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# The continuing quest for better subcutaneously administered prandial insulins: a review of recent developments and potential clinical implications

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## Abstract

The class of rapid-acting insulin analogues were introduced more than 20 years ago to control postprandial plasma glucose (PPG) excursions better than unmodified regular human insulin. Insulins, lispro, aspart and glulisine all achieved an earlier onset of action, greater peak effect and shorter duration of action resulting in lower PPG levels and a reduced risk of late postprandial hypoglycaemia. However, the subcutaneous absorption rate of these analogues still fails to match the physiological profile of insulin in the systemic circulation following a meal. Recent reformulations of aspart and lispro have generated a second generation of more rapid-acting insulin analogue candidates, including fast-acting aspart (faster aspart), ultra-rapid lispro and BioChaperone Lispro. These modifications have the potential to mimic physiological prandial insulin secretion better with an even earlier onset of action with improved PPG control, shorter duration of effect and reduced risk of hypoglycaemia. Recent phase 3 trials in type 1 and type 2 diabetes show that faster aspart and ultra-rapid lispro compared with conventional aspart and lispro, achieved fewer PPG excursions with a small increase in post-meal hypoglycaemia but similar or marginally superior glycated haemoglobin levels, and suggest the need for parallel optimization of basal insulin replacement. Phase 1 trials for BioChaperone Lispro are equally encouraging with phase 3 trials yet to be initiated. Comparative analysis of the clinical and pharmacological evidence for these new prandial insulin candidates in the treatment of type 1 and type 2 diabetes is the main focus of this review.

**KEYWORDS**
clinical trials, hypoglycaemia, insulin therapy, pharmacodynamics, pharmacokinetics, postprandial glucose, type 1 diabetes, type 2 diabetes

## 1 | INTRODUCTION

An essential component in diabetes management is to achieve and maintain good glycaemic control in an attempt to reduce the risk of micro- and macrovascular complications.[1-3] Both fasting plasma glucose and postprandial plasma glucose (PPG) contribute to overall glycaemic control, as assessed clinically by the monitoring of glycated haemoglobin (HbA1c) levels. The greater recognition of the contribution of postprandial hyperglycaemia to elevated HbA1c and consequent risk for diabetes complications highlights the

importance of reducing PPG excursions,[4] which remains a challenging aspect in clinical practice.[5]

The primary aim of subcutaneously administered mealtime-related insulin formulations is to replicate the dynamics of endogenous prandial insulin secretion, thereby controlling PPG excursions.[6] In contrast to unmodified regular human insulin (RHI), the current rapid-acting insulin analogues (insulins lispro, aspart and glulisine), developed more than 20 years ago, through faster subcutaneous absorption, have an earlier onset and shorter duration of action.[7-9] These "first-generation" rapid-acting insulin analogues, when compared with RHI in type 1 diabetes (T1DM) in a multiple daily injection regimen, improve HbA1c by 0.15%[10] and by 0.20%[11] when delivered via subcutaneous insulin pumps. However, when rapid-acting analogues and basal insulin preparations are both optimized, HbA1c decreases by more than 0.3% versus RHI,[12,13] while also decreasing the rate of hypoglycaemia.[13]

The enhanced absorption meant patient convenience was improved, as administration of these analogues closer to, or at mealtimes became possible.[12,13] In current practice, to optimize PPG control the analogues are recommended to be administered up to 20 min before meals or within 20 min after starting a meal.[5,14-16] Despite their enhanced subcutaneous absorption, the physiological mealtime insulin response is not fully replicated, as the tissue barrier still delays insulin entry in blood with consequent elevated PPG.[9,17] Attempts to overcome PPG by increasing the dose resulted in an increased risk of delayed inter-prandial hypoglycaemia. Further improvements are required to simulate endogenous mealtime insulin secretion better[18] and alleviate the inconvenience of anticipating meal timing, content and/or dosing requirements.[5,14-16]

Further adjustments have been made to the pharmaceutical formulations of insulin to match normal prandial insulin secretion better, to control meal-related glucose excursions without increasing the risk of delayed hypoglycaemia.[17,19,20] Initial attempts at a "second generation" of rapid-acting insulin analogues involved the co-administration of recombinant hyaluronidase enzyme (rHuPH20) to insulin lispro, aspart or glulisine thereby disrupting the interstitial matrix of the subcutaneous tissue and facilitating absorption.[21,22] These analogues did not progress into phase 3 clinical trials and the programme was discontinued. Subsequent approaches included altering the excipients with several compounds developed by Biodel (BIOD-100/123/238/250, Albireo Pharma Inc, Boston, Massachusetts); the first (BIO-100) involved adding ethylenediaminetetraacetic acid and citrate to RHI,[23] followed by BIOD-123[24] and BIOD-250[25] with magnesium sulphate added to lispro, which

also reduced discomfort at the local injection site. These excipients acted to destabilize the insulin hexamer enhancing its dissociation into dimers and monomers.[23] This programme has also been discontinued.[26] However, the remaining members of the second generation of rapid-acting insulin analogues that have or are due to enter phase 3 trials, namely fast-acting aspart (hereafter called faster aspart), ultra-rapid lispro and BioChaperone Lispro, are the main focus of this review, describing their individual structure, mechanism of action and pharmacology, along with evidence from their respective phase 1 and 3 clinical studies.

## 2 | SECOND GENERATION RAPID-ACTING INSULIN ANALOGUES

### 2.1 | Structure and mechanism of action

The three candidates differ in terms of primary structure and mechanism of faster absorption (Table 1). Faster aspart contains two additional excipients, niacinamide and L-arginine. The niacinamide acts to increase subcutaneous blood flow to enhance absorption while the amino acid L-arginine serves as a stabilizing agent.[27] Ultra-rapid lispro (LY900014) contains the excipients citrate and treprostinil. The citrate enhances vascular permeability at the injection site, while treprostinil accelerates lispro absorption by increasing local vasodilation with no measurable systemic exposure.[28,29] BioChaperone Lispro contains the excipients citrate and BioChaperone BC222.[30] Citrate increases vascular permeability at the injection site, while BioChaperone BC222 forms a physical complex with insulin protecting it from enzymatic degradation while enhancing both its stability and solubility increasing the rate of hexamer dissociation and monomer absorption from the subcutaneous tissue.

### 2.2 | Pharmacokinetic/pharmacodynamic studies

The pharmacological properties for each of the second-generation rapid-acting analogues have been characterized in a number of phase 1 trials.[31-33] Most of these trials were single-dose studies comparing each treatment with conventional aspart or lispro in subjects with T1DM, administered by either subcutaneous injection or via continuous subcutaneous insulin infusion (CSII). The majority of the faster aspart trials have been published,[34] while results of the trials for ultra-

**TABLE 1** Current second-generation rapid-acting insulin analogues in development

| Drug | Company | Core insulin structure | Added excipients | Mechanism of action |
|---|---|---|---|---|
| Faster aspart[27] | Novo Nordisk, Bagsværd, Denmark | Insulin aspart | Niacinamide (vitamin B3), L-arginine | Increased subcutaneous blood flow |
| Ultra-rapid lispro[28,29] | Eli Lilly, Indianapolis, IN | Insulin lispro | Treprostinil, citrate | Enhanced vascular permeability and increased local vasodilation |
| BioChaperone Lispro[30] | Adocia, Lyon, France | Insulin lispro | BioChaperone BC222,[a] citrate | Enhanced diffusion |

[a]An oligosaccharide modified with natural molecules.

rapid lispro are currently only in abstract form.[29,35-44] Two of the BioChaperone Lispro trials have been published[30,45] with several trials reported as abstracts.[46-51] Key findings from the completed trials are summarized below.

## 2.2.1 | Features following subcutaneous injection

The pharmacokinetics of faster aspart (0.2 U/kg dose) were characterized in a pooled analysis of six studies in 218 adults with T1DM showing that faster aspart was detected in the blood 5 min earlier than aspart with onset of exposure (time to reach 50% of the maximum concentration) 9.5 min earlier and an offset of exposure (time to late half-maximum exposure) 12.2 min earlier (Table 2, Figure 1A).[52] Initial insulin exposure during the first 30 min after administration was two-fold higher with faster aspart. Three 12-h euglycaemic clamp trials characterized the pharmacodynamics of faster aspart.[52] Similar to the pharmacokinetic profile, early glucose-lowering, as measured by the glucose infusion rate (GIR) during the first 30 min was 74% greater for faster aspart (Figure 2A). In meal tests in persons with T1DM, faster aspart (0.2 U/kg) improved PPG when given immediately before a liquid meal (Figure 3A); mean reductions versus aspart during the first 2 h were in the range of 10–26 mg/dL (0.6–1.4 mmol/L) in adults and 4–27 mg/dL (0.2–1.5 mmol/L) in children/adolescents.[53,54]

The pharmacological features of ultra-rapid lispro were characterized in a single-dose study in 36 people with T1DM showing that ultra-rapid lispro was detected in the blood 8.8 min earlier (15.5 vs. 24.3 min) than lispro (Table 2) with a twofold higher insulin exposure over the first 30 min (Figure 1B).[36] Ultra-rapid lispro also showed a greater early glucose-lowering effect, as measured by GIR, when compared with lispro (Figure 2B). In meal tests, ultra-rapid lispro improved PPG control when given immediately before a mixed meal (composition not reported) in persons with either T1DM[36,37,40] or type 2 diabetes (T2DM).[39] Glucose excursions with ultra-rapid lispro were lower by 39%–47% during the first 2 h after the start of this (presumably liquid) meal (Figure 3B).[37,39] In a further multiple comparison study in 68 people with T1DM, time to onset of ultra-rapid lispro exposure occurred earlier than with faster aspart, lispro and aspart (Table 2).[43] Initial insulin exposure during the first 30 min after administration of ultra-rapid lispro was also higher than faster aspart (1.2-fold), lispro (2.9-fold) and aspart (2.4-fold). Offset of exposure occurred earlier than with the other analogues. PPG excursions

**TABLE 2** Key pharmacokinetic and pharmacodynamic results of second-generation rapid-acting insulins versus comparators in subjects with T1DM

| Comparator | Administration | Faster aspart | Ultra-rapid lispro | | | BioChaperone Lispro | | |
|---|---|---|---|---|---|---|---|---|
| | | Aspart | Lispro | Aspart | Faster aspart | Lispro | Aspart | Faster aspart |
| **Pharmacokinetics** | | | | | | | | |
| Onset ($t_{Early50\%Cmax}$) | sc injection | **−9.5 min**[52] | **−8.8**[36] to **−12.5**[43] **min** | **−13.9 min**[43] | **−5.9 min**[43] | **−10.7 min**[a][48] | NR | NR |
| | CSII | **−11.8 min**[55] | **−8.6 min**[40] | NR | NR | NR | **−11.7 min**[30] | −0.7 min[30] |
| Offset ($t_{Late50\%Cmax}$) | sc injection | **−12.2 min**[52] | **−7.0**[36] to **−13.8**[43] **min** | **−21.1 min**[43] | **−9.5 min**[43] | **−28.2 min**[a][48] | NR | NR |
| | CSII | **−35.4 min**[55] | **−12.2 min**[40] | NR | NR | NR | NR | NR |
| Early exposure ($AUC_{30\ min}$) | sc injection | ↑**~2-fold**[52] | ↑**~2.2**[36]- to **2.9**[43]-**fold** | ↑**2.4-fold**[43] | ↑**1.2-fold**[43] | ↑**2.5**[a][48]- to **2.7**[49]-**fold** | NR | NR |
| | CSII | ↑**~3-fold**[55] | ↑**1.5-fold**[40] | NR | NR | NR | NR | NR |
| **Pharmacodynamic** | | | | | | | | |
| Onset ($t_{Early50\%GIRmax}$) | sc injection | **−9.5 min**[52] | **−12.2 min**[b][35] | NR | NR | **−10.0 min**[47] | NR | NR |
| | CSII | **−11.1 min**[55] | NR | NR | NR | NR | **−13.0 min**[30] | +1.3 min[30] |
| Offset ($t_{Late50\%GIRmax}$) | sc injection | **−14.3 min**[52] | 0 min[b][35] | NR | NR | NR | NR | NR |
| | CSII | **−24.0 min**[55] | NR | NR | NR | NR | **−38.2 min**[30] | **−19.6 min**[30] |
| Early effect ($AUC_{GIR,30\ min}$) | sc injection | ↑**~1.7-fold**[52] | NR | NR | NR | ↑**>3-fold**[47] | NR | NR |
| | CSII | ↑**~2-fold**[55] | NR | NR | NR | NR | NR | NR |

Table shows mean time difference versus comparators. Items in **bold** are statistically significant. Table adapted from oral presentation by Tim Heise at American Diabetes Association Symposium on June 25, 2018.

Abbreviations: AUC, area under the insulin concentration curve; CSII, continuous subcutaneous insulin infusion; GIR, glucose infusion rate; NR, not reported; sc, subcutaneous; $t_{Early50\%Cmax}$, time to 50% of maximum insulin concentration in the early part of the pharmacokinetic profile; $t_{Late50\%Cmax}$, time to late half-maximum insulin exposure; T1DM, type 1 diabetes.

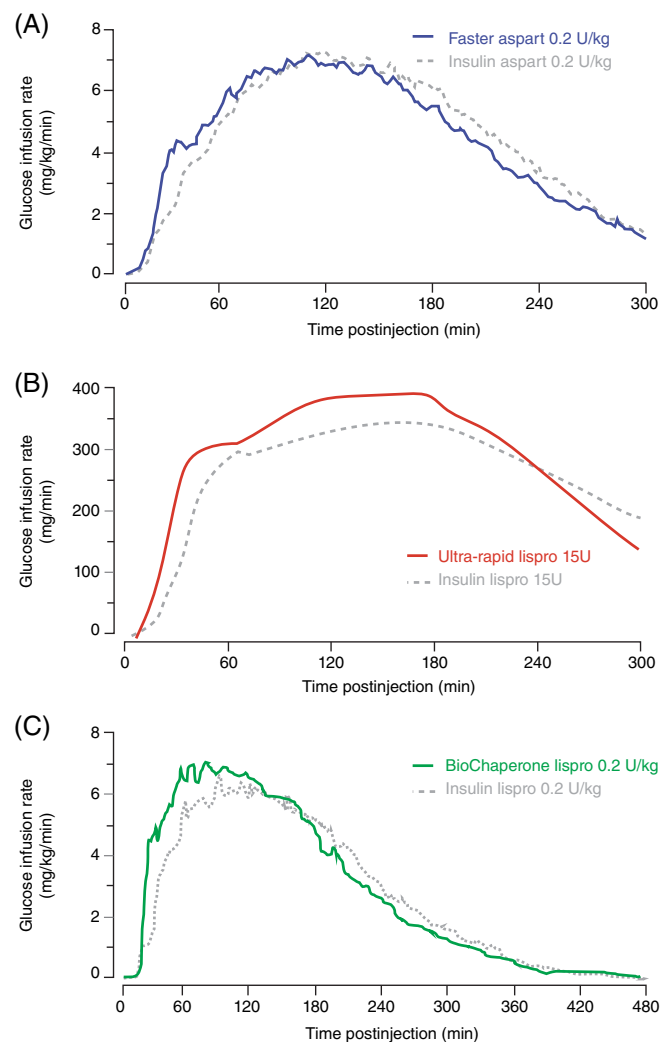[a]Mean data from two studies in patients with T1DM.[48]

[b]In healthy subjects.
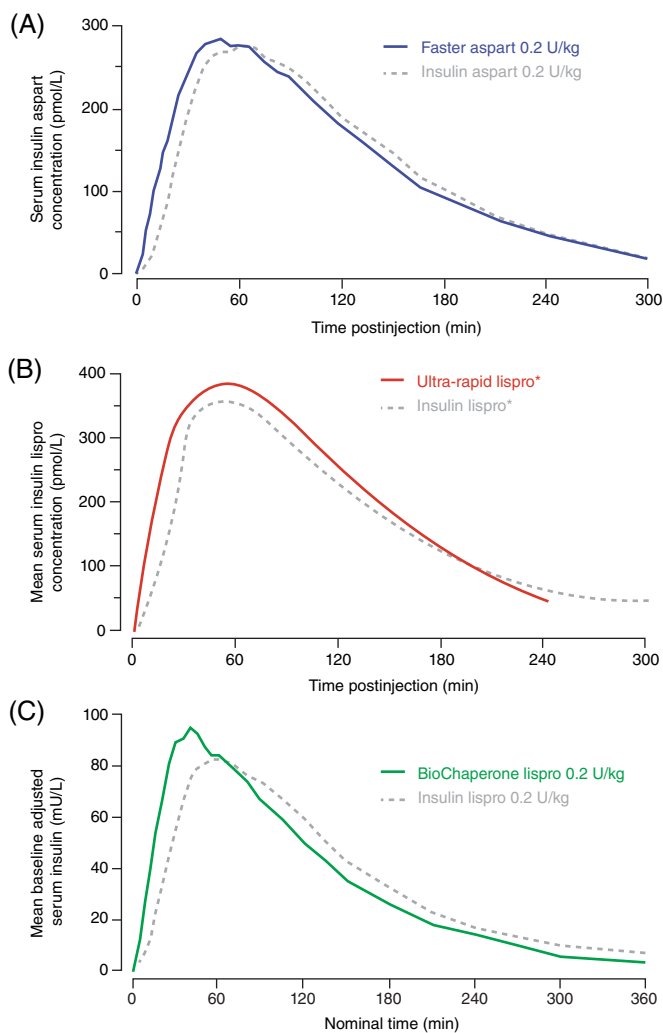
**FIGURE 1** Pharmacokinetic action profiles (serum insulin levels) after subcutaneous injection of (A) faster aspart [adapted from Heise et al[52] under Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/)], (B) ultra-rapid lispro (adapted from Kazda et al[36]) and (C) BioChaperone Lispro (adapted from Andersen et al[47]), all versus insulin aspart or lispro in people with type 1 diabetes. *Dose based on individual insulin-carbohydrate ratios



**FIGURE 2** Pharmacodynamic action profiles (glucose infusion rate) in clamp studies (fasting) after subcutaneous injection of (A) faster aspart [adapted from Heise et al[52] under Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/)], (B) ultra-rapid lispro (adapted from Leohr et al[35]) and (C) BioChaperone Lispro (adapted from Andersen et al[47]), all versus insulin aspart or lispro in healthy volunteers or people with type 1 diabetes

following a liquid meal test (100 g of carbohydrate) were numerically lower with ultra-rapid lispro than faster aspart and significantly lower versus lispro and aspart.

The pharmacokinetics of BioChaperone Lispro (0.2 U/kg) were characterized in a pooled analysis of two studies in 76 adults with T1DM showing that BioChaperone Lispro was detected in the blood 11 min earlier than lispro (Figure 1C) with offset of exposure occurring 28.2 min earlier (Table 2).[48] Initial insulin exposure during the first 30 min after administration was more than twofold higher with BioChaperone.[48] BioChaperone Lispro showed a greater glucose-lowering effect, as measured by GIR, within the first hour compared with lispro (Figure 2C).[47] In standardized liquid (80 g carbohydrate) or individualized solid (50% carbohydrate) meal tests in persons with T1DM[45,49] or T2DM,[50] BioChaperone Lispro reduced glucose

excursions by 22%–61% during the first 2 h compared with lispro (Figure 3C).

## 2.2.2 | Features when used in *continuous subcutaneous insulin infusion (pumps)*

When faster aspart was given via CSII as a bolus of 0.15 U/kg on top of a basal rate of 0.02 U/kg/h, plasma insulin levels were threefold higher than aspart during the first 30 min.[55] Onset of exposure occurred 11.8 min earlier (20.7 vs. 32.5 min) with faster aspart and the glucose-lowering effect during the first 30 min was increased by more than 100%.

When ultra-rapid lispro was given via CSII (bolus dose 15 U, basal dose not reported), insulin exposure [area under the insulin
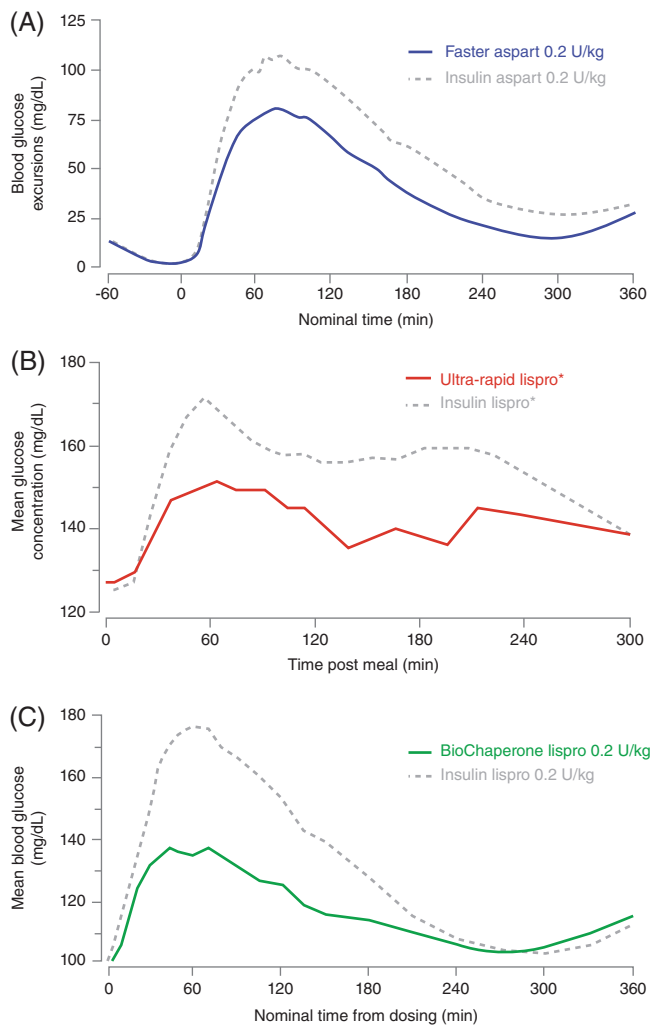
**FIGURE 3** Postprandial blood glucose profiles after subcutaneous injection of (A) faster aspart following a standardized liquid meal (67% carbohydrate, 600 kcal) (adapted from Heise et al[53]), (B) ultra-rapid lispro following a mixed meal (adapted from Kazda et al[36]) and (C) BioChaperone Lispro following a standardized liquid meal (adapted from Andersen et al[49]), all versus insulin aspart or lispro in people with type 1 diabetes. *Dose based on individual insulin-carbohydrate ratios

concentration curve (AUC)] was more than 50% higher than lispro during the first 15 min and the onset of exposure occurred 8.6 min earlier (15.6 vs. 24.1 min) (Table 2).[40]

When BioChaperone Lispro was given via CSII (0.15 U/kg bolus on top of basal rate 0.01 U/kg/h), early insulin exposure (AUC) during the first hour was more than 60% higher than aspart, with offset of exposure occurring 38.2 min earlier (Table 2).[30] In the same study, early insulin exposure during the first hour was 14% higher than faster aspart with offset of exposure occurring 19.6 min earlier.

In summary, despite differences in the structure and mechanism of action, the pharmacokinetic profiles of the three candidates are quite similar (Table 2), demonstrating an earlier and higher peak concentration with a shorter duration of action relative to their predecessors (Figure 1). The differences in onset of action range from 9 to 14 min with an offset of effect in the range of 7–28 min with respect to their

half-maximal metabolic effects (Table 2).[56] This degree of difference is qualitatively similar to that seen previously between the current conventional rapid-acting insulin analogues and RHI. However, none has been compared against insulin glulisine, which has been shown to have a slightly faster onset of action than both aspart and lispro.[57-60]

## 2.3 | Phase 3 clinical trials

Eight phase 3 trials have reported the efficacy and safety of faster aspart (Table 3A).[61-70] Seven phase 3 trials are evaluating the efficacy and safety of ultra-rapid lispro versus lispro,[71-77] with preliminary results for three of these trials reported as abstracts.[71,74,76,78] The phase 3 trial programme for BioChaperone Lispro is yet to be announced.

### 2.3.1 | Trials in adults with type 1 diabetes

Two similarly designed studies compared mealtime faster aspart (administered 0–2 min before a meal) with mealtime aspart in a basal-bolus regimen in a 52-week trial with insulin detemir (Onset 1) and in a 26-week trial with insulin degludec (Onset 8).[61-64] In Onset 1, HbA1c was reduced with faster aspart versus aspart by 0.15% after week 26[61] and by 0.10% at week 52.[62] No significant difference in HbA1c was observed in Onset 8 [estimated treatment difference (ETD) of −0.02% in favour of faster aspart].[63] The rate of severe or blood glucose (BG)-confirmed hypoglycaemia was comparable in both trials. PPG increment at 1-h post-meal in a liquid meal test was reduced with faster aspart versus aspart in both trials at week 26,[61,63] and at week 52 in Onset 1 (see Table 3A for details).[62] When faster aspart was administered within 20 min after meal initiation PPG increment at 1-h post-meal in a meal test was higher versus mealtime aspart in both trials.[61,63] Mean PPG levels based on the results of self-monitored plasma glucose (SMPG) profiles with consumption of solid mixed meals, were reduced with faster aspart across all meals in both trials.[62,63] In the 26-week Onset 8 trial, the self-measured PPG increment at 1 h was also reduced for faster aspart but there was a trend for higher levels at bedtime.[63] Hypoglycaemia within the first hour from meal initiation was increased with faster aspart in Onset 1 at 26 and 52 weeks,[61,62] while in Onset 8, a reduced rate of hypoglycaemia 3–4 h after meal initiation was seen with faster aspart.[63] The cause of the discrepancy between these two studies is not apparent, although the use of different basal insulins may play a role.

A single trial (PRONTO-T1D) compared mealtime ultra-rapid lispro (administered 0–2 min before a meal) with lispro in a basal-bolus treatment regimen (Table 3B).[71,78] The change from baseline in HbA1c after 26 weeks was similar with both treatments (ETD −0.08%, P = 0.06). Administration of ultra-rapid lispro 20 min after the start of a meal was less effective (but still non-inferior) than pre-meal lispro (HbA1c ETD +0.13%, P = 0.003). PPG increment at 1 and 2 h post-meal in a liquid meal test at week 26 (see Table 3B for details) was reduced with ultra-rapid lispro. Similarly, PPG increment at 1 h based

**TABLE 3A**  Key features and results of phase 3 trials comparing mealtime faster aspart with different comparators

| Parameter | T1DM basal-bolus | | | T2DM basal-bolus | | | T1DM pump | |
|---|---|---|---|---|---|---|---|---|
| | Onset 1[61,62] | Onset 8[63,64] | Onset 7[65] | Onset 2[66] | Onset 9[70] | Onset 3[67] | Onset 4[68] | Onset 5[69] |
| Comparator | Aspart | Aspart | Aspart | Aspart | Aspart | Basal insulin only | CSII aspart | CSII aspart |
| Basal insulin used | IDet | IDeg | IDeg | Gla-100 | IDeg | IDet/Gla-100/NPH | – | – |
| Participants (n) | 381 vs. 380 | 342 vs. 342 | 260 vs. 258 | 345 vs. 344 | 546 vs. 545 | 116 vs. 120 | 25 vs. 12 | 236 vs. 236 |
| Duration (weeks) | 52 | 26 | 26 | 26 | 16 | 18 | 6 | 16 |
| **Glycaemic control** | | | | | | | | |
| ΔHbA1c, % | **−0.15** | −0.02 | **−0.17** | −0.02 | −0.04 | **−0.94** | −0.14 | **+0.09**[a] |
| HbA1c <7.0%, OR | 1.47 | 0.88 | 1.33[b] | 1.01 | NR | 9.31 | NR | 0.76 |
| **Meal test** | | | | | | | | |
| Composition | Liquid[c] | Liquid[d], 78 g CHO | Liquid[d], 1.5 g CHO/kg | Liquid, ~80 g CHO | Liquid[c] | NA | NA | Liquid[c] |
| Consumption time | ≤12 min | ≤12 min | NR | ≤12 min | NR | NA | NA | ≤12 min |
| ΔPPG$_{1\text{-}h}$ mmol/L | **−1.18** | **−0.90** | NS[d] | **−0.59** | **−0.40** | NA | NA | **−0.91** |
| ΔPPG$_{2\text{-}h}$ mmol/L | −0.67 | −0.35 | NS[d] | −0.36 | −0.30 | NA | NA | **−0.90** |
| **SMPG** | | | | | | | | |
| ΔPPG$_{1\text{-}h}$ mmol/L | NR | **−0.48**[e] | **−0.93**[f] | NR | **−0.25**[f] | **−1.14**[e] | NR | **−0.46**[e,f] |
| ΔPPG$_{2\text{-}h}$ mmol/L | −0.25[e] | NR | NR | NR | NR | **−2.48**[e] | −0.77[f,g] | NR |
| PPG$_{2\text{-}h}$ ≤ 7.8 mmol/L, OR | 1.33 | **1.54**[h] | NR | 1.18 | NR | 41.9 | NR | NR |
| PPG$_{2\text{-}h}$ ≤ 7.8 mmol/L without SH, OR | NR | NR | NR | 1.23 | NR | 44.2 | NR | NR |
| **Hypoglycaemia** | | | | | | | | |
| Overall[i], RR | 1.01 | 0.84 | 1.11 | 1.09 | **0.81** | 8.24 | 0.98[j] | 1.00 |
| PM within 1 h, RR | **1.48** | 1.09 | NS | 1.29 | 1.16 | NR | NR | **1.78** |
| PM within 2 h, RR | NR (NS)[k] | **0.75**[l] | NS | **1.60** | 0.97 | NR | NR | NR (NS) |

Table shows mean difference versus comparators. Confidence intervals around point estimates are not shown for simplicity. Items in **bold** are statistically significant.

Abbreviations: -, no basal insulin; Δ, change; aspart, insulin aspart; CHO, carbohydrate; ΔHbA1c, ETD in mean ΔHbA1c from baseline (%); ΔPPG$_{1\text{-}h}$, ETD in 1-h PPG increment; IDeg, insulin degludec; IDet, insulin detemir; ETD, estimated treatment difference; Gla-100, insulin glargine 100 U/mL; NA, not applicable as no meal test was performed in the study; NR, not reported; NS, no statistically significant difference; OR, estimated odds ratio; PM, post-meal; PPG, postprandial glucose; RR, rate ratio; SH, severe hypoglycaemia; SMPG, self-monitored plasma glucose; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

[a] P < 0.02 in favour of aspart, P < 0.001 for non-inferiority of faster aspart versus aspart.
[b] Odds of achieving HbA1c <7.5%.
[c] 78–80 g CHO (Ensure, Abbott Nutrition, Columbus, Ohio).
[d] Meal test performed in a subgroup of subjects from selected sites aged ≥8 years at screening.
[e] Estimated change from baseline in mean PPG increments (SMPG profiles).
[f] Based on PPG increment across all meals.
[g] Converted from mg/dL to mmol/L using the conversion factor 0.0555.
[h] OR of 1-h PPG ≤7.8 mmol/L.
[i] Hypoglycaemia defined as severe or blood glucose confirmed (<3.1 mmol/L [56 mg/dL]) events.
[j] After adjusting for imbalance in severe or blood glucose-confirmed hypoglycaemia in the run-in period.
[k] Meal-related hypoglycaemia within 2 h after meal.
[l] During period 1–2 h after meal.

on SMPG was reduced with ultra-rapid lispro at breakfast, with no difference at midday or following the evening meal. Severe, over-all and early (≤4 h) postprandial BG-documented hypoglycaemia was similar between treatments with fewer episodes observed with mealtime ultra-rapid lispro in the late (>4 h) postprandial period.

## 2.3.2 | Trials in children and young persons with type 1 diabetes

A single trial (Onset 7) in children and young persons (1–17 years) compared faster aspart with aspart in a basal-bolus regimen.[65] HbA1c was reduced with faster aspart versus aspart by 0.17% at week 26 with a comparable rate of severe or BG-confirmed hypoglycaemia. PPG increment at 1 h based on the SMPG profile was reduced with faster aspart at breakfast, dinner and across all meals (0.93 mmol/L improvement). Administration of post-meal faster aspart was less effective (but still non-inferior) than aspart with the 1-h PPG incre-ment from SMPG across all meals also slightly worse than aspart (+0.43 mmol/L). No studies are available with ultra-rapid lispro or BioChaperone Lispro.

## 2.3.3 | Trials in type 2 diabetes

Two studies compared mealtime faster aspart with aspart in a basal-bolus regimen in a 26-week trial with insulin glargine 100 U/mL (glargine-100) (Onset 2)[66] and in a 16-week trial with insulin degludec (Onset 9).[70] No significant difference in HbA1c at the end of treat-ment was observed in either trial (ETD −0.02% in Onset 2, −0.04% in Onset 9; both in favour of faster aspart). The rate of severe or BG-confirmed hypoglycaemia was comparable in the 26-week trial, but significantly lower for faster aspart in the 16-week trial. PPG incre-ment at 1 h post-meal in liquid meal tests at the end of each trial was reduced with faster aspart. However, PPG across all daily meals based on the SMPG was comparable in the 26-week trial but significantly lower in the 16-week trial (along with a reduced 1-h PPG increment after lunch and the evening meal) for faster aspart. The improved PPG control in the 16-week trial was counter-balanced by an increase in early (0–2 h) post-meal hypoglycaemia.

A further 18-week trial evaluated the addition of faster aspart versus placebo to basal insulin and metformin (Onset 3).[67] As expected, a significant improvement in HbA1c (ETD −0.94%) and self-monitored 2-h PPG across all meals was seen with the basal-bolus using faster aspart versus basal insulin only.

A single trial (PRONTO-T2D) has compared mealtime ultra-rapid lispro with lispro in a basal-bolus regimen (Table 3B).[76] HbA1c was reduced with both treatments by a similar amount after 26 weeks (ETD +0.06%) with a comparable rate of severe or BG-confirmed hypoglycaemia. PPG increment at 1 and 2 h post-meal in a liquid meal test at week 26 was reduced with ultra-rapid lispro, with the benefits extending out to 4 h. PPG increment at 1 and 2 h and daily mean PPG

**TABLE 3B** Key features and results of reported phase 3 trials comparing mealtime ultra-rapid lispro with mealtime lispro

| Parameter | T1DM basal-bolus PRONTO-T1D[71,78] | T2DM basal-bolus PRONTO-T2D[76,79] |
|---|---|---|
| Comparator | Mealtime lispro | Mealtime lispro |
| Basal insulin used | Gla-100/IDeg | Gla-100/IDeg |
| Participants (n) | 451 vs. 442 | 336 vs. 337 |
| Duration (weeks) | 26 (52) | 26 |
| Glycaemic control | | |
| Δ HbA1c (%) | −0.08 | +0.06 |
| Meal test[a] | | |
| Composition | Liquid[a], ~100 g CHO (~57% kcal) | Liquid[a] |
| Consumption time | NR | NR |
| $\Delta PPG_{1-h}$, mmol/L | **−1.55** | **−0.66** |
| $\Delta PPG_{2-h}$, mmol/L | **−1.73** | **−0.96** |
| $\Delta PPG_{3-h}$, mmol/L | **NR (P < 0.001)** | **NR (P < 0.001)** |
| $\Delta PPG_{4-h}$, mmol/L | **NR (P < 0.05)** | **NR (P < 0.05)** |
| Hypoglycaemia rate[b] | | |
| Documented, RR | 0.92 | 1.02 |
| Post-meal ≤1 h, RR | 1.16 | 1.14 |
| Post-meal ≤2 h, RR | 1.11 | 1.33 |
| Post-meal >1 to ≤2 h, RR | 1.07 | **2.31** |
| Post-meal >2 to ≤4 h, RR | 1.01 | **1.44** |
| Post-meal ≤4 h, RR | 1.06 | NR |
| Post-meal >4 h, RR | **0.62 (P < 0.001)** | 0.95 |

Table shows mean difference versus mealtime lispro. Confidence intervals around point estimates are not shown for simplicity. Items in **bold** are statistically significant.
Abbreviations: Δ, change; lispro, insulin lispro; ΔHbA1c, ETD in mean HbA1c Δ from baseline (%); $\Delta PPG_{1-h}$, ETD in 1-h PPG increment; IDeg, insulin degludec; ETD, estimated treatment difference; Gla-100, insulin glargine 100 U/mL; NR, not reported; PPG, postprandial glucose; RR, relative rate; SH, severe hypoglycaemia; SMPG, self-monitored plasma glucose; T1DM, type 1 diabetes; T2DM, type 2 diabetes.
[a]Standardized liquid mixed meal tolerance test (MMTT).
[b]Hypoglycaemia defined as blood glucose documented [<3.0 mmol/L (54 mg/dL)] events with or without symptoms.

levels/excursions based on the SMPG profile were reduced with ultra-rapid lispro.[79]

## 2.3.4 | Trials in pumps and closed-loop systems

Two trials (Onset 4 and 5) evaluated the use of faster aspart versus aspart when delivered via CSII pumps. Pump compatibility of faster aspart over 6 weeks in terms of the risk of catheter occlusions was

investigated in 37 persons with T1DM.[68] Although there was a trend towards better glycaemic control with faster aspart and a similar risk of hypoglycaemia, unexplained hyperglycaemia and premature infusion set changes (<72 h) were more common. There were 21 premature infusion-set changes in 11 (44%) of the faster aspart users compared with four in two (17%) of the aspart users.[80] Only one-third of those in the faster aspart group could be attributed to purely technical issues (e.g. empty reservoir, kinked or dislodged infusion-set tubing) compared with three-quarters explainable in aspart users. No confirmed cases of microscopic occlusions of the infusion sets (Quick-Set® or Silhouette® [Medtronic, Northridge, CA]) were seen when faster aspart (25 persons) or aspart (12 persons) were used in connection with a MiniMed Paradigm® (Medtronic, Northridge, California) pump.

In the larger Onset 5 trial, the change from baseline in HbA1c after 16 weeks was slightly in favour of aspart (ETD 0.09%, $P < 0.02$) with a comparable rate of severe or overall BG-confirmed hypoglycaemia.[69] PPG increment at 1 and 2 h post-meal in a liquid meal test at 16 weeks was reduced with faster aspart. Changes from baseline in 1- and 2-h interstitial glucose (IG) increments assessed by continuous glucose monitoring were also significantly lower with faster aspart across all meals. However, the proportion of IG values in the target range of 4–10 mmol/L (71–180 mg/dL) was the same in each treatment group. Nocturnal, pre-meal and 4 h post-meal (particularly the evening meal) IG levels were higher with faster aspart. It was postulated that the elevated nocturnal IG levels with faster aspart might have been because of suboptimal pump settings for the evening meal bolus, lack of basal insulin compensation because of the shorter bolus insulin action, or suboptimal basal insulin rates at night.[81] Hypoglycaemia within the first hour from meal initiation was increased with faster aspart. Similar to Onset 4, a higher number of participants on faster aspart experienced events related to infusion-site reactions versus aspart {5.5% of participants [0.29 events/patient-years of exposure (PYE)] vs. 3.8% of participants (0.18 events/PYE), respectively}. In addition, a greater number of participants required non-regular change of the infusion set [45.8% of participants (2.76 events/PYE) vs. 31.8% of participants (2.87 events/PYE), respectively].

Two small trials have reported on the use of faster aspart in closed-loop delivery systems. The first trial in 20 participants with T1DM showed a similar proportion of time in target range (primary endpoint) versus aspart.[82] A further study in 15 adults with T2DM showed that faster aspart achieved comparable glucose control (time in target range) vs aspart although a higher dose of faster aspart was required to achieve this outcome.[83]

Two trials (PRONTO-Pump and PRONTO-Pump 2) are evaluating ultra-rapid lispro use via CSII pumps.[74,75] Pump compatibility of ultra-rapid lispro versus lispro over 6 weeks in terms of the rate of infusion set failures (premature infusion set changes because of a pump occlusion alarm or unexplained hyperglycaemia) was investigated in 49 persons with T1DM (PRONTO-Pump).[74] Although there was no difference in the rate of infusion set failures between the two treatments, premature infusion set changes (≤72 h) were more common with the use of ultra-rapid lispro. There were 77 premature infusion-

set changes in ultra-rapid lispro users versus 52 in lispro users (aggregate rate: 1.13 vs. 0.78 events per 30 days, $P = 0.028$). A trend towards better glycaemic control with ultra-rapid lispro during the 6 weeks was observed with no difference in the risk of hypoglycaemia. The results of the PRONTO-Pump 2 study are not yet available.[75]

## 2.4 | Regulatory status

Faster aspart was approved in 2017 in Europe and the USA for use in adults with diabetes,[84,85] and subsequently in both regions for use in children or adolescents aged ≥1 year. Prescribing guidelines recommend faster aspart should be given immediately before a meal, although it may be given up to 20 min after starting a meal if necessary.[85,86] Faster aspart is also approved in Europe and the USA for CSII by external delivery systems.[85,86] Regulatory applications for ultra-rapid lispro have been submitted in Europe and Japan, and were intended in the USA in late 2019.[87]

## 3 | WHAT IS THE POTENTIAL ROLE FOR THE SECOND-GENERATION OF RAPID-ACTING INSULINS?

Faster aspart is the first and most extensively investigated of the three newer rapid-acting insulins and the only one currently approved for clinical use. Trials in patients with T1DM show a significant improvement in PPG increment at 1 h (mean decrease −0.90 to −1.18 mmol/L) compared with aspart.[61,63,69] The limitation of the liquid meal tests in these trials should be noted as in real-life, solid mixed meals are more commonly consumed with a slower and more prolonged absorption period. The observed improvement in the 1 to 2-h PPG increment is sometimes offset by a slightly higher 4-h PPG (Onset 5), suggesting a need for optimizing the basal insulin and/or adjusting the prandial insulin during an extended inter-prandial period. This is conceptually similar to what was observed more than 20 years ago with the introduction of rapid-insulin analogues.[13,88] Trials in people with T2DM show a similar but lesser, yet statistically significant, reduction in the 1-h PPG increment (mean decrease −0.40 to −0.59 mmol/L) compared with aspart.[66,70] Despite reducing PPG levels in the trials reported, the overall glucose-lowering ability of faster aspart compared with aspart (based on HbA1c levels) was comparable in T2DM[66,70] or slightly better in T1DM.[61-63,65] SMPG profile data in several trials indicate that faster aspart has a minimal effect on reducing PPG after mixed meals. It could be that the duration of increased bioavailability in the early phase of their absorption is too short with mixed meals thereby exposing patients to late postprandial hyperglycaemia 3–4 h after meals. Several studies observed a slight increase in hypoglycaemia within the first 1–2 h following pre-meal faster aspart,[61,62,66,69] although other studies showed no difference in the risk. In this regard, the possible risk of early hypoglycaemia in individual patients should be considered in relation to meal composition,

thereby placing the patient at the centre of controlling postprandial glycaemic excursions with glucose monitoring.[16]

Preliminary data for ultra-rapid lispro from two phase 3 trials have recently been presented. In people with T1DM, ultra-rapid lispro improved PPG increment at 1 h (mean decrease −1.55 mmol/L) in a liquid meal test compared with lispro. Similarly, in persons with T2DM, a lesser, although significant, improvement in the 1-h PPG increment (−0.66 mmol/L) was observed. In both trials, PPG excursions with ultra-rapid lispro were significantly lower within 30 min and persisted for up to 4 h after the test meal. Despite reducing PPG levels, HbA1c levels were comparable with lispro in both populations. Safety data reported to date do not indicate an increase in postprandial hypoglycaemia risk compared with lispro. The limited data currently presented preclude comparison with the data for faster aspart.

Each of the phase 3 clinical studies comparing faster aspart or ultra-rapid lispro with aspart/lispro have generally given each drug just before the meal (0–2 min), although some studies had a third group with the faster-acting analogues given post-meal. No study has compared the current rapid-acting insulins (aspart/lispro/glulisine) given 15–20 min before the meal with the new faster-acting analogue given at the time of the meal (0–2 min). In this situation, the faster-acting analogue might not demonstrate superior 1 and 2-h PPG control. Similarly, it is not known whether the risk of hypoglycaemia with aspart/lispro/glulisine given 15–20 min before the meal is similar or lower than the faster-acting analogues given with a meal.

CSII is an increasingly popular and effective method of subcutaneous insulin administration.[56] Insulins with a faster onset and offset of glucose-lowering effect are particularly attractive in a CSII setting to improve PPG control further while limiting the risk of late post-meal hypoglycaemia.[89] However, the results of the two clinical trials of faster aspart appear to suggest that this analogue is less stable and has a higher occlusion rate of CSII catheters than aspart. The cause of this lower physico-chemical stability is currently being explored and in view of the uncertainty about a more frequent need to replace the infusion sets and a lack of practical guidance on the optimal use of faster aspart,[81] the current rapid-acting insulin therapies could probably remain the preferred analogues for use in CSII. Limited data have so far been presented for ultra-rapid lispro.[74] Neither insulin has been evaluated in children or young persons with diabetes. The potential that these new rapid-acting insulins could improve the performance of closed-loop automated insulin delivery systems (e.g. the artificial pancreas) remains of great interest,[90] with ongoing trials evaluating their use in this environment.

# 4 | CONCLUSIONS

The new second-generation of rapid-acting insulin analogues described in this review have applied different modifications in pharmaceutical formulation to enhance further the rate of subcutaneous absorption of the insulin, which is an attempt to achieve better control of PPG when compared with their predecessors. This has been successfully achieved. However, there is only a minimal improvement in overall glycaemic control (HbA1c), and no lesser risk of inter-prandial hypoglycaemia as observed in a limited number of long-term studies in persons with T1DM and T2DM. To achieve optimal glycaemic control, individualized adjustments of basal insulin (subcutaneous bolus or CSII) and/or additional small boluses of the faster-acting insulin analogue may also be required to accommodate prolonged inter- or postprandial periods. Because the majority of trials evaluating PPG excursions have used liquid meals, additional information is required for solid meals with different compositions mimicking real-life conditions.

Future studies are needed to answer the question as to which patients would benefit most from these new insulin analogues, as compared with those who would not. At present, it is tempting to speculate that the newer rapid-acting insulin analogues would be of particular value for individuals with marked post-breakfast hyperglycaemia, because of the dawn phenomenon[91] and/or insulin resistance, individuals on corticosteroids, fertile women in the second half of the menstrual cycle and those individuals who regularly or intermittently consume meals with a high content of refined carbohydrates. On the other hand, there are limited data available on the benefit of these new insulins in people experiencing delayed gastric emptying who may be at greater risk of hypoglycaemia soon after their meals. In addition, it is also important to recognize the possible need to optimize basal insulin supplementation, when introducing these newer prandial insulins. Therefore, future trials should clarify their role in various clinical scenarios typically encountered in daily clinical practice. Their application in CSII devices also remains at an early phase with compatibility issues to be clarified.

## AUTHOR CONTRIBUTIONS
Both authors contributed equally to the literature search, interpretation and writing of this review. Both authors approved the final submitted version.

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