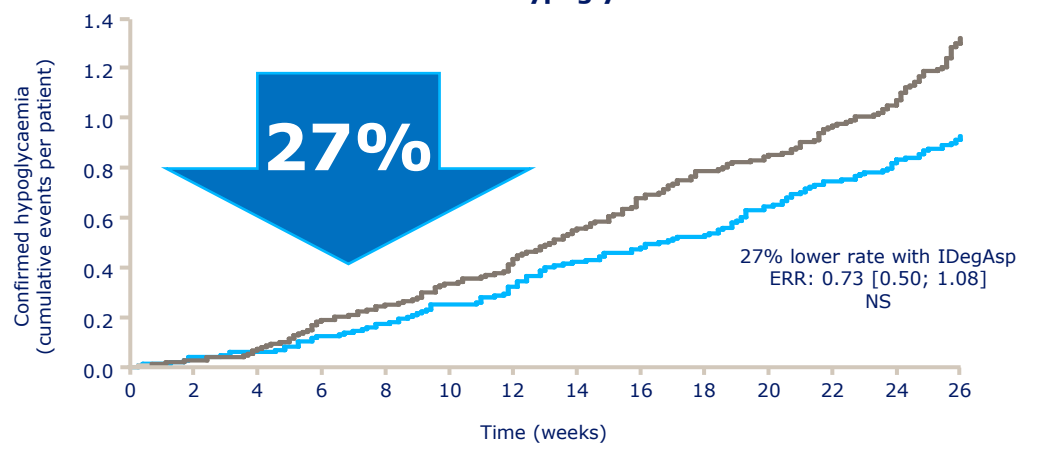
HbA_{1c}



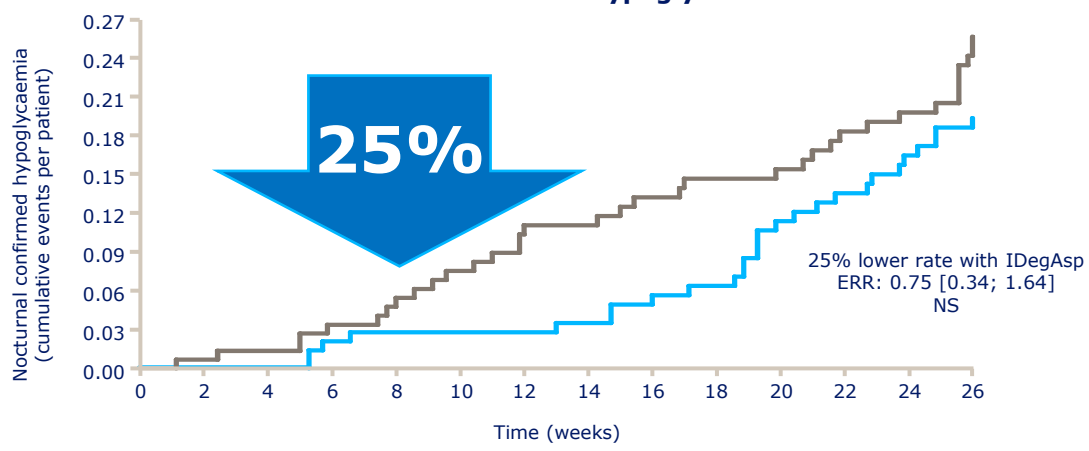
FPG



Confirmed hypoglycaemia



Nocturnal confirmed hypoglycaemia



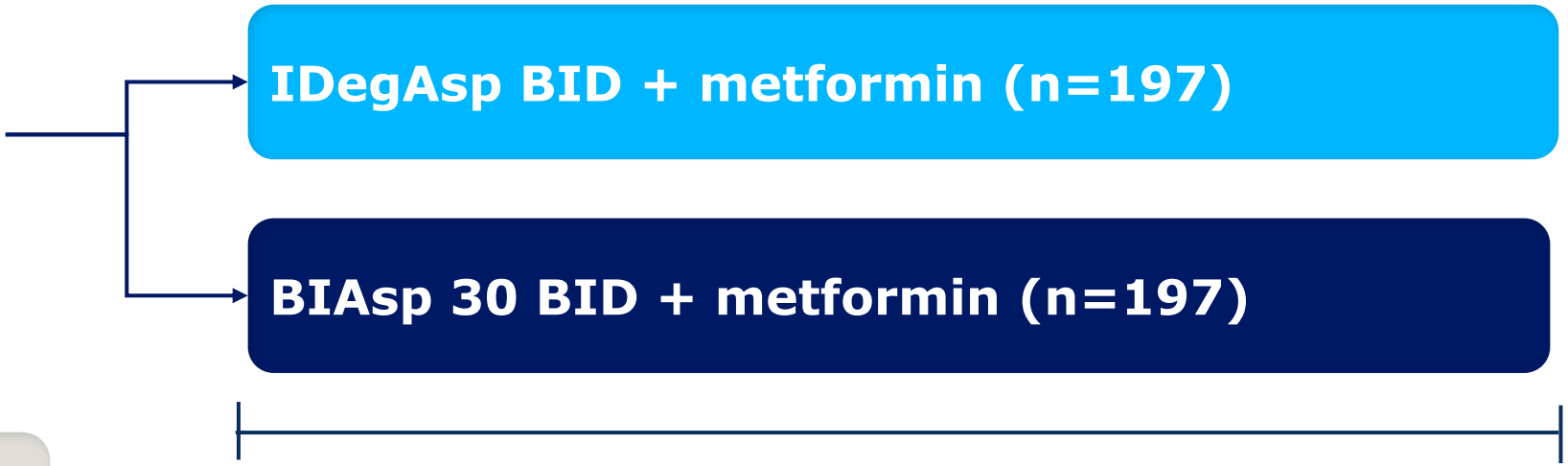
[a]Calculated, not measured. ERR, estimated rate ratio; ETD, estimated treatment difference; FPG, fasting plasma glucose; IDegAsp, insulin degludec/insulin aspart; IGlar U100, insulin glargine U100; NS, not significant; OD, once daily; T2D, type 2 diabetes

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

Insulin-naïve T2D BID
BOOST START TWICE DAILY

Insulin-naïve T2D BID: study design

BOOST START TWICE DAILY



Inclusion criteria

- Type 2 diabetes ≥6 months
- Insulin naïve treated with metformin (≥1,000 mg daily) ± 1 OAD for ≥3 months
- HbA_{1c} 7.0–10.0%
- BMI ≤40 kg/m^2
- Age ≥18 years

Randomised 1:1 (IDegAsp BID : BIAsp 30 BID)
Open-label

IDegAsp or BIAsp 30 administered with breakfast and the main evening meal

BIAsp 30, biphasic insulin aspart 30; BID, twice daily; BMI, body mass index; IDegAsp, insulin degludec/insulin aspart; OAD, oral antidiabetic drug; T2D, type 2 diabetes

Franek *et al. Diabetic Med* 2016;33:497-505

Conclusions

BOOST Japan and BOOST START TWICE DAILY

- IDegAsp can be initiated in OD or BID regimens
- Reduction in FPG was similar for IDegAsp and IGlar
- Rates of overall and nocturnal confirmed hypoglycaemia were lower with IDegAsp
- IDegAsp was well tolerated

BIAsp, biphasic insulin aspart; BID, twice daily; FPG, fasting plasma glucose; IDegAsp, insulin degludec/insulin aspart; IGlar, insulin glargine; OD, once daily

1.Onishi *et al. Diabetes Obes Metab* 2013;15:826–32; 2. Franek *et al. Diabetic Med* 2016;33:497–505

novo nordisk®

Initiation with IDegAsp

Superior efficacy

Significantly greater HbA1c reduction v/s glargine

Improved safety

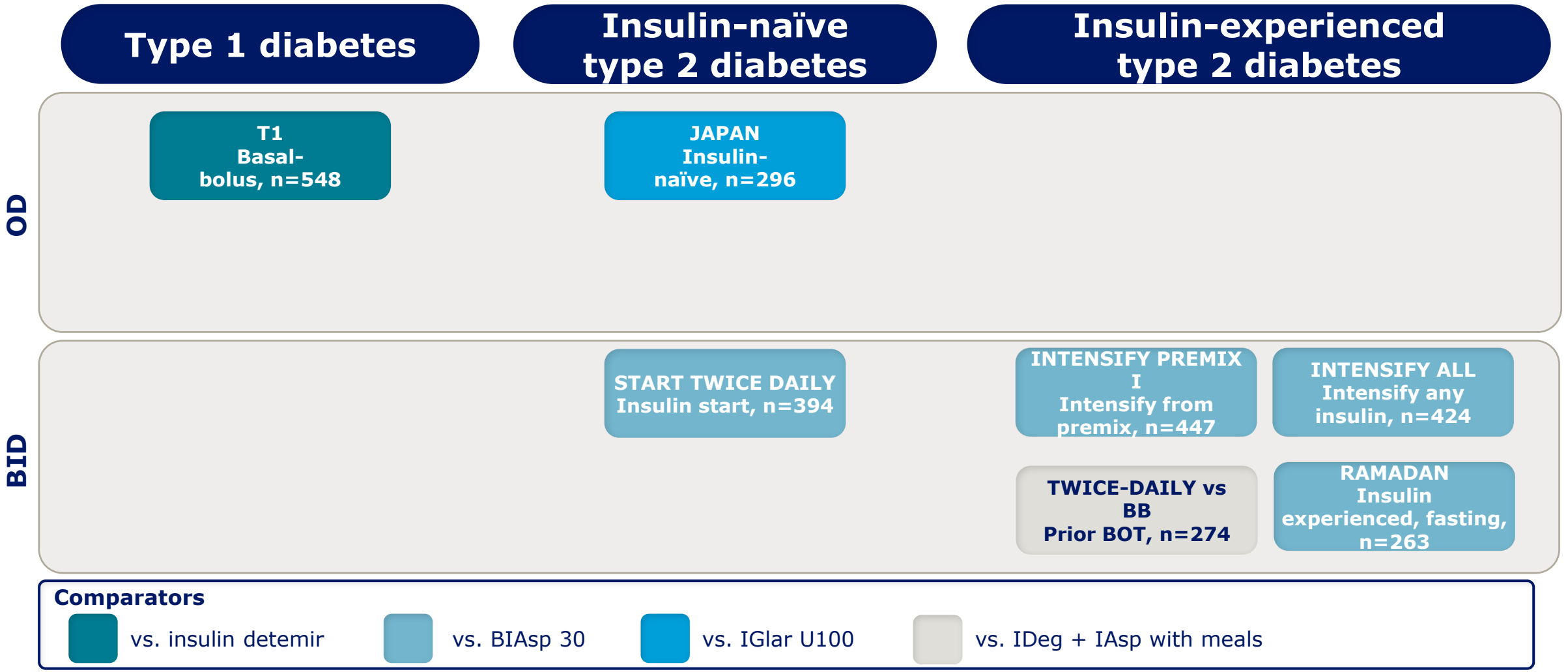
Lower rates# of hypoglycemia v/s glargine

Simplicity

Offers FPG as well as PPG control with a single pen

IDegAsp is delivered once daily with main meal #Numerically lower

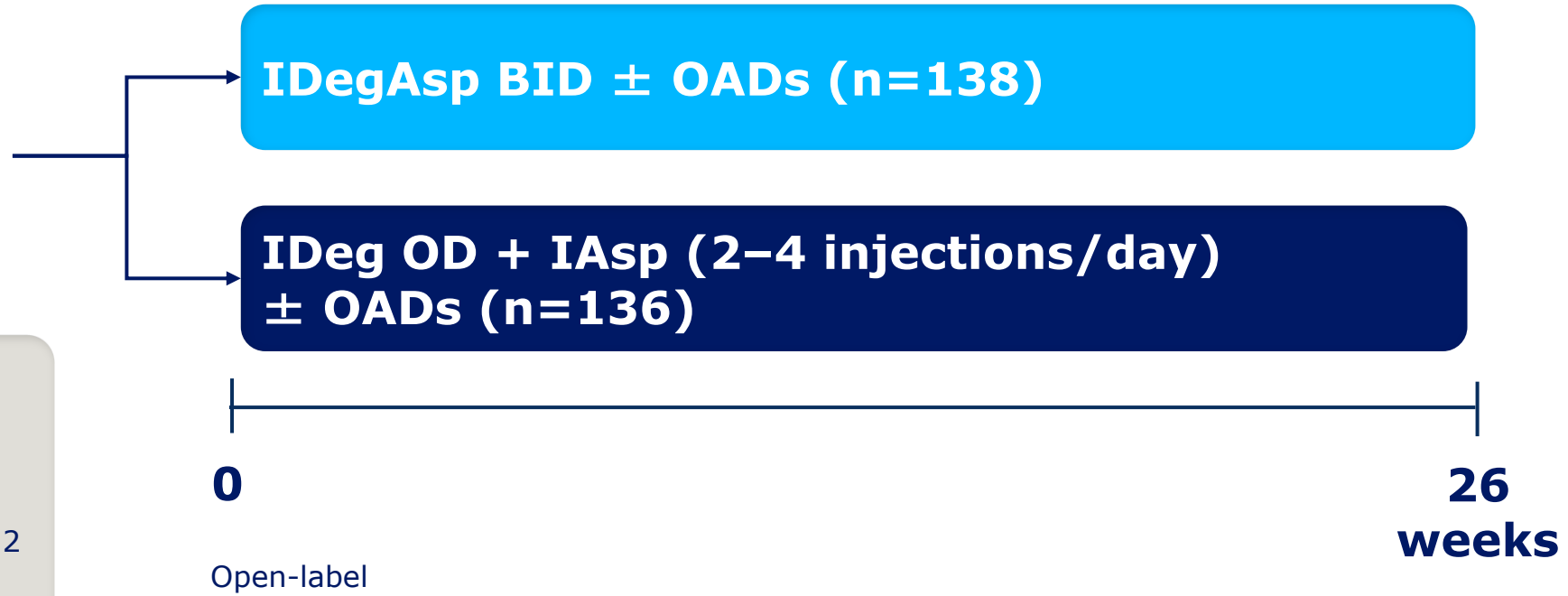
IDegAsp phase 3 clinical trial programme overview



BB, basal–bolus; BIAsp 30, biphasic insulin aspart 30; BID, twice daily; BOT, basal-oral therapy; IAsp, insulin aspart; IDegAsp, insulin degludec/insulin aspart; IDeg, insulin degludec; IGlar U100, insulin glargine U100; OD, once daily

Insulin-experienced T2D BID: study design

BOOST TWICE-DAILY vs BASAL-BOLUS



Inclusion criteria

- Type 2 diabetes ≥26 weeks
- Currently treated with basal insulin (IDet, IGlar U100, NPH) ± OADs for ≥12 weeks
- HbA_{1c} 7.0–10.0%
- BMI ≤40 kg/m^2
- Age ≥18 years

Pre-trial OADs included metformin, DPP-4 inhibitor, sulphonylurea/glinides or α-glucosidase inhibitor. Basal insulin and sulphonylurea/glinides (if administered) were discontinued at randomisation. 64% of patients had been previously treated with IGlar U100

BID, twice daily; BMI, body mass index; IAsp, insulin aspart; IDeg, insulin degludec; IDegAsp, insulin degludec/insulin aspart; IDet, insulin detemir; IGlar U100, insulin glargine U100; NPH, neutral protamine Hagedorn; OAD, oral antidiabetic drug; OD, once daily; T2D, type 2 diabetes

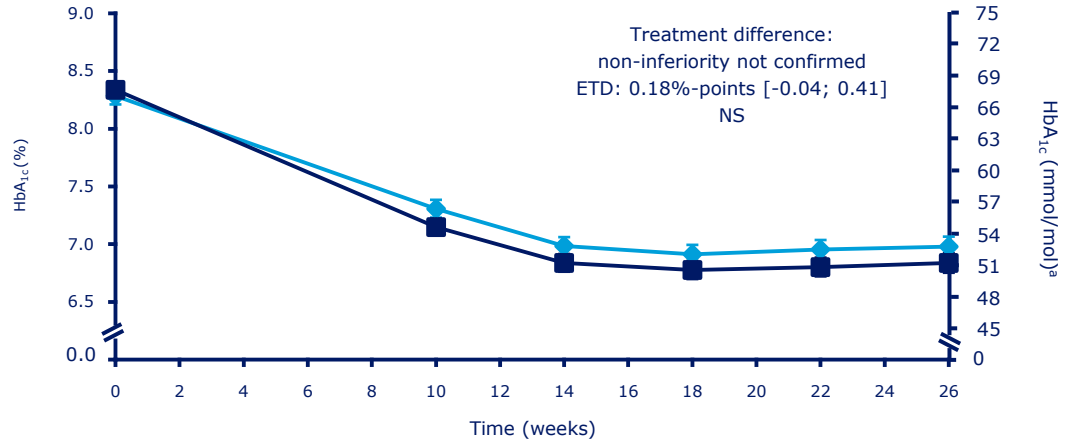
Rodbard *et al. Diab Obes Metab* 2016;18:274-80

Insulin-experienced T2D BID: results

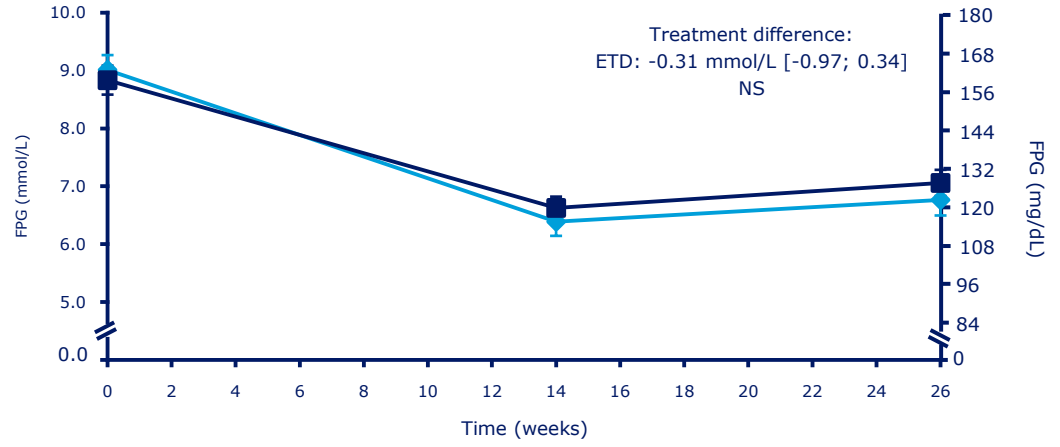
BOOST TWICE-DAILY vs BASAL-BOLUS

IDegAsp BID (n=138)
IDeg OD + IAsp (n=136)

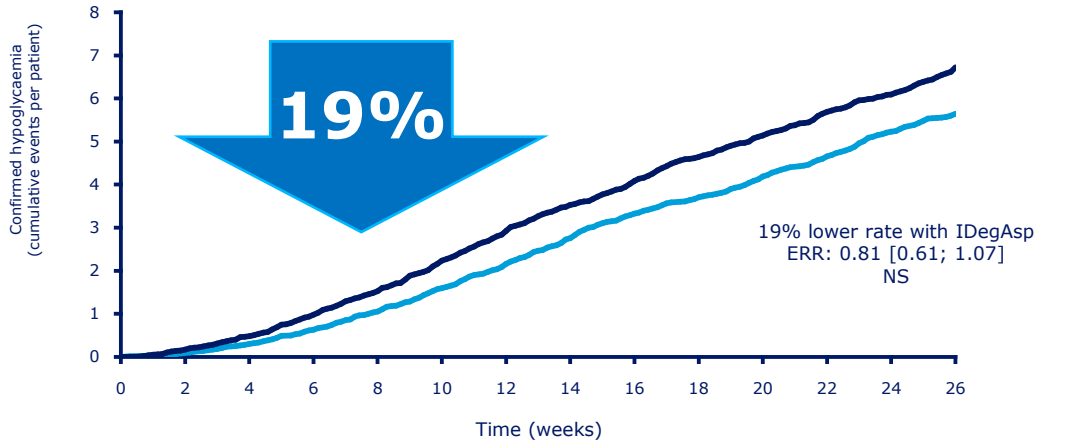
HbA_{1c}



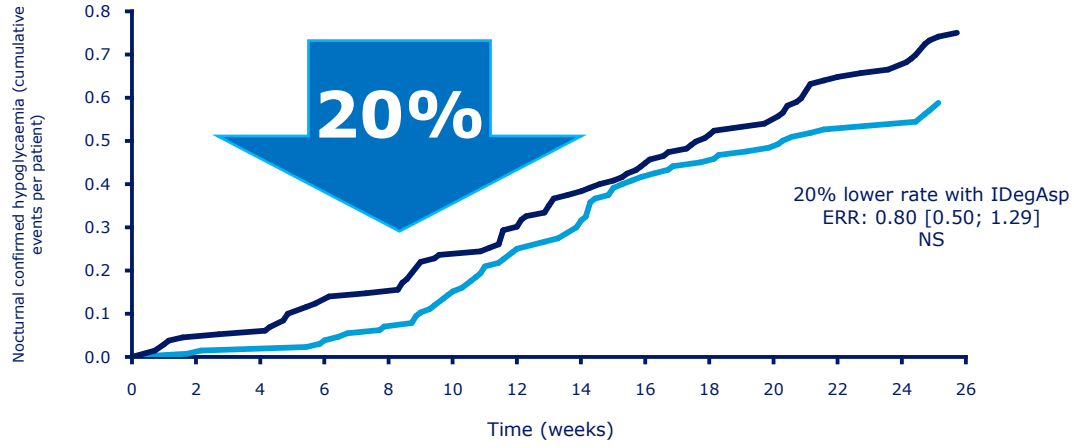
FPG



Confirmed hypoglycaemia



Nocturnal confirmed hypoglycaemia

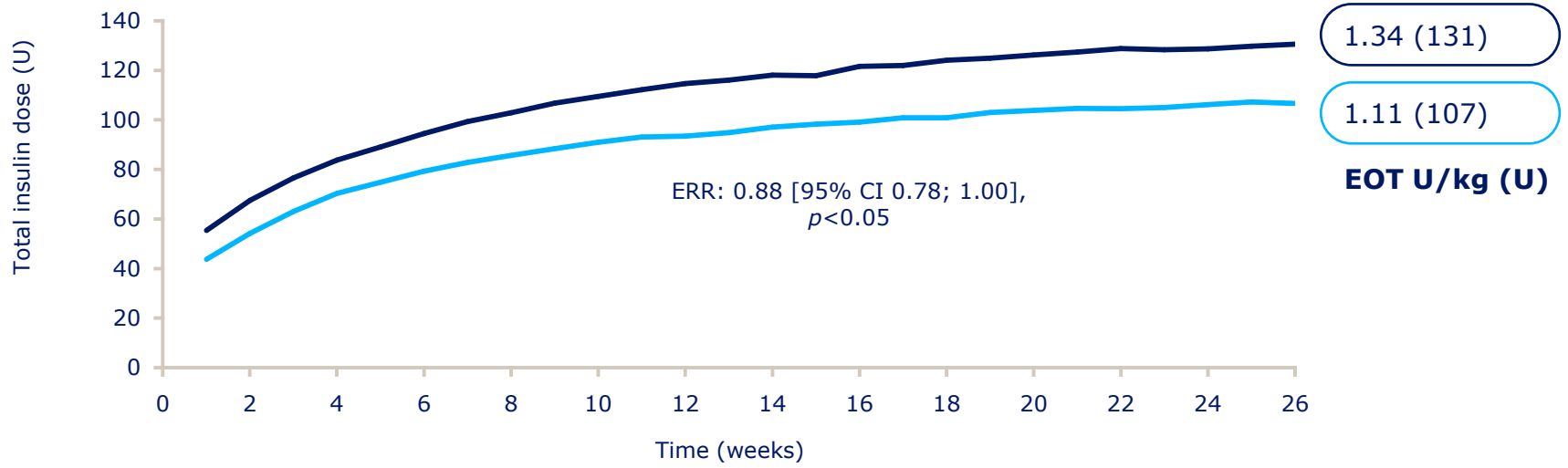


[a]Calculated, not measured. BID, twice daily; ETD, estimated treatment difference; ERR, estimated rate ratio; FPG, fasting plasma glucose; IAsp, insulin aspart; IDeg, insulin degludec; IDegAsp, insulin degludec/insulin aspart; NS, not significant; OD, once daily; T2D, type 2 diabetes

Rodbard *et al. Diab Obes Metab* 2016;18:274-80

Insulin-experienced T2D BID: insulin dose

BOOST TWICE-DAILY vs BASAL-BOLUS



IDegAsp BID vs IDeg OD + IAsp	Mean ratio (U/kg)
Basal insulin dose	**1.05**
Bolus insulin dose	**0.55**
Total insulin dose	**0.83**

SAS, safety analysis set; LOCF, last observation carried forward. Comparisons: Estimates adjusted for multiple covariates
BID, twice daily; ERR, estimated rate ratio; IAsp, insulin aspart; IDeg, insulin degludec; IDegAsp, insulin degludec/insulin aspart; OD, once daily; T2D, type 2 diabetes
Rodbard *et al. Diab Obes Metab* 2016;18:274-80; Cooper *et al. Diabetologia* 2014;57(Suppl. 1):S69

Conclusion

BOOST TWICE-DAILY vs BASAL-BOLUS[3]

- Both intensification strategies effectively improved glycaemic control
- IDegAsp required less dose with less injection prick

Intensification with IDegAsp

Superior efficacy

Significantly greater reductions in FPG and PPG*

Improved safety

Lower rates# of hypoglycemia v/s basal and bolus

Simplicity

Fewer injections than basal and bolus therapy

IDegAsp is delivered twice daily with main meals *Post-breakfast value #Numerically lower

IDegAsp is delivered in the FlexTouch® pen

Maximum dose/injection:
80 U

Injection sites:
Rotate frequently within the chosen area

Storage:
Opened pens – 2–8°C or room temperature for 4 weeks
Unopened pens – 2–8°C until expiry date

Needle:
Do not re-use needles

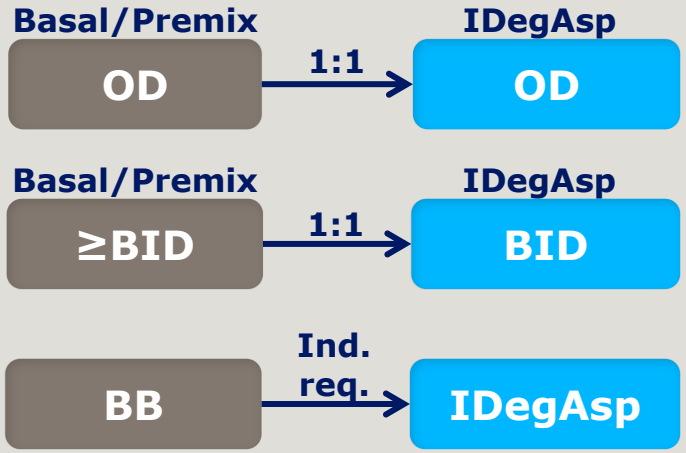
IDegAsp, insulin degludec/insulin aspart
Ryzodeg® August 2016 (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002499/WC500139011.pdf)

Dosing of IDegAsp in T2D

INITIATION

- Administer OD or BID with the main meal(s)
- Administer:
  - alone or
  - in combination with OADs or bolus insulin
- Recommended (total) daily starting dose 10 U
- Requires subsequent individual dosage adjustments

SWITCHING

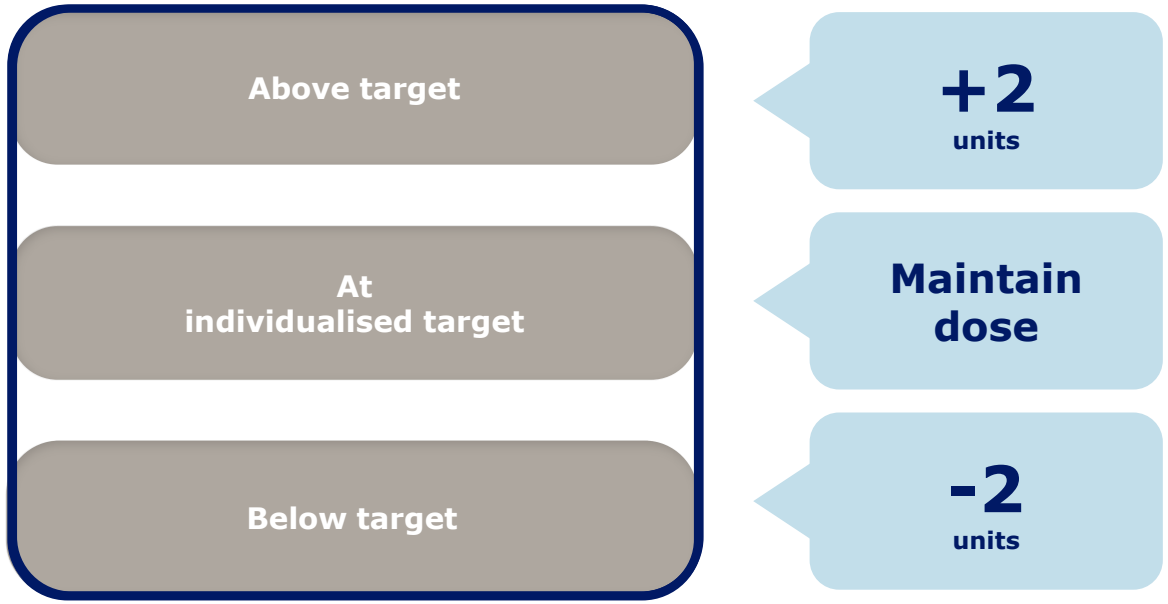


- Recommend using close glucose monitoring for first few weeks

BB, basal–bolus; BID, twice daily; IDegAsp, insulin degludec/insulin aspart; Ind. req., individual requirements; OAD, oral antidiabetic drug; OD, once daily; T2D, type 2 diabetes

Ryzodeg® August 2016 (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002499/WC500139011.pdf)

Suggested once-weekly titration schedule for IDegAsp in T2D

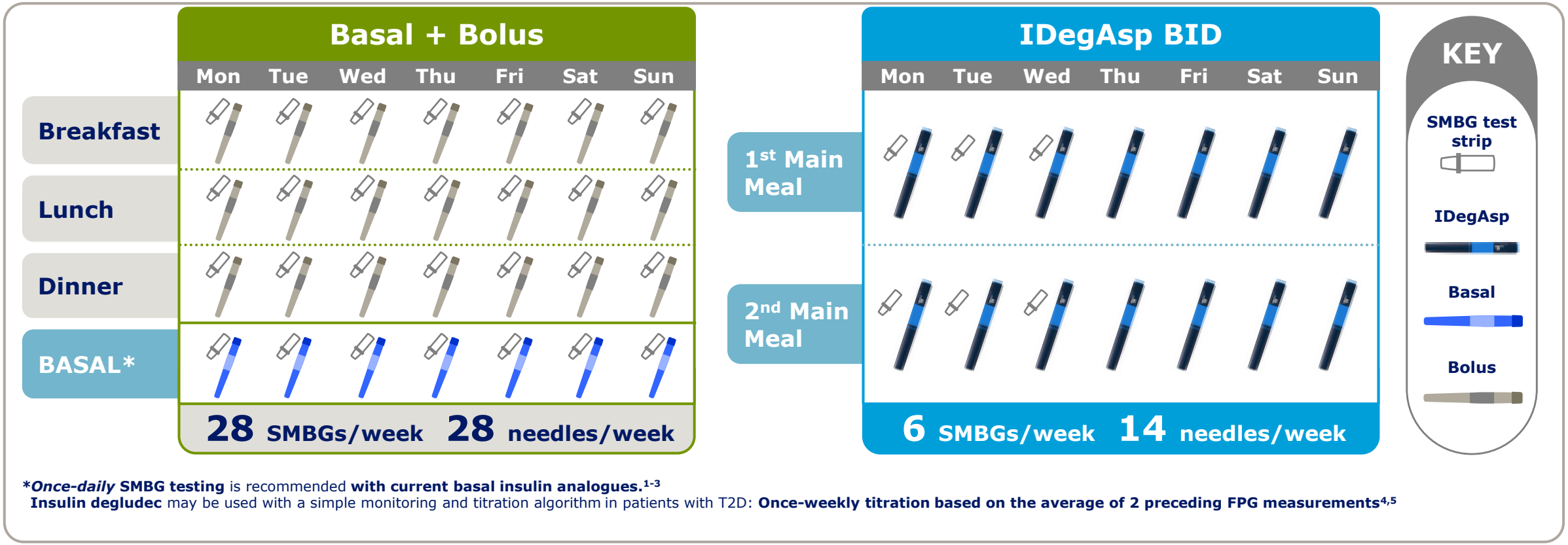


- Dose adjustments based on lowest of the 3 preceding FPG measurements
- FPG target should be individualised
- Do not increase dose if hypoglycaemia or symptoms suggestive of hypoglycaemia are present
- For twice-daily dosing, consider adjusting one dose at a time during weekly titration

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

1. Fulcher *et al. Diabetes Care* 2014;37:2084–90; 2. Gerety *et al. Endocr Pract* 2016;22:546–54; 3. 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

Dosed twice-daily IDegAsp offers less complex dosing for patients with T2D compared with basal–bolus



***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]

BID, twice daily; FPG, fasting plasma glucose; IDegAsp, insulin degludec/insulin aspart; SMBG, self-measured blood glucose; T2D, type 2 diabetes

1. Starting patients on Levemir®. http://www.levemirpro.com/prescribing/dosing.aspx; 2. Davies *et al. Diabetes Care* 2005;28:1282–8; 3. Titration guide for Lantus® http://www.lantus.com/hcp/dosing-titration/titration-guide.aspx; 4. 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. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM327017.pdf; 5. Rodbard *et al. Diabet Med* 2013;30:1298–304; 6. NICE. Guidance on the use of long-acting insulin analogues for the treatment of diabetes – insulin glargine. Technology App no 53. Dec 2002; 7. ADA. Diabetes Care. 2014;37(Suppl. 1):S14-S80; 8. Fulcher *et al. Diabetes Care* 2014;37:2084-90; 9. Kaneko *et al. Diabetes Res Clin Pract* 2015;107:139-47; 10. FDA Briefing Document. NDA 203313 and NDA 203314 Insulin degludec and insulin degludec/aspart. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM327015.pdf

Advantages of IdegAsp

- ***Versus premixed***
  - Improved FPG control Duration of action
  - Low within-subject day-to-day variability
  - Reduced hypoglycaemia risk No ‘shoulder’ effect
  - Mealtime flexibility Duration of action of basal component [30 h
  - Distinct prandial and basal glucose-lowering effects during od and bid dosing
  - No need for resuspension Existence of insulin degludec and insulin aspart as separate and stable soluble forms in the co-formulation
- ***Versus basal-bolus***
  - Reduced number of daily injections Distinct prandial and basal glucose-lowering effects during od and bid dosing
- ***Versus basal-only***
  - Additional flexible mealtime coverage Distinct prandial and basal glucose-lowering effects during od dosing

Summary

IDegAsp

Some patients are reluctant to intensify as required by disease progression due to hypoglycaemia and the complexity of basal and bolus treatment

IDegAsp is a combination of insulin degludec and insulin aspart in a single injection

Fewer injections and a lower risk of hypoglycaemia can help reduce the treatment and cost burden of insulin therapy

In insulin-naïve and/or Experienced patients with T2D, IDegAsp BID provides effective glycaemic control with a lower risk of hypoglycaemia

Summary

IDegAsp

Initiation with IDegAsp is well tolerated with better glycaemic outcome & reduction of overall and nocturnal hypoglycaemia

IDegAsp BID offers the potential for **a simple alternative to basal–bolus** treatment in patients who require intensification of basal insulin

BID, twice daily; IAsp, insulin aspart; IDeg, insulin degludec; IDegAsp, insulin degludec/insulin aspart

Thank you for your attention