Controlling glycemic variability in people living with type 1 diabetes receiving insulin glargine 300 U/mL (Gla-300)

Julia K Mader,1 Stefan Götz,2 Stefan Bilz,3 Peter Bramlage,4 Thomas Danne

ABSTRACT

Short-term glycemic variability is associated with the risk of hypoglycemia and hyperglycemia in people living with type 1 diabetes and can potentially affect clinical outcomes. Continuous glucose monitoring (CGM) is of increasing importance to evaluate glycemic variability in greater detail. Specific metrics for assessing glycemic variability were proposed, such as the SD of mean glucose level and associated coefficient of variation, and time in target glucose range to guide study designs, therapy and allow people with diabetes more transparency in interpreting their own CGM data. Randomized controlled trials (RCT) and real-world evidence provide complementary information about the efficacy/effectiveness and safety of interventions. Insulin glargine 300 U/mL (Gla-300) has a longer lasting and less variable action than insulin glargine U100 (Gla-100) with a lower risk of hypoglycemia. While insulin degludec U100 (iDeg-100) was associated with lower glucose values but more time below range in one randomized study compared with Gla-300, Gla-300 was associated with a higher per cent time in range, but also above the therapeutic range. However, a real-world study did not find differences during the day between Gla-300 and iDeg-100. The upcoming InRange RCT is the first head-to-head comparison of Gla-300 with iDeg-100 using CGM in an international population using CGM metrics as the primary endpoint. The non-interventional COMET-T real-world study will determine the real-world effectiveness of Gla-300 using CGM metrics and cover a broad spectrum of clinical practice decisions irrespective of the prior basal insulin.

INTRODUCTION

Glycemic variability results in superoxide overproduction, increased oxidative stress, generation of inflammatory cytokines and endothelial dysfunction and damage,1 and is associated with an increased risk of diabetic macrovascular and microvascular complications, hypoglycemia, mortality and other adverse clinical outcomes.2 The introduction of insulin analogs and modern diabetes technology including continuous glucose monitoring (CGM) has significantly improved the current management of type 1 diabetes (T1D) and both strategies have been endorsed in the recently introduced American Diabetes Association/European Association for the Study of Diabetes (EASD) consensus report on the management of T1D in adults.3 The focus of this manuscript will be on studies dealing with insulin treatment and outcome assessment by CGM. The use of ambulatory glucose profiles made it possible to analyze treatment in more detail and to visualize the efficacy profiles of currently used insulin regimens. International guidelines and consensus reports defined CGM targets to guide treatment and to make studies more comparable. Results of these studies using CGM metrics in recent years showed advantages of second-generation basal insulin analogs, for example, a flatter glucose-lowering profile. More studies are to come and we will have a look at them later on.

Glycemic variability and guidance on the use and interpretation of CGM data

In current practice, glycated hemoglobin (HbA1c) is the principal measure of glycemic control. However, it reflects average glucose control over the preceding 2–3 months and does not provide information about short-term (within-day and between-day) variability in glucose levels.4 Methods used to assess short-term glycemic variability include self-monitoring of blood glucose (SMBG) and CGM. SMBG is a measurement at single point in time, with no surrounding information; it may therefore fail to detect asymptomatic or nocturnal hypoglycemia.5 In contrast, CGM provides both a comprehensive picture of the frequency and magnitude of any glucose variation and trends to predict where the glucose will head soon. It either determines interstitial glucose in real time (rtCGM) or as intermittent scanning CGM (isCGM), also called flash glucose monitoring. More recently, minimal or low day-to-day (considered to be a reproducible glucose-lowering effect between
injections) and within-day (consistent glucose-lowering effect over a 24-hour dosing interval) glycemic variability has been recognized a desirable target to achieve glycemic control. There are a multitude of consequences of increased glycemic variability in diabetes as it affects the patient both physically and mentally. For example, glycemic variability is linked to reduced quality of life, increased anxiety or absenteeism of work. Glycemic variability is important, reducing glycemic variability is associated with better treatment compliance and improved quality of life for the patient, improved diabetes management, and has the potential to reduce complications.

The Advanced Technologies & Treatments for Diabetes (ATTD) consensus report on CGM monitoring recommends coefficient of variation (%CV, a mean glucose of 150 mg/dL and an SD of 60 would have a CV of 40%) as the primary measure of glycemic variability, with SD as a secondary measure. CV is prioritized because it is a metric relative to the mean, making it more descriptive of hypoglycemic and hyperglycemic excursions than the SD alone. Stable glucose levels are defined as a CV <36% or, if achievable, <33%. A glycemic variability above this threshold was associated with an increased risk for hypoglycemia both in type 1 and type 2 diabetes. The report also recommends that time in range (TIR), time below range (TBR), time above range (TAR), low blood glucose index (LBGI) and high blood glucose index (HBGI) should be evaluated. The ATTD consensus report on CGM-TIR provides target percentages of time for various levels of TIR, TBR, and TAR. The recommended target for TIR (70–180 mg/dL) is >70% of readings (>16 hours 48 min/day). The targets for TBR are <4% (<1 hour) at <70 mg/dL and <1% (<15 min) at <54 mg/dL, while those for TAR are <25% (<6 hours) at >180 mg/dL and <5% (<1 hour 12 min) at >250 mg/dL (online supplemental figure S1). Modified targets are provided for subgroups such as older and high-risk populations and pregnant women.

The ATTD report notes that, even if the recommended targets are not achieved, small improvements, such as a 5% (1.2 hours/day) increase in TIR, can provide a clinically relevant improvement in glycemic control. This recommendation is based on data from several studies that demonstrated a correlation between TIR and HbA1c. An increase in CGM-assessed TIR (70–180 mg/dL) of 10% (2.4 hours/day) corresponded to a reduction in HbA1c of 0.6% in people living with T1D; only limited data are currently available.

**Insulin glargine 300 U/mL and its effects on glycemic variability**

Insulin glargine is widely used as a basal insulin analog in people living with T1D. The earlier 100 U/mL (Gla-100) formulation has been improved to a 300 U/mL (Gla-300) formulation, which provides a similar level of efficacy but has an extended duration of action, a flatter action profile, and, accordingly, a lower risk for hypoglycemia. Several randomized controlled trials (RCTs) involving Gla-300 in people living with T1D have included measures of glycemic variability. In addition, one study has reported real-world evidence (RWE) on glycemic variability in people treated with Gla-300. There is a lack of longer term prospective studies using CGM and of studies comparing second-generation basal insulin. Upcoming studies, including randomized clinical trials and real-world studies, will add to this body of evidence.

**RCTs versus RWE studies**

RCTs are the ‘gold standard’ for evaluating the efficacy and safety of treatments (online supplemental table S1). However, they generally involve a well-defined but selected population of people meeting specific inclusion and exclusion criteria and are conducted under controlled conditions with intense monitoring. These populations and conditions generally represent only a small part of those encountered in a routine clinical practice setting. Therefore, although RCTs provide valuable evidence on efficacy, there may be a gap between the efficacy observed in RCTs and the effectiveness seen in daily practice. In addition, the safety data obtained from RCTs have limitations; RCTs primarily identify frequent adverse events, and are less likely to identify low-frequency events or those which only occur after longer exposure.

Real-world studies are useful for determining the effectiveness and safety of treatments in routine clinical practice. They involve a broader range of people living with diabetes, including those with major comorbidities, multiple concomitant medications or other factors affecting health, who often fall outside the inclusion criteria for RCTs. Moreover, adherence to treatment (which can affect its effectiveness) may be lower in the standard care setting than in RCTs in which participants are monitored closely and have more frequent interaction with healthcare professionals. Thus, RWE provides information that is complementary to that obtained from RCTs. RWE provides additional insights regarding the potential advantages and disadvantages of treatments and treatment strategies in routine clinical practice, which may help healthcare practitioners provide patient-centered care, as well as providing information on treatment utilization patterns.

**Aims**

In this paper, we review the available evidence on glycemic variability in people living with T1D receiving Gla-300 compared with other treatments. We also outline the design of the two ongoing studies—InRange and COMET-T—which will complement the available data with further evidence.

**SEARCH STRATEGY**

PubMed was screened for publications concerning glycemic variability in people living with T1D receiving
Gla-300. For this purpose, the following search string was used on 14 June 2021: ‘T1D’ AND (‘glucose variability’ OR ‘glycemic variability’ OR ‘time in range’ OR ‘continuous glucose monitoring’ OR ‘flash glucose monitoring’) AND (glargine OR U300) confined to references no earlier than 2014. References were screened for eligibility based on the title and abstract.

Of the 38 publications identified from PubMed, a total of eight relevant references20–22 26–28 (three of those referring to one study25–28 ) were identified based on the title and abstract. In addition, two references were identified from hand searches (one poster presentation from the 56th EASD meeting—EASD 202025 and one study protocol29 ). Among these 10 references, eight concerned RCTs and two concerned observational research.

**RANDOMIZED CONTROLLED TRIALS**

**Study characteristics**

The eight papers on RCTs related to glycemic variability in people living with T1D receiving Gla-300 reported results for four trials20–22 26–28 and summarized the methodology for another study, for which the results are not yet available.26–28

Three of the completed studies compared Gla-300 with Gla-10030 31 32 and one compared Gla-300 with insulin degludec U100 (iDeg-100).22 24 All of the RCTs were open label, with two using a parallel-group design20 21 and two using a cross-over design.22 24 The number of participants ranged from 20 to 638 and the duration of treatment periods ranged from 4 to 16 weeks. The main characteristics and results of the RCTs are summarized in table 1.

**Glycemic variability**

The study published by Bergenstal et al was a 16-week, exploratory, open-label, parallel-group, two-period cross-over study, conducted in 59 adults with T1D randomized (1:1:1:1) to once-daily Gla-300 or Gla-100 given in the morning or evening (with a crossover in the injection schedule).20 This study showed there was a significantly lower increase in rCGM-based glucose during the last 4 hours of the 24-hour injection interval for Gla-300 compared with Gla-100 (p=0.0192) and the 24-hour glucose curves were smoother for Gla-300, irrespective of morning or evening injection. Nocturnal-confirmed or severe hypoglycemia rates were lower with Gla-300 versus Gla-100. The trend for less hypoglycemia observed with Gla-300 was also seen in Jinnouchi et al’s25 study. However, there were no significant differences between Gla-300 and Gla-100 for any glycemic variability metrics (assessed using rCGM), including TIR (the primary endpoint), TAR, TBR; total, within-day and between-day SD of mean glucose level; and total, within-day and between-day %CV (table 1).20 21

There were also no significant differences in the main glycemic variability parameters between U100 iDeg-100 and Gla-300 (table 1). The Kobe Best Basal Insulin Study 2 was an 8-week, multicenter, randomized, open-label, cross-over, comparative study involving 46 C-peptide-negative adult outpatients with T1D randomly assigned (1:1) to Gla-300 (first period)/iDeg (second period) or iDeg (first period)/Gla-300 (second period).24 This study found that iDeg-100 was non-inferior to Gla-500 with respect to fasting glucose SD (assessed using SMBG; primary endpoint). There were also no significant differences in CGM-assessed SD, CV, M-value, mean amplitude of glycemic excursions (MAGE), TIR and mean of daily difference (MODD).22 24 With iDeg-100, mean glucose levels were lower than with Gla-300. But this resulted in a longer TBR.

**Upcoming RCT: InRange**

The international InRange study will be the first head-to-head comparison of Gla-300 with iDeg-100 using CGM in an international population26–28 (figure 1). It is a multicenter, randomized, active-controlled, parallel-group, 12-week, open-label, phase IV comparative study. Adults with T1D were randomized to receive once-daily Gla-300 or iDeg-100 by subcutaneous injection in the morning. Following an 8-week titration period, CGM data were collected over 20 consecutive days.

The primary objective is to demonstrate that Gla-300 is non-inferior to iDeg-100 in terms of glycemic control and variability, assessed by CGM. The primary endpoint is percentage time spent in the glucose range of 70–180 mg/dL at week 12. Secondary endpoints include the total, within-day and between-day CV, as well as time below and time above glucose range. It is planned to recruit approximately 338 people with T1D. The preliminary results of this study were published at the International Conference on ATTD (ATTD 2022) and showed that Gla-300 was non-inferior to iDeg-100 on per cent TIR (70–180 mg/dL) and glucose CV, with a lower CV for Gla-300, in patients with T1D. Gla-300 and iDeg-100 had similar hypoglycemia and safety profiles.33

The InRange trial is the first study to use CGM metrics as the primary endpoint to compare the second-generation basal insulin analogs Gla-300 and iDeg-100 in people living with T1D. InRange is expected to provide further insight into the utility of CGM as an outcome measure in clinical practice.

**REAL-WORLD EVIDENCE**

**Study characteristics**

The REtrospective analysiS on pre-existing daTa On glaRgine-300 U/mL in typE 1 patients (RESTORE-1) study performed a retrospective chart review of more than 1000 Italian people living with T1D switching from first-generation basal insulins to Gla-300 or iDeg-100 but had no CGM data available. Treatment with both second-generation analogs was associated with similar improvements in glycemic control, without weight gain. Of note, there were no severe hypoglycemic events for Gla-300 and seven events for I Deg-100 (p=0.02).36
### Table 1  Principal characteristics of RCT publications with data on glycemic variability in individuals with T1D receiving Gla-300

<table>
<thead>
<tr>
<th>Groups</th>
<th>Method</th>
<th>n</th>
<th>Primary outcome</th>
<th>Results (primary outcome)</th>
<th>Other relevant results</th>
</tr>
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<tbody>
<tr>
<td><strong>Comparison of Gla-300 with Gla-100</strong></td>
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<tr>
<td>Jinnouchi et al.</td>
<td>CGM</td>
<td>20</td>
<td>Mean age 52.1 years; mean HbA1c 8.21%</td>
<td>Treatment ratio 0.96 (95% CI 0.79 to 1.16)</td>
<td>HbA1c and FBG stable across periods, trend towards less hypoglycemia during 24 hours and at night with Gla-300, TEAE 45% with Gla-300, 20% with Gla-100 but unrelated to study drug.</td>
</tr>
<tr>
<td><strong>Bergenstal et al.</strong></td>
<td>CGM</td>
<td>59</td>
<td>Mean age 44.2 years; mean diabetes duration 22.1 years; mean HbA1c 7.46%</td>
<td>Mean %TIR (≤80 to ≤140 mg/dL)</td>
<td>TIR similar between groups (31.8% vs 31.0%; p=n.s.)</td>
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<td>Less increase in CGM-based glucose during the last 4 hours of the injection interval (p=0.0192) and 24-hour curves were smoother for Gla-300. Mean %TBR and %TAR, total SD, within-day SD, between-day SD, and SD of daily means similar between groups (p=n.s.). Nocturnal-confirmed or severe hypoglycemia rates were lower with Gla-300 versus Gla-100 (4 vs 9 events per participant year; rate ratio 0.45 (95% CI 0.24 to 0.82)).</td>
</tr>
<tr>
<td>Pettus et al.</td>
<td>CGM</td>
<td>638</td>
<td>Mean age 45.5 years; mean diabetes duration 22.7 years; mean HbA1c 8.0%</td>
<td>Mean %TIR (≤70 to ≤180 mg/dL)</td>
<td>Similar between groups (55.40% vs 55.18%; p=n.s.)</td>
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<td>No difference in TIR, glycemic variability, or the rate of nocturnal symptomatic hypoglycemia. Exploratory: Gla-300 patients with an HbA1c &lt;7.5% at week 16 had greater improvement in TIR total, during day or night. Small increases in hypoglycemia.</td>
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<tr>
<td><strong>Comparison of Gla-300 with iDeg-100</strong></td>
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<tr>
<td>Miura et al.</td>
<td>SMBG and CGM</td>
<td>46</td>
<td></td>
<td>iDeg-100 non-inferior to Gla-300 (mean difference −6.6 mg/dL; p=n.s.)</td>
<td>CGM: SD, CV, M-value, MAGE, TIR and MODD similar between groups (p=n.s.). Mean glycemic value lower for iDeg-100 than Gla-300. TAR (&gt;180 mg/dL) shorter and TBR (&lt;70 mg/dL) longer for iDeg.</td>
</tr>
<tr>
<td>Battelino et al.</td>
<td>CGM</td>
<td>338</td>
<td>Mean %TIR (≤70 to ≤180 mg/dL)</td>
<td>Results not yet reported</td>
<td>Relevant secondary endpoints will include total, within-day and between-day CV, as well as TBR and TAR.</td>
</tr>
</tbody>
</table>

AUC, area under the curve; CGM, continuous glucose monitoring; CV, coefficient of variation in glucose level; FBG, fasting blood glucose; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; HbA1c, glycated hemoglobin; iDeg-100, insulin degludec 100 U/mL; MAGE, mean amplitude of glycemic excursions; MODD, mean of daily difference; n.s., not statistically significant; RCT, randomized controlled trial; SMBG, self-monitoring of blood glucose; T1D, type 1 diabetes; TEAE, treatment-emergent adverse events; TIR, time in range.
To date, the OneCare study is the only RWE study including CGM data for glycemic variability in people living with T1D who were switched from a first-generation basal insulin analog (Gla-100 or detemir) to either Gla-300 or iDeg-100. OneCare was an observational, retrospective, cross-sectional study in Spain analyzing 14 days of consecutive CGM use with data from the FreeStyle Libre device (Abbott), captured 3–24 months after the switch. The primary endpoint was the percentage of TIR (70–180 mg/dL). The main characteristics and results of the studies are summarized in table 2.

Glycemic variability

In OneCare, there were no significant differences between Gla-300 (n=104) and iDeg-100 (n=95) with respect to 24-hour or daytime TIR, TAR and TBR, and nighttime TBR, when assessed using CGM at ≥3 months after switching from Gla-100/insulin detemir (table 2). However, significant differences favoring Gla-300 over iDeg-100 were seen for nighttime TIR (70–140 and 70–180 mg/dL) and TAR (>180 mg/dL). Values for 24-hour CV, average daily risk range, MAGE, LBGI, HBGI, and MODD did not differ between the groups.

Upcoming RWE: COMET-T

COMET-T is a non-interventional, multicenter, prospective RWE study in people living with T1D with insufficiently controlled glucose levels (figure 2). Eligible participants have to be on basal-bolus insulin treatment for at least 3 months without reaching their individual treatment target. Data are collected before and 24 weeks after switch to Gla-300 using a CGM or isCGM system that they also used before. It is planned to include up to 380 people living with T1D recruited in Germany, Austria, and Switzerland.

The primary aim is to document changes in the TIR (70–180 mg/dL) using Gla-300 in combination with any bolus insulin over a 24-week observational period (table 2). A secondary aim is to document the safety and tolerability of Gla-300 in clinical practice. The change in TIR after 24 weeks was defined as the primary endpoint. Secondary endpoints include the TAR defined as >180 mg/dL and the TBR defined as <70 and <54 mg/dL. Further endpoints are the glucose CV with SD, HbA1c, mean fasting blood glucose (FBG) and FBG ≤100 mg/dL, insulin dose (total and basal), body weight, and hypoglycemia.

COMET-T will add to the body of evidence by investigating the effects of a change of basal insulin to Gla-300. The study is performed under real-world conditions and will reflect the effects a physician can expect when changing the basal insulin to Gla-300.

Compared with OneCare, COMET-T is a prospective study (vs retrospective), covers different basal insulins as the reference treatment (vs Gla-100 or iDeg-100), and different CGM devices available in clinical practice (vs FreeStyle Libre only). Furthermore, COMET-T covers an observational period of 24 weeks. In addition, COMET-T adds to the evidence to be provided by InRange as it extends the comparison into different basal insulins and is reflective of daily clinical practice unlike InRange, which only covers a specific population of people with diabetes.

DISCUSSION

Our review of available studies involving Gla-300 found differences in nocturnal glycemic variability between Gla-300 and Gla-100. Jinnouchi et al reported a trend for less hypoglycemia during 24 hours and nighttime with

Figure 1 InRange study design. CGM, continuous glucose monitoring; Gla-300, insulin glargine 300 U/mL; HbA1c, glycated hemoglobin; iDeg-100, insulin degludec 100 U/mL; MDI, multiple daily injection; QD, once daily; SMPG, self-monitored plasma glucose; T1D, type 1 diabetes.
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Results (primary outcome)

Groups Method n

300 with iDeg-100

24 hours: %time in light range (≥70 to <180 mg/dL) (%TIR, >180 mg/dL) and >250 mg/dL) %TBR (%TIR between groups (all p=n.s.).

Gla-300

Daytime: %TIR (52.4% vs 49.3%, p=n.s.)

Night-time: %TIR (26.9% vs 46.2%, p=0.018) and %time in tight range (52.4% vs 46.2%, p=0.018) lower with Gla-300 versus iDeg-100 (40.1% vs 47.2%, p=0.02); %TBR similar between groups.

Gla-300 versus Gla-100.

ADRR, average daily risk range; CGM, continuous glucose monitoring; CV, glucose variability; DTSQ, Diabetes Treatment Satisfaction Questionnaire; FBG, fasting blood glucose; Gla-300, insulin glargine 300 U/mL; HbA1c, glycated hemoglobin; HBGI, high blood glucose index; iDeg-100, insulin degludec 100 U/mL; iDet, insulin detemir; LBGI, low blood glucose index; MAGE, mean amplitude of glycemic excursions; MODD, mean of daily difference; n.s., not statistically significant; RWE, real-world evidence; TIR, time in range.

Figure 2 COMET-T study design. CGM, continuous glucose monitoring; DTSQ, Diabetes Treatment Satisfaction Questionnaire; FBG, fasting blood glucose; Gla-300, insulin glargine 300 U/mL; HbA1c, glycated hemoglobin.

Gla-300 than with Gla-100, potentially being a reflection of the longer durability and less variable effect of Gla-300. This was also observed by the Bergenstal et al, which found a lesser increase in CGM-based glucose during the last 4 hours of the injection interval and a smoother 24-hour curve, irrespective of morning or evening injection. Also, rates of both mild and severe hypoglycemia were reduced by 50% when compared with Gla-100. On the other hand, the primary endpoints of these studies generally indicated equivalence with respect to TIR and 24-hour glucose variability.

Evidence for the relative merits of Gla-300 versus iDeg-100 is limited so far with only the Miura et al and RESTORE-1 data being available. While RESTORE-1 showed less severe hypoglycemia with Gla-300 but had no CGM data available, Miura et al’s study found iDeg-100 being non-inferior to Gla-300 with respect to FBG and other metrics of glucose variability. While lower mean glycemic values were achieved with iDeg-100 when compared with Gla-300, the time below the therapeutic range (<70 mg/dL) was longer with iDeg-100. It is possible these differences in day-to-day glycemic variability between iDeg-100 and Gla-300 are attributable to their different chemical structures impacting on product absorption after injection and the release of insulin monomers into the circulation. Finally, a real-world study comparing iDeg-100 and Gla-300 revealed a more favorable night-time profile of Gla-300 with TIR, time in tight range and the TAR all being higher with Gla-300.

Against this background, both the InRange randomized study and the COMET-T observational real-world study appear timely. InRange was designed to assess differences in the mean percentage in TIR between iDeg-100 and Gla-300 with 338 participants planned to be included. It is larger than the previous study by Miura et al with 46 participants which, moreover, used SMBG rather than CGM metrics as the primary endpoint. As such it may be able to identify potential differences with either drug option with respect to TIR, TBR, TAR, and CV.

COMET-T adds a real-world perspective in addition to the data available from the retrospective OneCare project. In COMET-T, many different basal insulins as the reference points and with a variety of CGM devices allowed. Furthermore, the increased number of participants may allow for subgroup analyses by basal insulin...
and CGM type. Nonetheless, further data both from RCTs and RWE studies are certainly needed to establish CGM metrics for routine clinical use and for the assessment of potential differences between treatment options.

Limitations
There were several limitations associated with this review. First, the scope of this review is limited to studies published up to June 2021 and relevant subsequent studies will not have been included in this review. However, this review provides a valuable summary of the findings up to this point. Second, it was not within the scope of this review to provide analytical critique of the available studies compared with a systematic review. However, the findings of the current review can act as an evidence synthesis tool, providing an evidence-based precursor to conducting a systematic review. Finally, it would be interesting to better understand the impact of these long-acting insulins on diurnal and nocturnal glycemic variability, but this is outside the scope of this current manuscript. Results of further studies, including InRange and COMET-T, may help provide further data on this.

CONCLUSIONS
Glycemic variability assessed by CGM compliments standard parameters of glycemic control like the HbA1c or measurement of FBG. Reduction of glycemic variability may benefit people living with T1D in several ways by reducing the risk of hypoglycemia, improving quality of life and potentially even reducing the risk for long-term complications. Our review of available RCT and RWE studies on the glucose profile in people using Gla-300 versus Gla-100 on the one hand and iDeg-100 on the other revealed that Gla-300 has a longer lasting and less variable action than Gla-100 with a reduced risk of hypoglycemia. While iDeg-100 was associated with lower glucose values but higher TBR in a randomized study, Gla-300 was associated with a higher per cent time in and above the therapeutic range, but no differences during the day in a real-world study. The upcoming InRange and COMET-T will add important information to this body of evidence.

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