Practical use of insulin degludec/insulin aspart in a multinational setting: beyond the guidelines

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- ✓ Insulin degludec/insulin aspart (IDegAsp) is a fixed-ratio co-formulation of insulin degludec, which provides long-lasting basal insulin coverage, and insulin aspart, which targets postprandial glycaemia.
- ✓ This review provides expert opinion on the practical clinical use of IDegAsp, including: dose timings relative to meals, when and how to intensify treatment from once-daily (OD) to twice-daily (BID) dose adjustments, and use in special populations (including hospitalized patients).
- ✓ IDegAsp could be considered as one among the choices for initiating insulin treatment, preferential to starting on basal insulin alone, particularly for people with severe hyperglycaemia and/or when postprandial hyperglycaemia is a major concern.

The recommended starting dose of IDegAsp is 10 units with the most carbohydrate-rich meal(s),followed by individualized dose adjustments. Insulin doses should be titrated once weekly in two-unit steps, guided by individualized fasting plasma glucose targets and based on patient goals, preferences and hypoglycaemia risk. Options for intensification from IDegAsp OD are discussed, which should be guided by HbA1c, prandial glucose levels, meal patterns and patient preferences. Recommendations for switching to IDegAsp from basal insulin, premixed insulins OD/BID, and basal-plus/basal–bolus regimens are discussed. IDegAsp can be co-administered with other antihyperglycaemic drugs; however, sulphonylureas frequently need to be discontinued or the dose reduced, and the IDegAsp dose may need to be decreased when sodiumglucose co-transporter-2 inhibitors or glucagon-like peptide-1 receptor agonists are added. Considerations around the initiation or continuation of IDegAsp in hospitalized individuals are discussed, as well as in those undergoing medical procedures.

Type 2 diabetes (T2D) is a complex, progressive disease; many people require insulin treatment for glycaemic control.1 Basal insulin products are used to supplement residual endogenous insulin secretion throughout the day and improve fasting plasma glucose (FPG), while bolus insulins are used to address prandial insulin requirements and limit postprandial hyperglycaemia. Basal–bolus regimens, where basal and bolus insulins are administered as separate injections,2 increase an individual's treatment burden and inconvenience, and may limit medication adherence. To overcome these barriers, premixed insulins can be used, which contain a fixed proportion of protaminated and non-protaminated (hence soluble) insulin in a single injection.

The protaminated fraction of the insulin undergoes a protracted absorption from the subcutaneous injection depot into the circulation, whereas the free fraction is rapidly absorbed as an insulin bolus. However, premixed insulin formulations have limitations: accurate dosing is dependent on adequate resuspension; protaminated insulins still have a shorter duration of action and greater glycaemic variability than basal insulin analogues; and the absorption kinetics of the two components are not clearly separated, resulting in a prolonged and potentially excessive peak glucose-lowering effect compared with rapid-acting insulins (i.e. a ‘shoulder effect’). In recent years, and in light of the aforementioned limitations, fixedratio co-formulation products have been developed. These are composed of two antihyperglycaemic drugs that maintain their distinct pharmacokinetic (PK) and pharmacodynamic (PD) properties despite being administered as a co-formulation9 and can allow for a comparatively simple insulin regimen, with fewer injections and greater flexibility in dosing time than basal-plus/basal–bolus therapy.

Available fixed-ratio coformulations include insulin degludec/insulin aspart (IDegAsp), insulin degludec/liraglutide and insulin glargine/lixisenatide.IDegAsp is the first fixed-ratio co-formulation of two different insulin analogues, comprising insulin degludec (degludec) (70%), a basal insulin analogue with an ultra-long duration of action, and rapid-acting insulin aspart (IAsp) (30%), thereby providing basal and prandial insulin cover when administered with meals. Combining two analogues together has not previously been possible because of either incompatibilities in the required pH of the formulation (with insulin glargine), or the formation of hybrid insulin hexamers (with insulin detemir), with unpredictable PK profiles. Unique to degludec is the assembly of dihexamers that are held together by side-chain zinc contacts, forming a highly stable structure. At high zinc concentrations, there is probably little or no association between degludec monomers and monomers of the co-formulated IAsp, either in the formulation or the injection depot. The resulting soluble product has a superior PK profile to that of conventional premix insulins, reflecting the flat and prolonged stable levels of basal insulin achieved by the degludec component, and a clear separation of the bolus component; thus there is no observed ‘shoulder effect’ with IDegAsp.

IDegAsp has been extensively investigated in people with T2D and also in people with type 1 diabetes (T1D), through the BOOST clinical trial programme. Previous guidance on the use of IDegAsp has been published. The main meal is usually the evening meal; however, based on clinical practice, in some regions (e.g. Mexico, parts of India and other regions), the main meal is often the midday meal. Despite the main meal being the evening meal in Japan, IDegAsp is often administered before breakfast as part of BID regimens, as this may promote adherence. In our experience, adherence in OD regimens may also be improved with IDegAsp administration at breakfast. Therefore, the main meal concept is recommended to determine dose timings as per the label, but in clinical practice other factors may also contribute.

In summary, the timing of IDegAsp administration should be based on the carbohydrate content of the meal (main meal concept).However, considerations around promoting compliance (adherence strategy) may also influence optimal injection timing.

Need for Innovation; Why??

Key challenges in T2DM management

Inadequate glycaemic control

Many patients have suboptimal glycaemic control, increasing the risk of long-term complications[1,2]

Hypoglycaemic events

Hypoglycemic events are costly and a barrier to good glycaemic control[3-5]

Treatment complexity

Complex treatment regimens are associated with reduced adherence to treatment[6,7]

Cost of diabetes

Diabetes places a huge financial burden on healthcare systems[8,9]

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.

Because of the progressive nature of T2D, intensification from maximum tolerated doses of oral antidiabetic drugs (OADs) to injectable glucose-lowering therapy eventually becomes necessary in many people. The ADA/EASD 2018 guidelines and ADA 2020 Standards of Medical Care in Diabetes recommend a glucagon-like peptide-1 receptor agonist (GLP-1RA) as the first choice for people with T2D who require injectable therapy. This recommendation is based on the lower risk of hypoglycaemia compared with basal insulin, and potential weight-sparing effect with these agents. For people at high risk of cardiovascular disease (CVD), the selection of a GLP-1RA with proven cardiovascular benefit as the first choice is particularly important. Of note, however, for people with HbA1c >11.0% (97 mmol/mol) or evidence of catabolism, a GLP1RA is not ideal, and insulin is recommended as the first injectable therapy. Based on clinical experience, country-dependent limitations in access to these drugs, driven by high costs, also influence medication use, particularly where they are not reimbursed by health authorities.

We recommend that IDegAsp OD could be considered as one among the choices for initiating insulin treatment for people with T2D. This fixed-ratio insulin co-formulation may be preferable to initiating basal insulin alone, particularly for people in whom extreme and symptomatic hyperglycaemia is a major concern, and in whom postprandial hyperglycaemia is an additional concern. Based on clinical experience, we recommend that intensification to IDegAsp OD may also be appropriate in people with a low body mass index (BMI),in whom weight gain is less of a concern, and whose lower BMI may reflect beta-cell insufficiency, which is likely to necessitate insulin therapy. However, for people with obesity, established CVD, at high risk of CVD or with diabetic kidney disease, a GLP-1RA may be more suitable, as discussed above.

We would consider initiating IDegAsp OD in people with HbA1c ≥ 7.0% (53 mmol/mol) and postprandial glucose ≥180 mg/dL (10.0 mmol/L) already on maximum OAD therapy. However, if fasting blood glucose levels are low (<100 mg/dL [5.6 mmol/L]), basal insulin would not be the therapy of choice. The rationale for our dose of IDegAsp may be used, at the clinician's discretion. Similarly, body weight should also be considered when initiating dosing of IDegAsp; 0.3 units/kg is recommended for premix insulin in the 2018 ADA/EASD guidelines, although this information is omitted from the 2020 ADA guidelines. Titration of IDegAsp should be individualized based on patient preference and goals, and the risk of adverse events. To guide insulin dose titration, individualized FPG targets are used, and titration is typically carried out in two-unit steps.). Postprandial glucose levels are not usually considered when determining titration algorithms. Titrating once weekly is advisable in the majority of people because of the long half-life of degludec;individuals should be advised that it can take up to 48–72 hours for degludec to reach steady state, so dose changes should not be made before this.

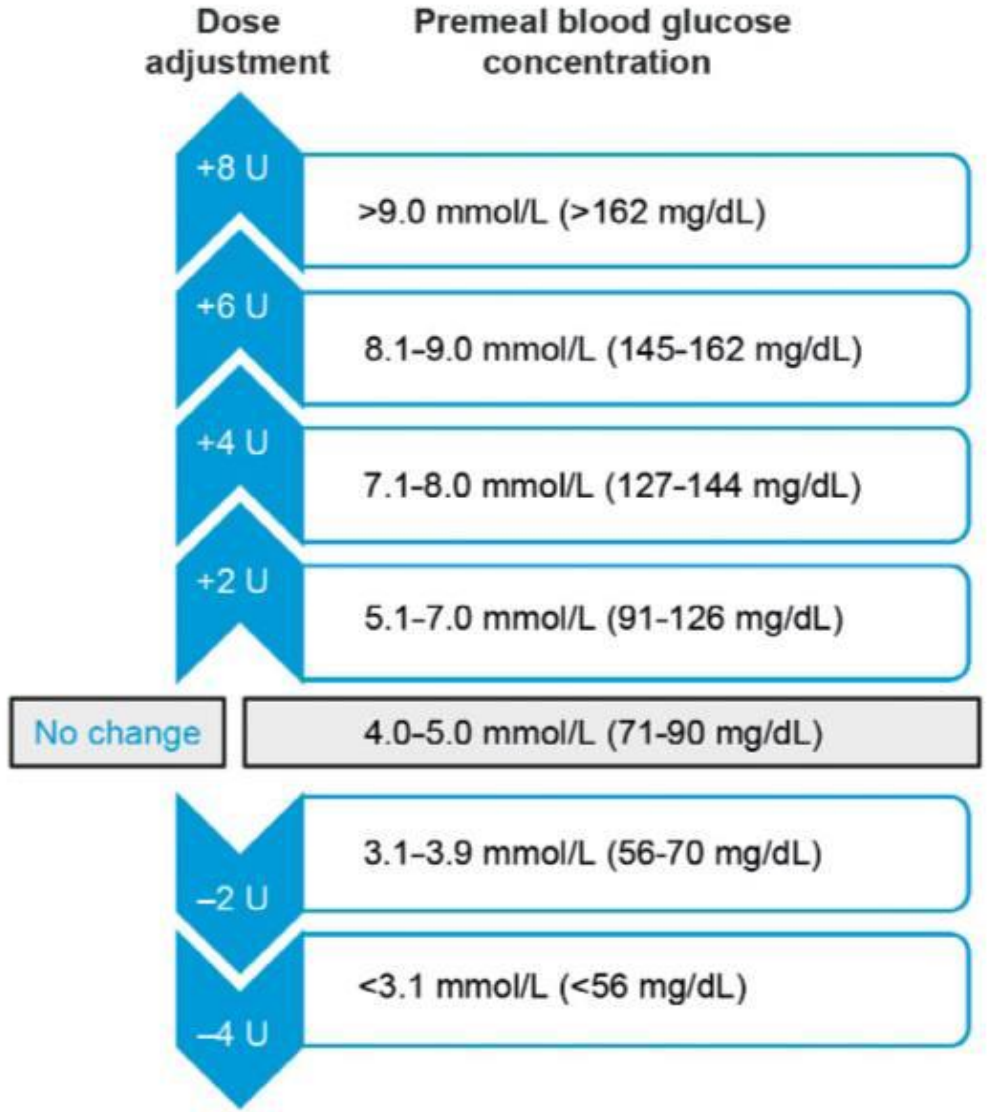


FIGURE 2 IDegAsp initial titration algorithm used in the phase III clinical trial programme.[27] IDegAsp, insulin degludec/insulin aspart co-formulation; U, units

Regular self-monitoring of blood glucose (SMBG), or 24-hour glucose monitoring if available, should be used to guide dose adjustments and to assess response, particularly at initiation. Ideally, selfmonitoring should be started immediately, and should initially be measured before breakfast, before evening meal and during the night. Pretreatment monitoring is also desirable, to provide a baseline for comparison. However, pragmatic approaches to self-monitoring may
be warranted: for example, in elderly people initiating small doses, who may have trouble with the burden of learning simultaneously to self-inject and take measurements. Clinical trials of IDegAsp have used a stringent FPG target of 71–90 mg/dL (4.0–5.0 mmol/L) with once-weekly dose adjustments of 2–8 units (Figure 2).

However, for people at higher cardiovascular risk, a less stringent FPG target of 91–126 mg/dL (5.0–7.0 mmol/L) has been used.46 Based on real-world experience, we recommend that a target of 80–130 mg/L (4.4–7.2 mmol/L) might be appropriate in clinical practice. Titration regimens must therefore be adjusted to reflect both individualized targets and patient characteristics (e.g. obesity, age or renal dysfunction). We recommend that monitoring should be continued at least twice weekly until the individualized target FPG is reached. More frequent monitoring may be needed depending on clinical context, or for specific purposes such as confirming fitness to drive.

If adequate glycaemic control is not achieved with IDegAsp OD, treatment can be intensified to (a) IDegAsp BID, (b) IDegAsp OD plus prandial IAsp at one or more meals, if the postprandial target is not met, or(c) IDegAsp BID, plus a single dose of IAsp at the third meal. If required, intensification from IDegAsp OD should not be delayed and should be guided by HbA1c, prandial glucose levels, meal patterns and patient preference. In the 38-week Step-by-Step trial, people with T2D and inadequate glycaemic control on basal insulin were randomized to receive IDegAsp OD or IGlar U100 + IAsp OD for 26 weeks, with dose intensification to IDegAsp BID or IGlar U100 + IAsp BID/-three times daily (TID) at weeks 26 and 32, respectively, if HbA1c targets of <7.0% (53 mmol/mol) were not met. At week 38, reductions in HbA1c were similar in both arms (ETD: 0.09% [−0.04; 0.22]95% CI). IDegAsp OD/BID are effective treatment intensification options versus multiple injection basal–bolus therapies, achieving similar glycaemic control, with significantly less nocturnal hypoglycaemia.

Intensification to IDegAsp BID is recommended if there are postprandial glucose excursions after two meals in 1 week and the excursions are unresponsive to diet manipulation. The maximum permissible dose of IDegAsp is limited by the IAsp dose required for a particular meal by the patient, as well as the FPG target (case study 2).We recommend a maximum OD dose of 30–40 units before splitting the dose. When intensifying to BID, the total daily dose of IDegAsp OD is split over two doses, administered at the two meals with the greatest carbohydrate content, with a minimum dosing interval of 4 hours. The dose ratio (not necessarily 1:1) should be based on the relative carbohydrate content of the meals and the postprandial glucose excursion following each meal.

Further intensification from IDegAsp OD to IDegAsp BID, with a single dose of IAsp at the main meal, is recommended if there are persistent excessive postprandial glucose excursions (i.e. three readings of ≥180 mg/dL [≥10.0 mmol/L] over 1 week on SMBG or capillary blood glucose; however, this may vary with individualized targets and monitoring frequency). Intensification to IDegAsp OD with IAsp BID after the two largest meals of the day may also be an option where persistent postprandial hyperglycaemia occurs in combination with normalized FPG: for example, in countries where meals are typically rich in carbohydrate. Although degludec has a duration of action longer than 42 hours at steady state, BID administration of IDegAsp does not result in accumulation of degludec because the same steady-state level is reached in the circulation with a given total daily dose of degludec whether it is administered OD or BID.

SWITCHING TO IDegAsp FROM OTHER TREATMENT REGIMENS

Switching from basal insulin

There are several important considerations when assessing the effectiveness of basal insulin treatment. The first consideration, often overlooked, is whether the patient is happy with their current regimen. Increasing doses of basal insulin without consideration of alternative therapies is common, and may lead to clinical inertia and prolonged poor glycaemic control. The second consideration is whether basal insulin offers appropriate glycaemic control; if HbA1c levels are elevated in the context of normal pre-breakfast FPG levels, this indicates postprandial hyperglycaemia and should trigger reassessment of the most suitable insulin regimen. IDegAsp may be considered for treatment intensification in people with T2D with inadequate glycaemic control on basal insulin. Furthermore, if nocturnal hypoglycaemia is a problem with basal insulin, switching to IDegAsp may be preferable.

In the Step-by-Step trial, similar glycaemic control was achieved with IDegAsp OD compared with IGlar U100 OD + IAsp OD, with significantly fewer nocturnal episodes (ERR: 0.61 [0.40; 0.93]95% CI). We recommend a threshold of 36–40 units of basal insulin, or 0.5 IU/kg/day,50 after which, if glycaemia is still insufficiently controlled (HbA1c ≥7.0%[53 mmol/mol], postprandial glucose ≥180 mg/dL [≥10 mmol/L]), alternative treatments, including IDegAsp, should be considered.

An important consideration when switching from basal insulin to IDegAsp is that the unit-for-unit conversion is not necessarily 1:1; therefore, the dose may need to be reduced for those experiencing hypoglycaemia or for those previously on insulin glargine 300 units/mL.

Switching from premix insulins OD/BID/TID

People receiving BIAsp 30 may benefit from switching to IDegAsp if glycaemic control is suboptimal or if they are experiencing hypoglycaemia. In addition to a superior PK/PD profile, with clearer separation of the basal and prandial components (Figure 1), IDegAsp also has the advantage of being presented in a soluble co-formulation, hence resuspension before administration is not required,in contrast to premixed insulin formulations. These properties can be expected to help mitigate the risk of hypoglycaemia. A 26-week trial, in which people were switched to IDegAsp or BIAsp 30 from their previous insulin regimen, showed lower rates of overall and nocturnal hypoglycaemia at similar HbA1c and improved FPG levels with IDegAsp than with BIAsp 30.

When switching from BIAsp 30 OD to IDegAsp, a unit-for-unit conversion may be used if the person has suboptimal glycaemic control (i.e. HbA1c >8.0% [64 mmol/mol]). If individuals are receiving BIAsp 30 BID, a unit-for-unit conversion of the total daily dose may be split over IDegAsp BID,administered with main meals; for individuals treated with BIAsp30 TID, this may be split over IDegAsp BID at main meals, with or without an additional IAsp dose to cover the third meal. However, if the HbA1c level is ≤8.0% [64 mmol/mol] or the patient is experiencing hypoglycaemic episodes, the initial dose of IDegAsp should be reduced by 10–20% compared with the original BIAsp 30 dose.

Switching from a basal-plus/basal–bolus regimen

IDegAsp is suitable for people who do not want to or cannot take multiple injections each day, and therefore provides an alternative to basal–bolus regimens. In a randomized trial in people with T2D, patient-reported outcome scores for social functioning were significantly higher for IDegAsp BID versus degludec OD + IAsp 2–4 times daily (ETD: 2.2 [0.3; 4.1]95% CI, $P < .05$). Although non-inferiority was not confirmed for mean change in HbA1c, there was no statistically significant difference between the treatment groups in either glycaemic control or hypoglycaemia. Therefore, the improvement in patient-reported outcome scores was probably a result of the reduced burden of injections with IDegAsp BID versus a basal–bolus regimen (degludec + IAsp). IDegAsp OD/BID achieved similar glycaemic control with significantly less nocturnal hypoglycaemic at a lower insulin dose and with fewer daily injections compared with IGlar U100 OD + IAsp OD/BID/TID.Switching from a basal–bolus regimen needs to be individualized to the patient, based on careful consideration of basal–bolus doses and detailed blood-glucose monitoring, with close ongoing assessmen . Other clinicians should be encouraged to seek advice from a diabetes specialist before undertaking such a change.

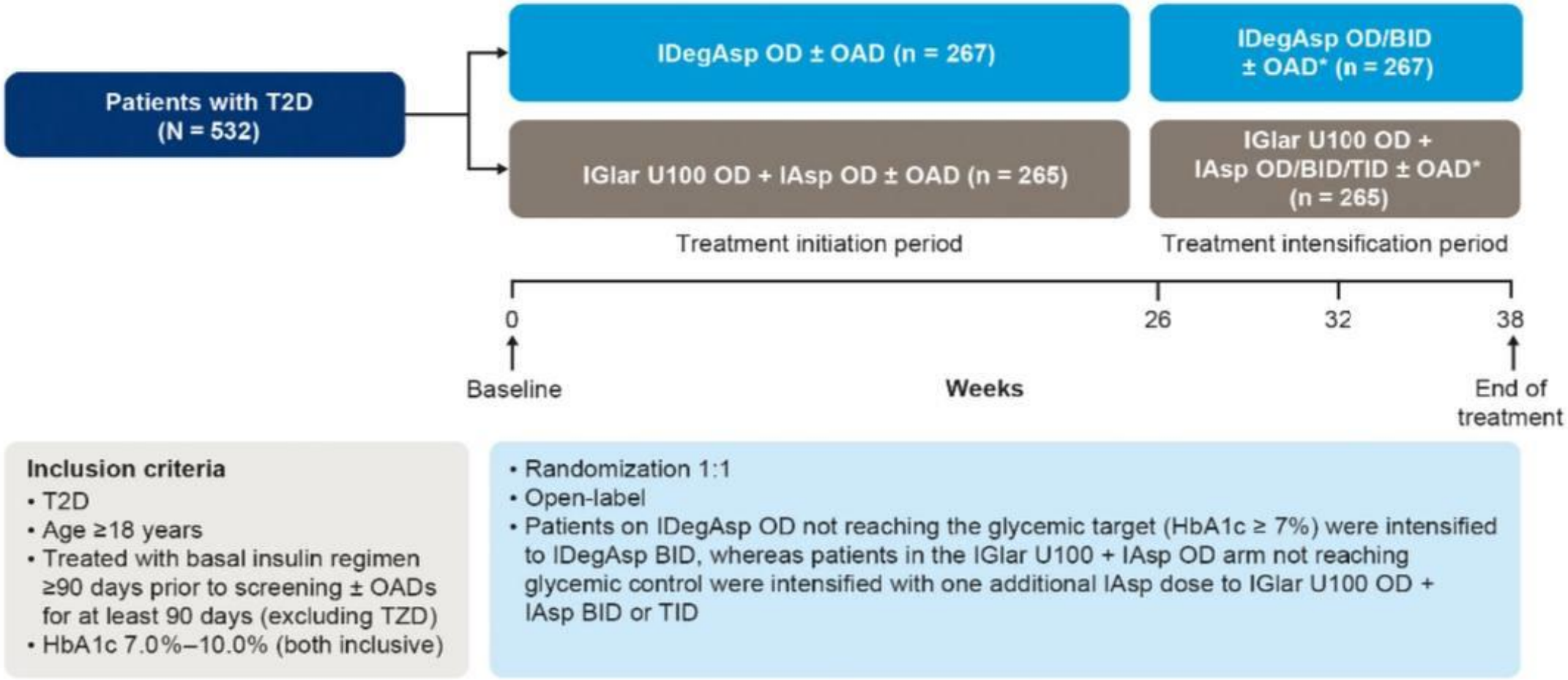


FIGURE 3 The Step-by-Step trial design for treatment intensification.[27] *Treatment intensification period was followed by 1-week washout period and then 30-day follow-up period; OADs included: metformin, DPP-4i, SGLT-2i, αGI (SU/glinides were discontinued at randomization). αGI, alpha-glucosidase inhibitor; BID, twice daily; DPP-4i, dipeptidyl peptidase 4 inhibitor; IAsp, insulin aspart; IDegAsp, insulin degludec/insulin aspart; IGlar U100, insulin glargine U100; OAD, oral antidiabetic drug; OD, once daily; T2D, type 2 diabetes; TID, three times daily; TZD, thiazolidinedione; SGLT-2i, sodium-glucose co-transporter inhibitor; SU, sulphonylurea. Reprinted and adapted from Philis-Tsimikas et al. *Diabetes Res Clin Pract*. 2019;147:157-165, © 2019 with permission from Elsevier.[27]

CO-ADMINISTRATION WITH OTHER ANTIDIABETIC MEDICATIONS

IDegAsp can be used in combination with most OADs. In our experience, if sodium-glucose co-transporter-2 (SGLT-2) inhibitors are added to IDegAsp, the insulin dose should be decreased by 10–20%; for people already receiving an SGLT-2 inhibitor, IDegAsp may be initiated and subsequently titrated weekly to reduce the risk of side effects. People using SGLT-2 inhibitors should be aware of, and follow, local guidelines on sick day rules.

Caution should also be taken when combining IDegAsp with sulphonylureas (SUs). We recommend that, for people receiving IDegAsp BID, SUs should be discontinued; with IDegAsp OD, SU treatment may need to be discontinued or the dose reduced.

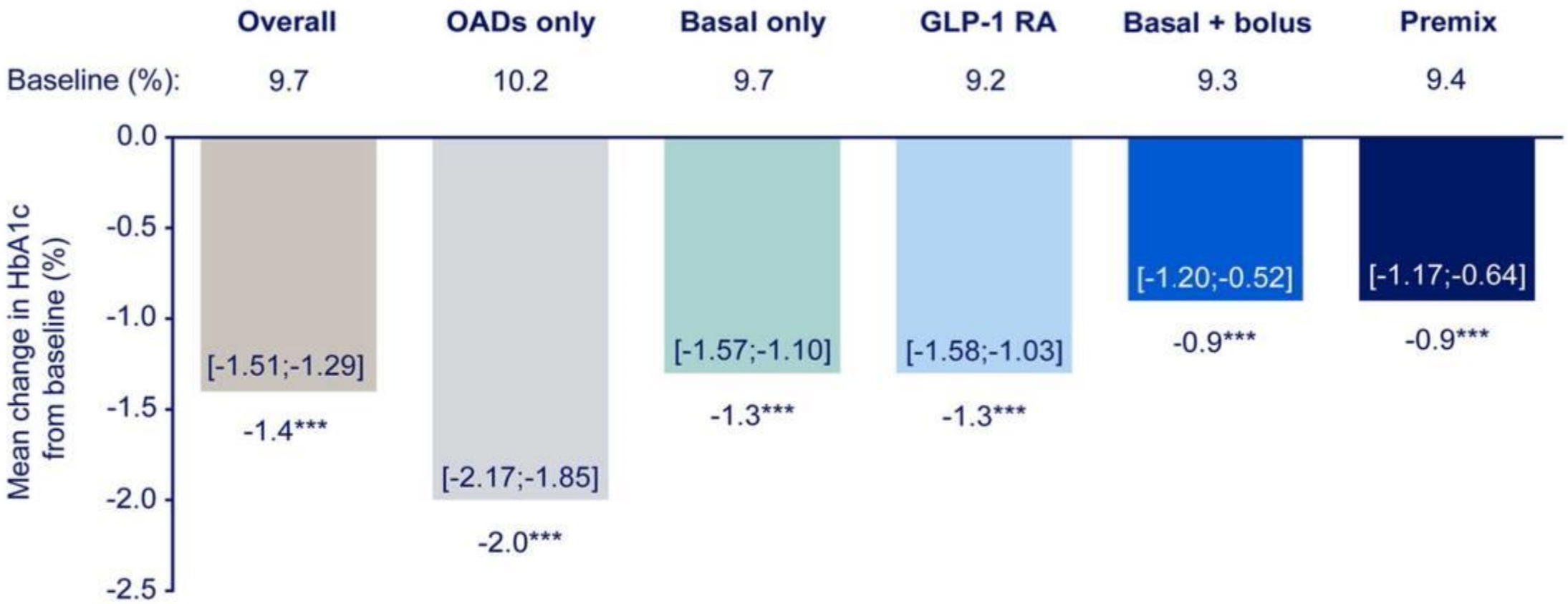


Fig. 1 Change in HbA1c from baseline to EOS. ***$P < 0.0001$. Data are mean [95% CI]. Baseline data are for participants contributing to the analysis. The full adjusted model included baseline value, time, time-squared for HbA1c measure, age, sex, BMI, previous antidiabetic regimen, and study site. To handle (quadratic) deviation from linearity, a random coefficient model with time and time squared as fixed coefficients, and patient and patient time as random coefficients was used. An unstructured covariance matrix was used to describe the variability for repeated measurements. *BMI* body mass index, *basal only* basal insulin only (± OADs); *basal–bolus* basal–bolus insulin (± OADs), *CI* confidence interval, *EOS* end of study, *GLP-1 RA* glucagon-like peptide 1 receptor agonist ± insulin (± OADs), *OAD* oral antidiabetic drug, *premix* premix insulin ± bolus insulin (± OADs)

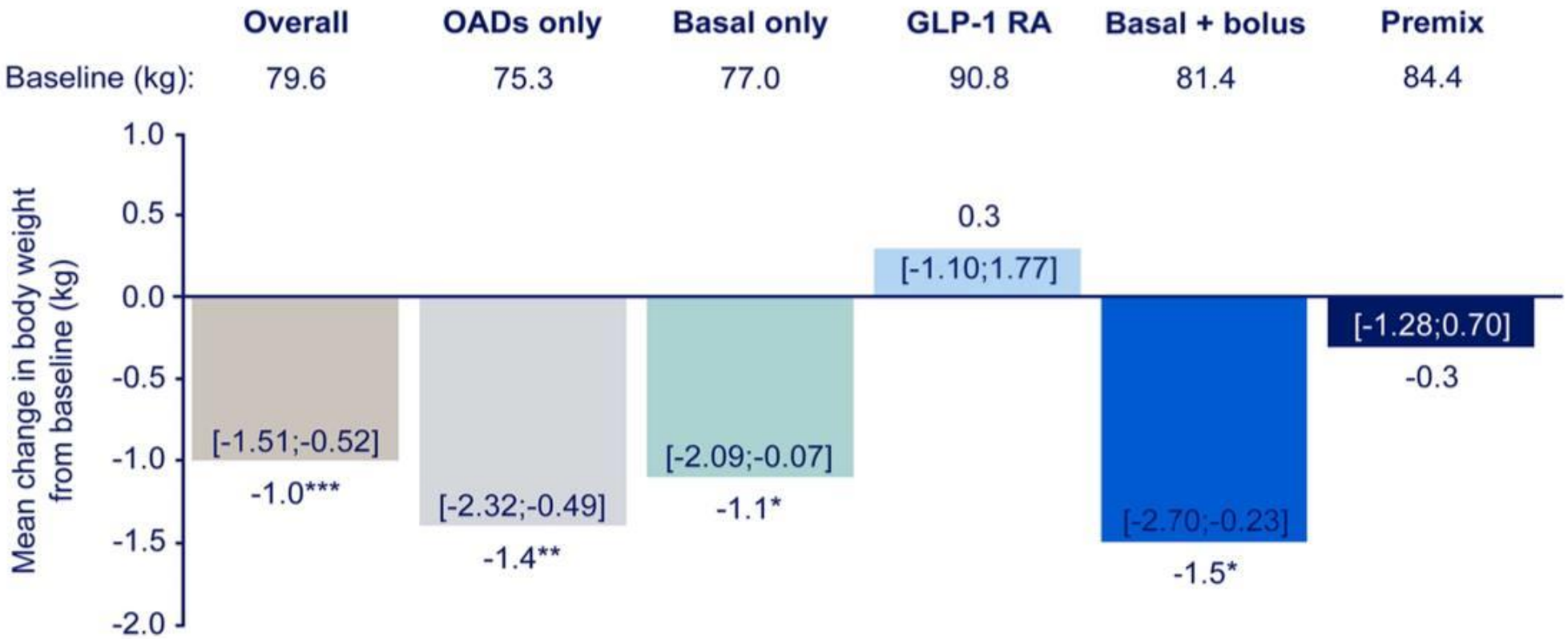


Fig. 2 Change in body weight from baseline to EOS. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.0001$. Data are mean [95% CI]. Baseline data are for participants contributing to the analysis. The full adjusted model included baseline value, time, time-squared of body weight measure, age, sex, BMI, previous antidiabetic treatment regimen, and study site. To handle (quadratic) deviation from linearity, a random coefficient model with time and time squared as fixed coefficients, and patient and patient time as random coefficients was used. An unstructured covariance matrix was used to describe the variability for repeated measurements. *BMI* body mass index, *basal only* basal insulin only (± OADs), *basal–bolus* basal–bolus insulin (± OADs), *CI* confidence interval, *EOS* end of study, *GLP-1 RA* glucagon-like peptide 1 receptor agonist ± insulin (± OADs), *OAD* oral antidiabetic drug, *premix* premix insulin ± bolus insulin (± OADs)

The long-term effects of pioglitazone use alongside insulin treatment are still uncertain. The combination has been associated with the development of heart failure in some people with longstanding
T2D and heart disease or a previous stroke. However, a recent systematic review suggested that pioglitazone is a feasible adjunct to insulin therapy. In addition, recent data showed that pioglitazone in combination with insulin may reduce the risks of all-cause mortality and non-cardiovascular death in people with T2D. No additional considerations are required when combining IDegAsp with metformin, α-glucosidase inhibitors or dipeptidyl peptidase-4 inhibitors (DPP-4is), which can all be continued at the same dose when IDegAsp is added. Based on our experience, when adding IDegAsp to a GLP-1RA,there is usually no decrease in insulin dose; an initial daily dose of 10 units is recommended. However, if a GLP-1RA is added to IDegAsp, the insulin dose may need to be decreased, depending on HbA1c levels (e.g. if HbA1c <7.5% [59 mmol/mol]).

Use in adults with T1D

In adults with T1D, IDegAsp OD as part of a simplified basal–bolus regimen with mealtime IAsp improved overall glycaemic control and was non-inferior to insulin detemir (IDet) OD + mealtime IAsp basal–bolus therapy. Treatment with IDegAsp also incurred a comparatively reduced risk of nocturnal hypoglycaemia.

Use in adolescents with T2D

The incidence of T2D in adolescents has increased globally in recent decades, which has been linked to obesity.58 The rapid decline of beta-cell function in adolescents merits the use of insulin treatment. Indeed, initial treatment with metformin and/or insulin alone or in combination is recommended in adolescents with T2D and marked hyperglycaemia (blood glucose ≥250 mg/dL [>13.9 mmol/L] and/or HbA1c ≥8.5% [69 mmol/mol]). an efficacy and safety evaluation has been made using data from adolescent and adults with T1D and adults with
T2D. This assessment supports the use of IDegAsp in adolescents with T2D.

In-hospital use

Rapid-acting insulin (preferentially as part of a basal–bolus regimen) is generally used when the patient is hospitalized and is preferred to combination insulins because of greater flexibility for titration. The decision as to whether IDegAsp should be continued or switched to another medication after admission to hospital is often made by the hospital group. In some regions, IDegAsp is discontinued because titration is not practical for inpatients because of the time needed for the degludec component to reach steady state, and the fixed ratio of the IAsp content . This may be pertinent when there are changes to diet, appetite, cases of sepsis or a need to take corticosteroids. An IDegAsp-based insulin regimen can be initiated or restarted when the patient is discharged.

In-hospital use

Peri-operative recommendations are region-specific. Based on the authors' experiences, for minor procedures, for example, cataract surgery, no dose alteration may be needed if the patient is able to eat normally; otherwise, IDegAsp may be omitted, or switched to degludec (if available), IGlar or IDet on the operation day. For major operations, IDegAsp treatment should be discontinued 24 hours before the operation. In instances of prolonged fasting, for example for colonoscopy, the insulin dose may need to be decreased by ≈30–50% ≈3 days before the procedure. People may be switched from IDegAsp to insulin basal–bolus regimens, or basal regimens with corrective rapid-acting insulin, during the perioperative period.

Use in people with renal impairment

IDegAsp is suitable for people with renal impairment.10 Glucose monitoring should be intensified and the insulin dose adjustments individualized. As reduced renal clearance of basal insulin may result in hypoglycaemia in those with severe impairment, the decision to use IDegAsp over rapid-acting insulin should be made on an individual basis, accounting for the degree of residual renal function. Extra caution is needed in individuals undergoing dialysis treatment, considering the frequency and modality of dialysis.

Elderly peopl

There are several concerns when treating elderly people with diabetes. The symptoms of hypoglycaemia can be particularly debilitating in elderly people because of frailty, and hypoglycaemia has been associated with an increased risk of fall-related events in elderly people who experienced hypoglycaemia compared with those who did not experience hypoglycaemia. A retrospective cohort study of people with T2D aged 60 years or older showed that mortality risk was lower for people with HbA1c 6.0–9.0% (42–75 mmol/mol) compared with those with an HbA1c of less than 6% (42 mmol/mol).64 Additionally, post hoc analysis of data from the ACCORD trial showed that a 1-year increment in baseline age was associated with a 3% increase in the risk of severe hypoglycaemia ($P < .0001$). For elderly people with frailty and multiple co-morbidities, less stringent HbA1c targets (<8% or ≤9% [<64 or ≤75 mmol/mol]) than those used for younger people may be adequate.

Elderly people

The convenience of a single injection pen and reduced number of injections with IDegAsp compared with basal–bolus therapy is likely to be advantageous in elderly people.3 Many elderly people are treated in nursing homes or at home by visiting nurses. The arrival times of nurses may not be consistent; therefore, flexibility in dose timing may be advantageous. IDegAsp can be administered at different times from day to day, provided it is coordinated with a main meal; this improved flexibility for mealtime variation may be considered an advantage of IDegAsp compared with other insulin regimens.

A recent post hoc subgroup analysis showed that, in people with T2D aged 65 years or older, IDegAsp provided effective glycaemic control consistent with the effects of BIAsp 30, with no significant differences in overall confirmed or nocturnal hypoglycaemic events.These results were broadly in line with those in the overall population. However, SUs, if taken, should be discontinued when IDegAsp treatment is started, because of the increased risk of hypoglycaemia.

Use of IDegAsp in special populations

Paediatrics

The safety and effectiveness of IDegAsp have been established in paediatric patients 2 year of age or older

Renal and Hepatic impairement

Can be used in renal and hepatic impaired patients

Glucose monitoring should be intensified and doses should be individualised

Elderly

Can be used in older patients. Glucose monitoring should be intensified and doses should be individualised

Pregnancy

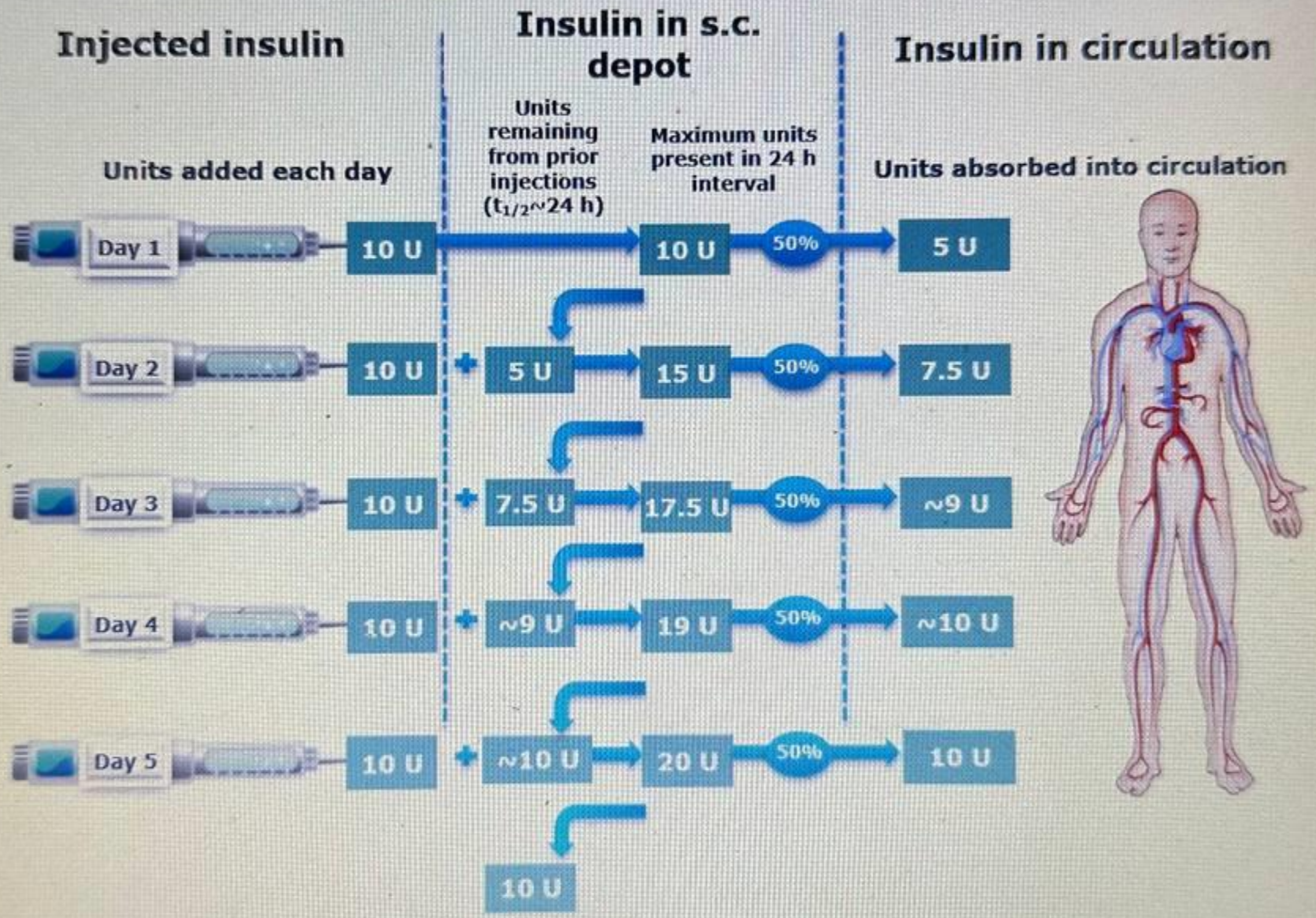
There is no clinical experience with use of IDegAsp in pregnant and Breast feeding women

Ryzodeg® August 2019. https://www.novo-pi.com/ryzodeg7030.pdf

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

Degludec once-daily administration without accumulation



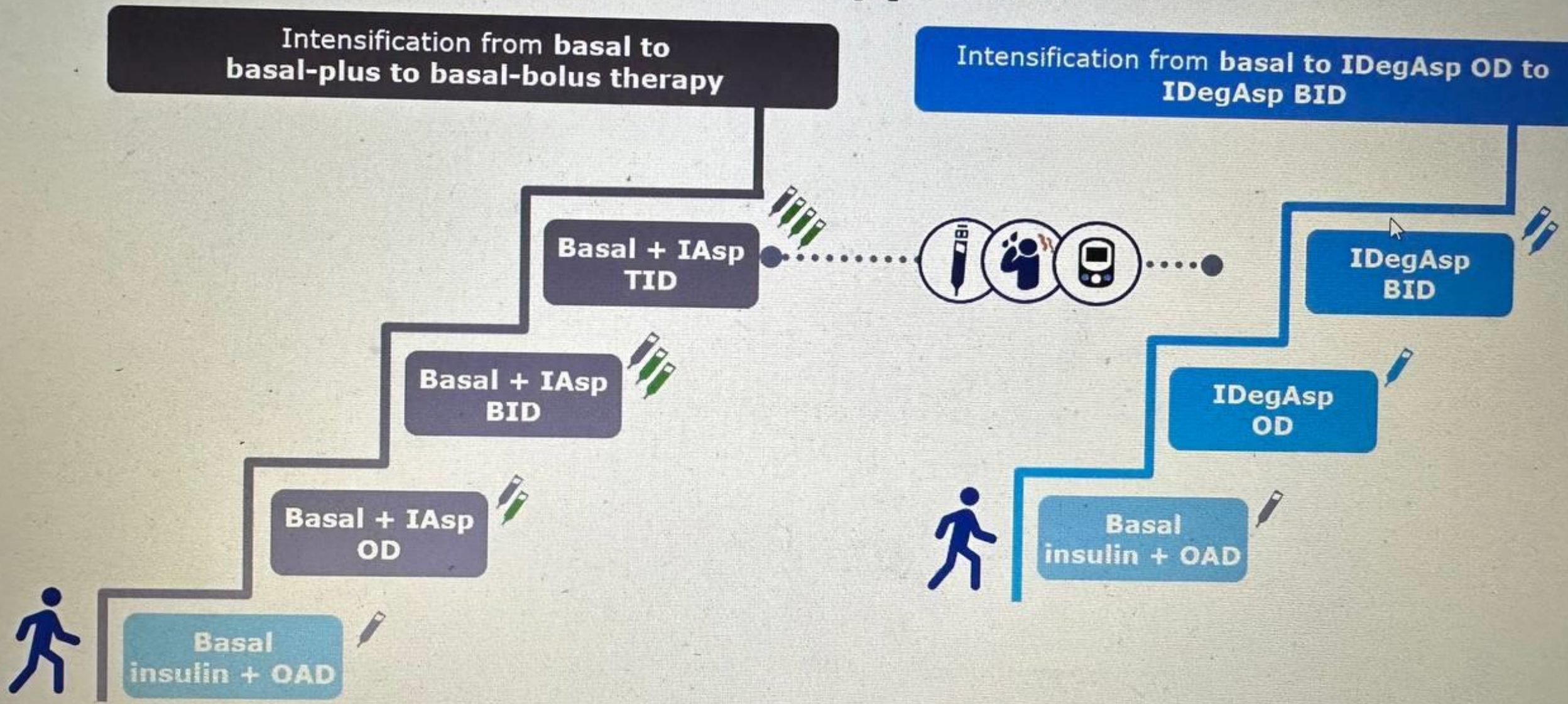
Elimination of any insulin follows first order kinetics. Therefore there is no stacking.

CONCLUSIONS

IDegAsp provides basal as well as prandial insulin cover in a single injection when administered with a meal. The co-formulation provides dosing flexibility and may allow fewer injections compared with basal–bolus regimens. We recommend IDegAsp as one among the choices for first insulin treatment for people with diabetes when insulin is indicated, and for whom weight loss is not a priority and access to medication is a concern. A GLP-1RA is recommended as the first injectable treatment for people at high risk of CVD.

Clinical evidence supports the use of IDegAsp in a wide variety of patient populations and can be used for either insulin initiation or intensification.

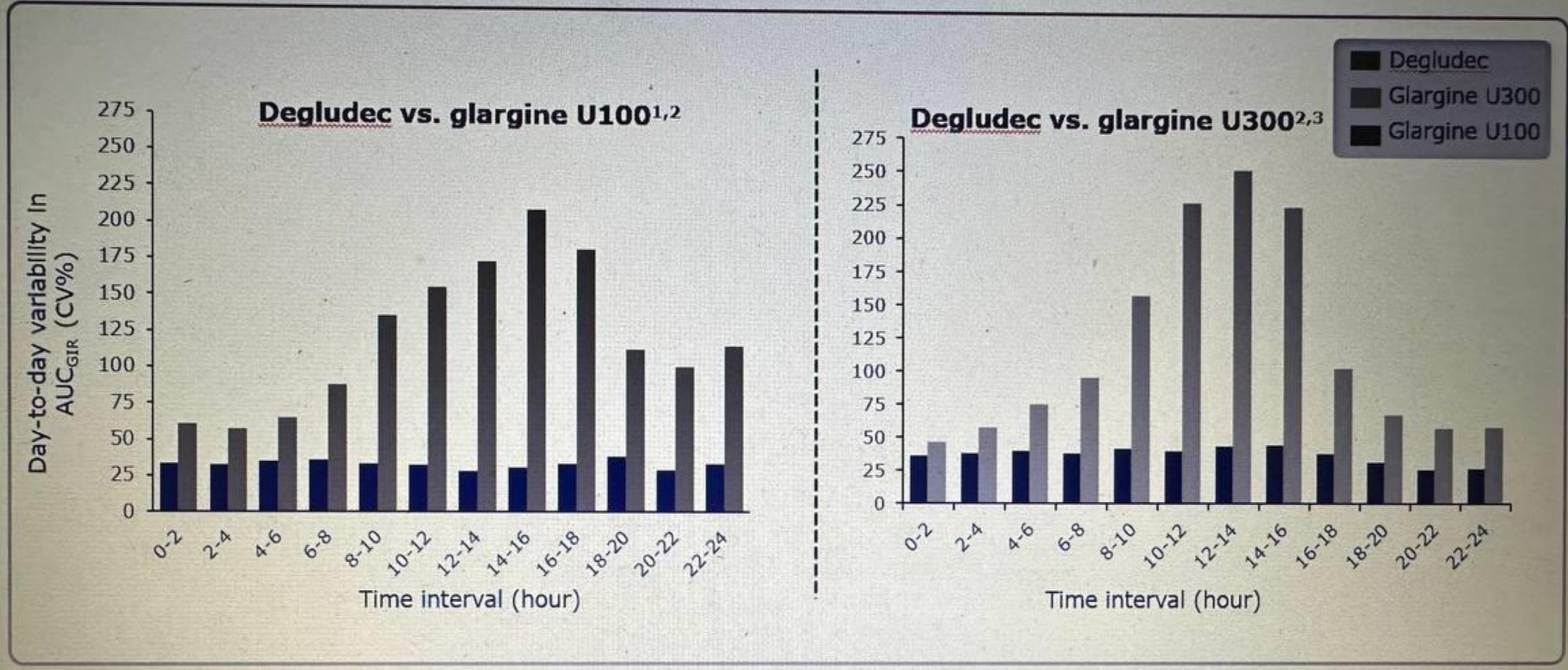
Basal insulin intensification approach



BID, twice daily; OAD, oral antidiabetic drug; OD, once daily; IAsp, insulin aspart; TID, thrice daily

Adapted from *American Diabetes Association. Diabetes Care* 2017;40(Suppl.1):S64–S74

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