



Fast-Acting Insulin Aspart: A Review of its Pharmacokinetic and Pharmacodynamic Properties and the Clinical Consequences

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Abstract

Fast-acting insulin aspart (faster aspart) is insulin aspart (IAsp) with two added excipients, L-arginine and niacinamide, to ensure formulation stability with accelerated initial absorption after subcutaneous administration compared with previously developed rapid-acting insulins. The pharmacokinetic/pharmacodynamic properties of faster aspart have been characterised in clinical pharmacology trials with comparable overall methodology. In subjects with type 1 (T1D) or type 2 (T2D) diabetes, the serum IAsp concentration–time and glucose-lowering effect profiles are left-shifted for faster aspart compared with IAsp. In addition, faster aspart provides earlier onset, doubling of initial exposure, and an up to 2.5-fold increase in initial glucose-lowering effect within 30 min of subcutaneous injection, as well as earlier offset of exposure and effect. Similar results have been shown using continuous subcutaneous insulin infusion (CSII). The improved pharmacological properties of faster aspart versus IAsp are consistent across populations, i.e. in the elderly, children, adolescents and the Japanese. Thus, the faster aspart pharmacological characteristics more closely resemble the mealtime insulin secretion in healthy individuals, giving faster aspart the potential to further improve postprandial glucose control in subjects with diabetes. Indeed, change from baseline in 1-h postprandial glucose increment is in favour of faster aspart versus IAsp when used as basal-bolus or CSII treatment in phase III trials in subjects with T1D or T2D. This review summarises the currently published results from clinical pharmacology trials with faster aspart and discusses the potential clinical benefits of faster aspart compared with previous rapid-acting insulin products.

1 Introduction

In patients with diabetes, postprandial glucose (PPG) reduction constitutes an important aspect in optimising overall glycaemic control and reaching glycaemic targets [1, 2]. In healthy individuals, insulin secretion occurs immediately after meal ingestion, thereby controlling PPG [3]. To address postprandial hyperglycaemia, the aspiration for patients with diabetes is a mealtime insulin with an absorption profile that mimics the endogenous postprandial insulin secretion in the healthy state [4–6].

Rapid-acting insulin is used in patients with type 1 diabetes (T1D) in basal-bolus treatment regimens or administered via continuous subcutaneous insulin infusion (CSII), and in patients with type 2 diabetes (T2D) who need to intensify

Key Points

Despite the advantages of rapid-acting insulins over regular human insulin with respect to pharmacokinetic/pharmacodynamic properties, there is still a need for accelerated insulin absorption and action to better mimic mealtime insulin secretion in the healthy state.

Faster aspart provides an overall left-shift of the pharmacokinetic/pharmacodynamic profiles resulting in earlier onset, twice as large initial exposure, and up to 2.5-fold greater initial glucose-lowering effect within the first 30 min, as well as earlier offset of exposure and effect compared with insulin aspart.

In phase III trials, the better resemblance of faster aspart pharmacological characteristics to healthy endogenous mealtime insulin secretion has been shown to lead to improved postprandial glycaemic control in subjects with diabetes relative to previously developed rapid-acting insulins.

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treatment by adding mealtime insulin to basal insulin plus oral antidiabetic drugs (OADs) [7]. Previously developed rapid-acting insulins (insulin aspart [IAsp], insulin lispro and insulin glulisine) provide faster absorption and earlier onset of glucose-lowering effect, leading to improved PPG control versus regular human insulin [8, 9]. However, their absorption rates are insufficient to optimise postprandial glycaemia when insulin administration occurs at meal initiation [10, 11]. Rather, the greatest PPG reduction is obtained when administering these insulin products 15–30 min before a meal [10, 11]. In line with approved labelling, and presumably for simplicity and practical reasons, many patients with diabetes employ only a limited or no interval between insulin administration and meal initiation [12]. Thus, there is a clinical need for mealtime insulins with ultra-fast absorption properties to further minimise the gap relative to meal-related insulin secretion in the healthy state.

Fast-acting IAsp (faster aspart) is IAsp in a new formulation developed to achieve accelerated initial absorption after subcutaneous administration compared with previously developed rapid-acting insulins [13–15]. The

pharmacological properties of faster aspart have been characterised in several clinical pharmacology trials [16–27]. Moreover, phase III trials have investigated the efficacy and safety of faster aspart versus IAsp in subjects with T1D or T2D [28–35]. This review summarises the results from clinical pharmacology trials with faster aspart and relates these findings to the clinical benefits associated with faster aspart compared with IAsp based on outcomes from the phase III trials.

2 Faster Aspart

Faster aspart is a new formulation of IAsp (NovoRapid®/NovoLog®), an analogue of human insulin where the proline in position B28 has been substituted with aspartate. Compared with IAsp, faster aspart was modified by adding two excipients—niacinamide (vitamin B₃) to increase the absorption rate following subcutaneous administration, and L-arginine (an amino acid) to ensure formulation stability. In the original IAsp formulation, most IAsp molecules exist as hexamers, which are too large to be easily absorbed [13]. Under conditions simulating the pharmaceutical formulation or the subcutaneous depot, niacinamide increases the fraction of the more readily absorbable IAsp monomers, thereby partly eliminating the absorption rate-limiting step of hexamer dissociation into monomers [13]. Accordingly, niacinamide promotes the trans-endothelial transport of IAsp [13]. Furthermore, studies in pigs indicate that niacinamide may increase skin blood flow via transient, local vasodilatation,

which could also promote absorption of IAsp molecules after subcutaneous administration [13].

Niacinamide and L-arginine are both included in the US FDA database of inactive ingredients in products for injection at higher concentrations than those occurring in faster aspart, and in the generally recognised as safe (GRAS) food substance database [36, 37]. Over several decades, studies with pharmacological doses of oral niacinamide in humans have shown a good safety profile [38]. Any local adverse effects of niacinamide at the injection site are unlikely since the half-life of niacinamide disappearance from the subcutaneous depot in pigs was shown to be only ~5 min [13]. The amino acid L-arginine occurs naturally in protein-rich food, and supplementation up to 5–10 times the average daily dietary intake is safe and well tolerated [39].

Before choosing the faster aspart formulation intended for further clinical development, systematic pharmacokinetic assessment of various formulations was undertaken in humans to reach an informed decision on the optimal formulation, while balancing absorption rate and formulation stability [27]. Niacinamide positively affects the absorption rate, partly through increased monomerization [13], which, however, also adversely affects formulation stability. In contrast, another excipient, zinc, increases oligomerization of insulin, and therefore negatively impacts the absorption rate, but is important in ensuring formulation stability [40]. Figure 1 shows a conceptual model based on clinical pharmacokinetic data describing how the rate of absorption depends on varying concentrations of niacinamide and zinc in the faster aspart formulation. Several faster aspart formulations with different combinations of niacinamide and zinc concentrations were tested in a clinical pharmacology trial, and,

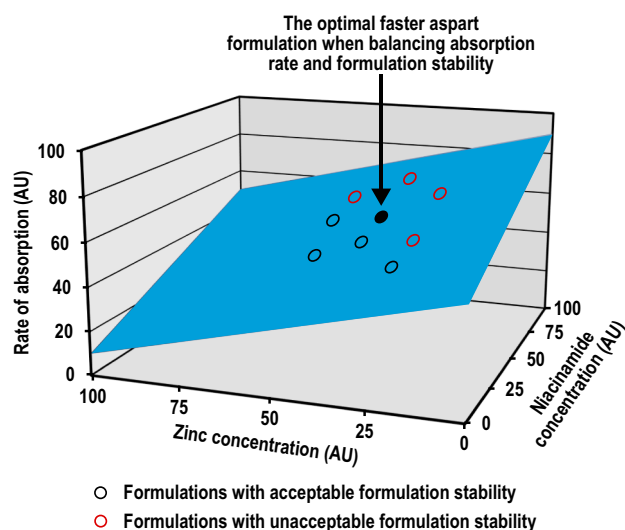


Fig. 1 Conceptual model showing the effect of varying zinc and niacinamide concentrations in the faster aspart formulation on the rate of absorption after subcutaneous administration. AU arbitrary units

among those with acceptable formulation stability, the one with the fastest absorption rate was chosen for further development. Recent investigations suggest that L-arginine also contributes to improved insulin stability through reduced insulin aggregation at high ionic strength [41].

3 Methodology

This review includes 12 clinical pharmacology trials [16–27] and 10 other clinical trials (most of them part of the Onset phase III clinical development programme) [28–35, 42, 43] with faster aspart, identified by PubMed searches for the terms ‘faster aspart clinical trial’ and ‘faster acting insulin aspart onset’, as well as a ClinicalTrials.gov search for phase I trials using the term ‘faster aspart’. To be included in this review, it was required that trials had been published in article form, however with two exceptions, where inclusion was assessed highly relevant for the completeness of the review [27, 33].

Across the trials characterising the faster aspart pharmacological properties, the overall design and methodology were standardised as much as possible, while allowing minor variations depending on the specific trial population and objectives. To ensure consistency regarding experimental procedures and data analysis, all trials were single-centre trials and few sites were involved throughout the faster aspart clinical pharmacology programme. All trials were single-dose trials, and IAsp was consistently included as a comparator, where relevant.

3.1 Pharmacokinetics

Blood samples were collected immediately before dosing and at frequent predefined time points until 12 h after dosing in most trials to capture the full duration of exposure in all subjects. In all trials, free serum IAsp concentrations were measured using a validated IAsp-specific enzyme-linked immunosorbent assay following polyethylene glycol (PEG) precipitation. In selected trials, total serum IAsp concentrations were measured using the same IAsp assay without PEG precipitation [21].

3.2 Pharmacodynamics

In most faster aspart clinical pharmacology trials, the glucose-lowering effect was evaluated in a euglycaemic glucose clamp using either ClampArt (Profil, Neuss, Germany) [19, 20, 24], Biostator (MTB Medizintechnik, Amstetten, Germany) [18], STG-22 glucose-controlled insulin infusion system (Artificial Endocrine Pancreas; NIKKISO Co. Ltd., Tokyo, Japan) [25] or a manual clamp [17]. To avoid interference from endogenous insulin on the glucose clamp

results, subjects with T1D were included in all clamp trials, except one specifically conducted to investigate the pharmacological properties of faster aspart in subjects with T2D [17]. To minimise endogenous insulin secretion, the clamp blood glucose (BG) target level was lower in subjects with T2D (5.0 mmol/L) [17] than in those with T1D (5.5 mmol/L) [18–20, 24, 25]. Still, as with all other clamp studies in subjects with T2D, there is a risk of endogenous insulin secretion, which may complicate the interpretation of the study results [44]. In two clinical pharmacology trials [22, 23] and in several phase III trials [28–33], a standardised 4–6 h meal test was conducted to assess PPG excursion with faster aspart versus IAsp. In all trials to assess the pharmacodynamics of faster aspart, the subject’s usual insulin was replaced and all insulin was terminated in due time to avoid any interference from exogenous insulin on the pharmacodynamic results.

4 Pharmacokinetics of Faster Aspart

The pharmacokinetics of faster aspart versus IAsp after subcutaneous injection were investigated in a pooled analysis of 218 adults with T1D based on six clinical pharmacology trials [16] and in 61 subjects with T2D based on one clinical pharmacology trial [17]. The pharmacokinetic profile was shifted to the left with faster aspart versus IAsp consistently across subjects with T1D or T2D (Fig. 2), suggesting that the faster aspart pharmacokinetic profile more closely mimics healthy endogenous insulin secretion relative to previously developed rapid-acting insulins.

4.1 Onset and Early Exposure

In the pooled analysis of adults with T1D, onset of appearance occurred ~5 min earlier, time to 50% of maximum concentration in the early part of the pharmacokinetic profile ($t_{\text{Early } 50\% C_{\text{max}}}$) was ~10 min shorter, and time to maximum concentration (t_{max}) was 7 min shorter for faster aspart versus IAsp (Fig. 3a) [16]. Throughout the faster aspart clinical pharmacology trials, onset of appearance, $t_{\text{Early } 50\% C_{\text{max}}}$ and t_{max} were used to assess the onset of exposure. Onset of appearance was defined as the time from dosing until the first serum IAsp concentration ≥ 10 pmol/L (the assay lower limit of quantification) and best reflects the true onset, whereas $t_{\text{Early } 50\% C_{\text{max}}}$ and t_{max} represent a composite of time to onset and rate of absorption [45]. Nevertheless, $t_{\text{Early } 50\% C_{\text{max}}}$ and t_{max} were also derived for faster aspart to bridge to previous trials with rapid-acting insulin reporting one or both of these endpoints [46–49].

In line with the left-shifted pharmacokinetic profile, greater early exposure was seen for faster aspart versus IAsp within the first 2 h after administration in the pooled analysis of adults with T1D (Fig. 3b) [16]. From the time of dose

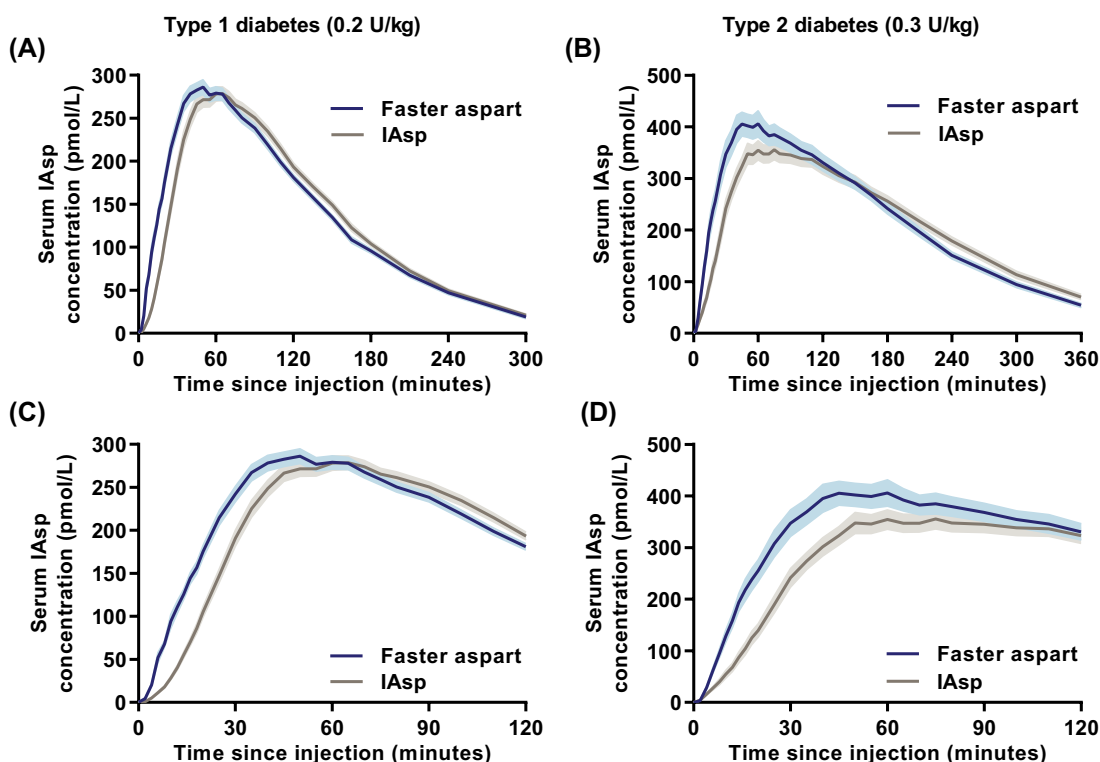


Fig. 2 Pharmacokinetic profiles for faster aspart versus IAsp in subjects with T1D and T2D. Mean 5-h (a), 6-h (b) or 2-h (c, d) serum IAsp concentration–time profiles after a subcutaneous dose of 0.2 U/kg in T1D (a, c) and 0.3 U/kg in T2D (b, d). Variability bands show the standard error of the mean. IAsp insulin aspart, T1D type 1 dia-

betes, T2D type 2 diabetes, U units. Modified from Heise et al. [16] under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (<http://creativecommons.org/licenses/by-nc/4.0/>) and from Pieber et al. [17]

administration until 30 min, faster aspart exposure was twice as large as IAsp exposure.

In subjects with T2D, earlier onset and greater early exposure were also shown with faster aspart versus IAsp [17]. Onset of appearance occurred 1.2 min earlier, $t_{\text{Early } 50\% C_{\text{max}}}$ was 8.5 min shorter and early exposure within the first 30 min after dosing ($\text{AUC}_{\text{IAsp},0-30\text{min}}$) was 89% larger for faster aspart versus IAsp (Fig. 3). Hence, the accelerated absorption of faster aspart versus IAsp occurs in both T1D and T2D.

4.2 Offset and Late Exposure

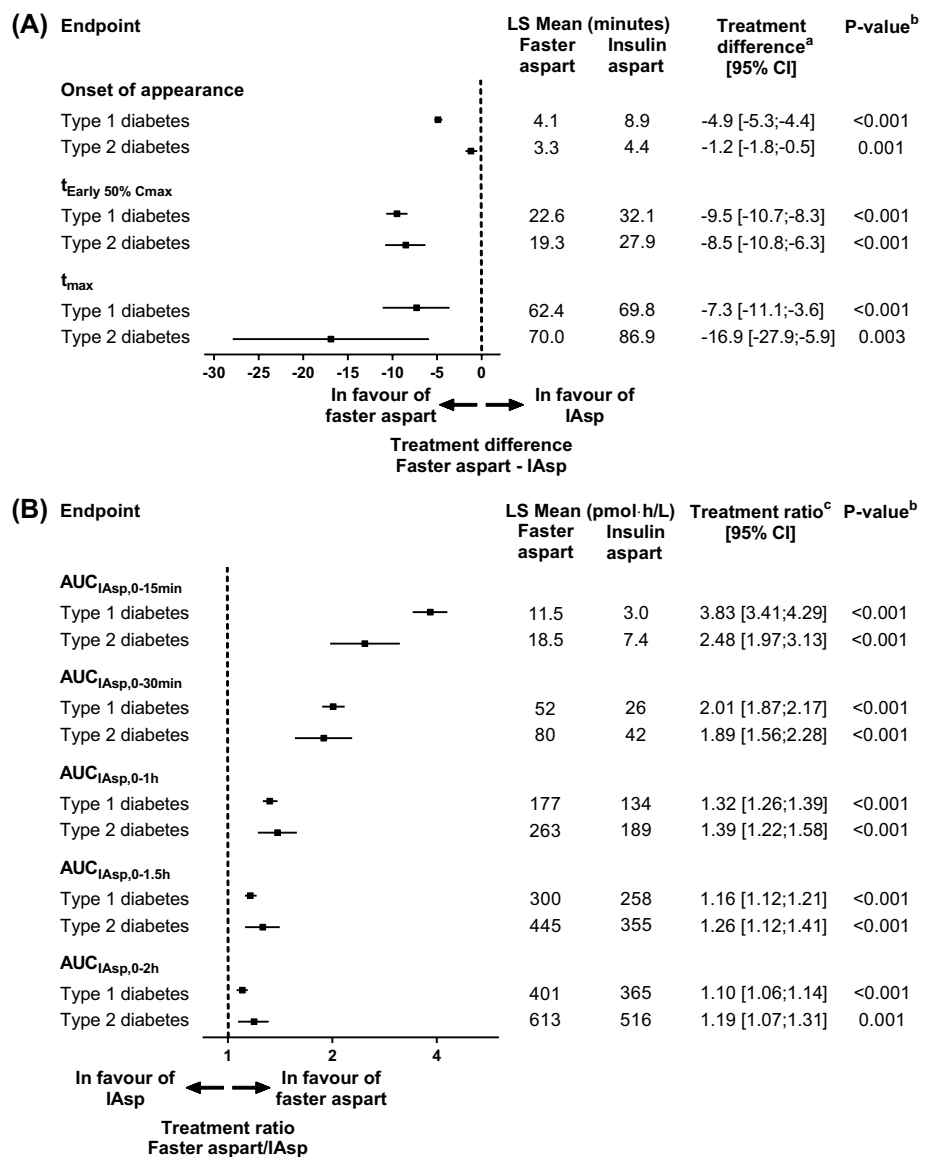
Approaching healthy postprandial insulin secretion implies not only earlier onset and faster absorption rate but also earlier offset and lower late-phase exposure in order to reduce the risk of late postprandial hypoglycaemia [5]. In the pooled analysis of adults with T1D, offset of exposure occurred earlier for faster aspart than for IAsp. The time to 50% of maximum IAsp concentration in the late part of the pharmacokinetic profile ($t_{\text{Late } 50\% C_{\text{max}}}$) was 12.2 min shorter ($p < 0.001$) and late exposure from 2 h onwards ($\text{AUC}_{\text{IAsp},2-t}$) was 11% smaller ($p < 0.001$) for faster aspart versus IAsp

[16]. In subjects with T2D, the corresponding differences for offset and late exposure were 36.4 min ($p < 0.001$) and 12% ($p = 0.002$), respectively, both in favour of faster aspart [17]. Thus, the better resemblance of the faster aspart pharmacokinetic profile to postprandial endogenous insulin secretion in healthy individuals pertains to both the early and late parts of the profile.

4.3 Overall Exposure

In the pooled analysis of adults with T1D, total exposure ($\text{AUC}_{\text{IAsp},0-t}$) and maximum concentration (C_{max}) did not differ between faster aspart and IAsp. The treatment ratios of faster aspart/IAsp were 1.01 (95% confidence interval [CI] 0.98–1.04, $p = 0.470$) and 1.04 (95% CI 1.00–1.08, $p = 0.085$), respectively [16]. In subjects with T2D, $\text{AUC}_{\text{IAsp},0-t}$ was similar for faster aspart and IAsp, with a treatment ratio of 0.99 (95% CI 0.94–1.04, $p = 0.646$), while C_{max} was slightly higher for faster aspart than for IAsp, with a treatment ratio of 1.13 (95% CI 1.02–1.24, $p = 0.018$) [17]. It is important for the interpretation of $t_{\text{Early } 50\% C_{\text{max}}}$ and $t_{\text{Late } 50\% C_{\text{max}}}$ that C_{max} is comparable between faster aspart and IAsp [45]. The higher C_{max} for faster aspart versus IAsp

Fig. 3 Onset of exposure (a) and early exposure (b) for faster aspart versus IAsp after a subcutaneous dose of 0.2 U/kg in subjects with T1D and 0.3 U/kg in subjects with T2D. ^aFaster aspart—IAsp. ^bFor treatment comparison of faster aspart versus IAsp. ^cFaster aspart/IAsp. *AUC* area under the curve, *CI* confidence interval, *IAsp* insulin aspart, *LS Mean* least square mean, *T1D* type 1 diabetes, *T2D* type 2 diabetes, *t*_{Early 50% C_{max}} time to 50% of maximum concentration in the early part of the pharmacokinetic profile, *t*_{max} time to maximum concentration, *U* units. Data from Heise et al. [16] and Pieber et al. [17]



in subjects with T2D implies that both *t*_{Early 50% C_{max}} and *t*_{Late 50% C_{max}} were artificially increased for faster aspart. If *C*_{max} had been similar for faster aspart and IAsp, the treatment differences for *t*_{Early 50% C_{max}} and *t*_{Late 50% C_{max}} in favour of faster aspart would probably have been even larger [17].

Absolute bioavailability of faster aspart was determined in healthy males receiving faster aspart subcutaneously in the abdomen, upper arm and thigh, and intravenously [26]. Absolute bioavailability of faster aspart was ~80% independent of injection region (abdomen 83%; upper arm 77%; thigh 77%) [26].

The dose–concentration relationship for faster aspart was investigated in subjects with T1D across a dose range of 0.1–0.4 U/kg [19]. Analysis of dose proportionality indicated that increases in *AUC*_{IAsp,0-t} and *C*_{max} with increasing dose were modestly larger than dose proportional and

suggested a 12% increase in total exposure and *C*_{max} following a 10% increase in faster aspart dose [19]. Comparable results were seen for IAsp, and it was concluded that this minor deviation from dose proportionality was not expected to influence dose titration in the clinical setting [19].

4.4 Pharmacokinetics Measured as Free or Total Insulin Aspart (IAsp)

Insulin can occur in the circulation as bound or free. The bound form occurs because of reversible binding to anti-insulin antibodies and is therefore primarily relevant to consider in previously insulin-treated individuals [50, 51]. Insulin pharmacokinetic assessment in subjects with diabetes must account for the potential assay interference coming from the presence of anti-insulin antibodies

[51]. In all the faster aspart clinical pharmacology trials, free IAsp was measured following removal of anti-insulin antibodies by PEG precipitation. Because it adds to the totality of data, and on request by regulatory bodies, total IAsp was also measured in selected trials [18, 22, 24, 25]. Subsequently, a pooled analysis of four clinical pharmacology trials in adults with T1D compared the pharmacokinetics of faster aspart and IAsp based on total and free IAsp measurements. Earlier onset, greater early exposure and faster offset of faster aspart versus IAsp were shown regardless of being based on free or total IAsp [21]. The faster aspart–IAsp difference in $t_{\text{Early } 50\% C_{\text{max}}}$ was -8.8 min for free and -7.6 min for total IAsp (both $p < 0.001$). $AUC_{\text{IAsp},0-30\text{min}}$ was 88% and 77% greater for faster aspart versus IAsp when measured as free and total IAsp, respectively (both $p < 0.001$). Finally, the faster aspart–IAsp difference in $t_{\text{Late } 50\% C_{\text{max}}}$ was -13.8 min for free and -14.0 min for total IAsp (both $p < 0.001$) [21].

5 Pharmacodynamics of Faster Aspart

The pharmacodynamics of faster aspart versus IAsp after subcutaneous injection were characterised in a pooled analysis of three glucose clamp trials including 119 adults with T1D [16] and in a glucose clamp trial including 61 subjects with T2D [17]. In accordance with the pharmacokinetic profile, the glucose-lowering effect profile was left-shifted for faster aspart versus IAsp in subjects with both T1D and T2D (Fig. 4).

5.1 Onset and Early Glucose-Lowering Effect

In the pooled analysis of adults with T1D, onset of action occurred ~ 5 min earlier, time to 50% of maximum glucose infusion rate (GIR) in the early part of the GIR profile ($t_{\text{Early } 50\% \text{ GIR}_{\text{max}}}$) was 9.5 min shorter and time to maximum GIR ($t_{\text{GIR}_{\text{max}}}$) was 10.5 min shorter for faster aspart versus IAsp (Fig. 5a) [16]. Onset of action was used as the best possible estimation of the difference in onset of glucose-lowering effect between two insulins. Onset of

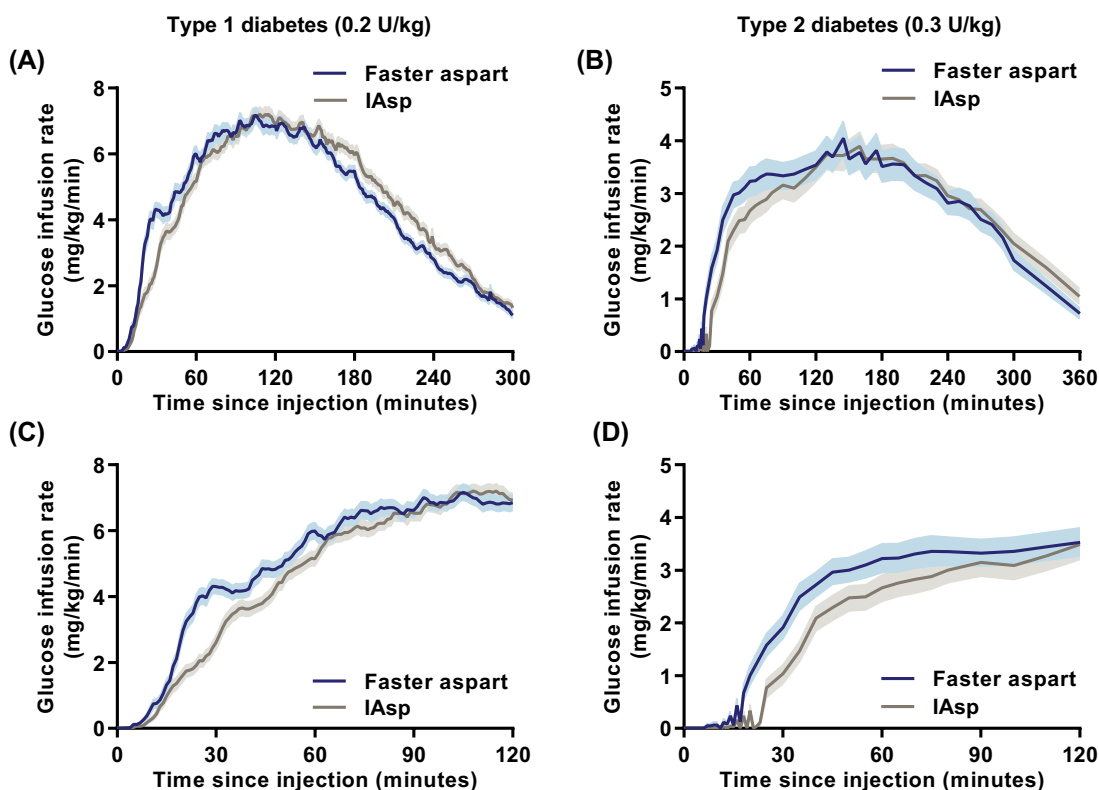
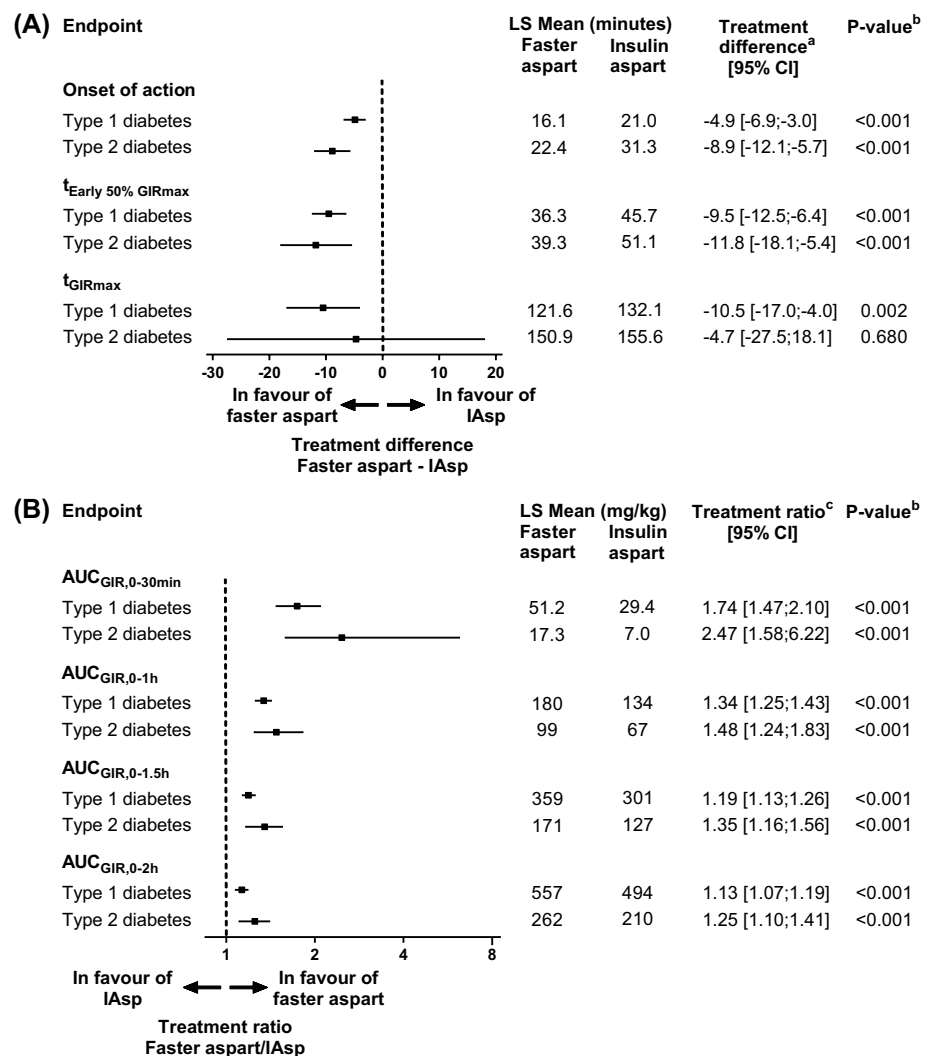


Fig. 4 Pharmacodynamic profiles for faster aspart versus IAsp in subjects with T1D and T2D. Mean 5-h (a), 6-h (b) or 2-h (c, d) glucose-lowering effect profiles after a subcutaneous dose of 0.2 U/kg in T1D (a, c) and 0.3 U/kg in T2D (b, d). Variability bands show the standard error of the mean. IAsp insulin aspart, T1D type 1 diabetes, T2D type

2 diabetes, U units. Modified from Heise et al. [16] under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (<http://creativecommons.org/licenses/by-nc/4.0/>) and from Pieber et al. [17]

Fig. 5 Onset of glucose-lowering effect (a) and early glucose-lowering effect (b) for faster aspart versus IAsp after a subcutaneous dose of 0.2 U/kg in subjects with T1D and 0.3 U/kg in subjects with T2D. ^aFaster aspart—IAsp. ^bFor treatment comparison of faster aspart versus IAsp. ^cFaster aspart/IAsp. *AUC* area under the curve, *CI* confidence interval, *GIR* glucose infusion rate, *IAsp* insulin aspart, *LS Mean* least square mean, *T1D* type 1 diabetes, *T2D* type 2 diabetes, *t*_{Early 50% GIRmax} time to 50% of maximum glucose infusion rate in the early part of the glucose infusion rate profile, *t*_{GIRmax} time to maximum glucose infusion rate, *U* units. Data are from Heise et al. [16] and Pieber et al. [17]



action was defined as the time from dosing until BG had decreased ≥ 0.3 mmol/L from baseline in a glucose clamp setting, where no glucose was infused from 60 min before dosing until the time of onset of action [19]. This definition includes the initial rate of action and therefore may overestimate the time to onset of action [45]. Furthermore, a glucose clamp is an artificial setting and therefore onset of action determined in a glucose clamp may not represent the true onset of action. Nevertheless, the current definition and derivation is relatively robust and clinically relevant, and gives a better estimate of first insulin action than provided by alternative glucose clamp-based endpoints such as time to reach 10% or 50% of maximum glucose-lowering effect or time to achieve 10% of total glucose-lowering effect [45, 46, 52, 53].

In accordance with the left-shifted GIR profile for faster aspart versus IAsp, greater early glucose-lowering effect was observed for faster aspart up to 2 h after dosing in the pooled analysis of adults with T1D (Fig. 5b) [16]. Within the first

30 min after dosing, the glucose-lowering effect was 74% greater for faster aspart versus IAsp.

Earlier onset and greater early glucose-lowering effect were also shown for faster aspart versus IAsp in subjects with T2D [17]. Onset of action occurred 8.9 min earlier, *t*_{Early 50% GIRmax} was 11.8 min shorter and early glucose-lowering effect up to 30 min after dosing (*AUC*_{GIR,0-30min}) was 147% larger for faster aspart versus IAsp (Fig. 5).

5.2 Offset and Late Glucose-Lowering Effect

End of action has previously been derived as the time when GIR is no longer necessary and BG has increased to 8.3 mmol/L at the end of a glucose clamp [44, 54]. However, this definition overestimates end of action and may not be the most clinically relevant measure for mealtime insulins, where timely disposal of the glucose load originating from a meal is the main focus rather than continuously maintaining euglycaemia. Therefore, in the faster aspart

clinical pharmacology trials, time to 50% of maximum GIR in the late part of the GIR profile ($t_{\text{Late } 50\% \text{ GIR}_{\text{max}}}$) and late glucose-lowering effect from 2 h onwards ($\text{AUC}_{\text{GIR}, 2-t}$) were estimated in the clamp setting to reflect the late-phase pharmacodynamic properties. In the pooled analysis of adults with T1D, $t_{\text{Late } 50\% \text{ GIR}_{\text{max}}}$ was 14.3 min shorter ($p < 0.001$) and $\text{AUC}_{\text{GIR}, 2-t}$ was 10% smaller ($p < 0.001$) for faster aspart versus IAsp [16]. In subjects with T2D, the corresponding differences for offset and late glucose-lowering effect were 14.4 min earlier ($p = 0.152$) and 9% smaller ($p = 0.083$) for faster aspart versus IAsp [17]. Thus, although the mean treatment differences were very similar in subjects with T1D and T2D, statistical significance was not reached in the lower number of subjects with T2D [17]. Importantly, at the time of $t_{\text{Late } 50\% \text{ GIR}_{\text{max}}}$, considerable glucose-lowering effect is, by definition, still left and therefore $t_{\text{Late } 50\% \text{ GIR}_{\text{max}}}$ does not represent complete offset of action. However, as appears from Fig. 4, the decline in metabolic action is consistent for faster aspart and IAsp, therefore the 14 min earlier offset for faster aspart should be in the right range even for later time points. It is therefore concluded that faster aspart provides earlier offset of glucose-lowering effect compared with IAsp, which may potentially reduce the risk of late postprandial hypoglycaemia seen when glucose-lowering effect exceeds meal glucose absorption during the late postprandial phase.

5.3 Overall Glucose-Lowering Effect

In both subjects with T1D and T2D, total ($\text{AUC}_{\text{GIR}, 0-t}$) and maximum (GIR_{max}) glucose-lowering effect were comparable between faster aspart and IAsp, suggesting that both treatments provide the same total glucose-lowering effect when administered at similar doses [16, 17]. In subjects with T1D, the treatment ratios of faster aspart/IAsp were 0.98 (95% CI 0.94–1.03, $p = 0.426$) and 1.01 (95% CI 0.96–1.05, $p = 0.814$), respectively [16]. In subjects with T2D, the treatment ratios of faster aspart/IAsp were 1.00 (95% CI 0.92–1.08, $p = 0.960$) and 1.03 (95% CI 0.96–1.11, $p = 0.373$), respectively [17].

The dose–response relationship for faster aspart was investigated in subjects with T1D within a dose range of 0.1–0.4 U/kg [19]. The increase in $\text{AUC}_{\text{GIR}, 0-t}$ was proportional when doubling the faster aspart or IAsp dose from 0.1 to 0.2 U/kg, while a less than proportional increase of 73% occurred when doubling the dose from 0.2 to 0.4 U/kg [19]. A previous dose–response trial with regular human insulin and insulin glulisine also showed a less than proportional increase in total glucose-lowering effect at doses up to 0.3 U/kg [55]. The relation between insulin concentration and glucose uptake is sigmoidal and the slope of the linear part, as well as the maximum level of glucose disposal, differ between individuals [56]. The finding of a less than proportional increase in glucose-lowering effect when doubling the dose to 0.3–0.4 U/

kg for several insulins, including faster aspart, can presumably be explained by saturation of insulin-stimulated glucose disposal in some subjects who reach their GIR_{max} at a dose level lower than the fixed maximum doses of 0.3–0.4 U/kg. Importantly, the lack of dose proportionality for glucose-lowering effect in a glucose clamp setting with fixed dose levels has limited consequences in clinical practice, where individual titration will ensure that patients stay on the linear part of their individual sigmoidal insulin dose–response curve [19].

5.4 Pharmacodynamic Variability

The variability in glucose-lowering effect between insulin doses is important for patients with diabetes aiming for optimal glycaemic control with minimal hypoglycaemia [57]. Within-subject variability in glucose-lowering effect was investigated for faster aspart versus IAsp in a crossover trial where subjects received three single doses of 0.2 U/kg faster aspart or 0.2 U/kg IAsp on separate dosing days [19]. Within-subject variability for faster aspart, determined as the coefficient of variation, was 20–25% for early glucose-lowering effect within 1 or 2 h after administration, 18% for $\text{AUC}_{\text{GIR}, 0-t}$ and 19% for GIR_{max} [19]. Within-subject variability did not differ statistically significantly between faster aspart and IAsp, and was in the same range for faster aspart as seen previously for regular human insulin, insulin lispro and insulin glulisine [48]. Due to the low within-subject variability in glucose-lowering effect, as previously observed with regular human insulin and previously developed rapid-acting insulins, patients may expect that the faster onset and greater initial glucose-lowering effect of faster aspart will be consistently seen from day to day.

5.5 Mechanisms Behind the Increased Early Glucose-Lowering Effect with Faster Aspart

As described in Sect. 8, the earlier onset and greater initial glucose-lowering effect of faster aspart versus IAsp leads to reduced PPG increment with faster aspart. The mechanisms behind were investigated in a meal test trial using triple-tracer methodology to determine PPG turnover in subjects with T1D [22]. During the first hour after meal ingestion, faster aspart induced not only a greater peripheral rate of glucose disappearance but also larger suppression of endogenous glucose production versus IAsp (Fig. 6). In healthy individuals, meal ingestion leads to rapid insulin secretion into the portal vein, aiming to lower BG concentrations via a reduction of hepatic glucose production and an increase in peripheral glucose uptake [3]. Appropriately balancing hepatic and peripheral effects is ensured through exposure of the liver to several-fold higher insulin levels than seen peripherally [58]. The fact that PPG reduction with faster aspart occurs partly via effects on the liver shows the importance of fast insulin

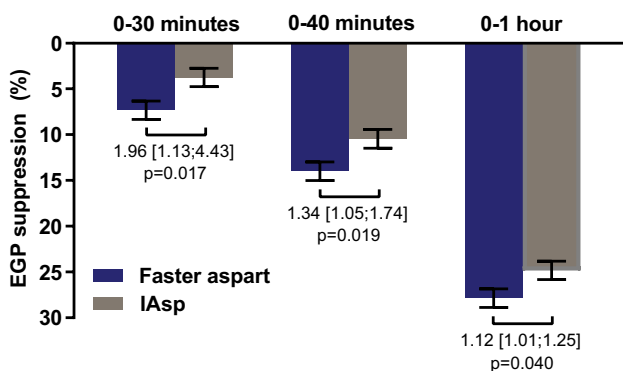


Fig. 6 Suppression of endogenous glucose production for faster aspart versus IAsp during a meal test after individualised subcutaneous dosing (0.06–0.28 U/kg) in subjects with T1D. Bars show LS mean ± standard error. Treatment comparisons show treatment ratios of faster aspart/IAsp [95% CI] and *p* values. *CI* confidence interval, *EGP* endogenous glucose production, *IAsp* insulin aspart, *LS Mean* least square mean. *T1D* type 1 diabetes. From Basu et al. [22]

absorption. Accordingly, it was recently shown that with faster aspart compared with IAsp, the PPG excursion following a mixed meal in subjects with T1D was considerably closer to the PPG excursion seen in healthy subjects investigated in the same study [59].

6 Pharmacological Properties of Faster Aspart in Continuous Subcutaneous Insulin Infusion (CSII)

As CSII use is increasing in diabetes, it is relevant to evaluate the performance of faster aspart administered by insulin pump [60]. The pharmacological characteristics of faster aspart in a CSII setting were investigated in subjects with T1D receiving a 0.15 U/kg bolus via CSII on top of a 0.02 U/kg/h basal rate [20]. In line with results for subcutaneous injection, the pharmacokinetic (Fig. 7) and pharmacodynamic profiles of the bolus dose were both left-shifted for faster aspart versus IAsp. Onset of exposure ($t_{\text{Early } 50\% C_{\text{max}}}$) occurred 11.8 min earlier ($p < 0.001$), $AUC_{\text{IAsp},0-30\text{min}}$ was approximately threefold larger ($p < 0.001$) and $t_{\text{Late } 50\% C_{\text{max}}}$ occurred 35.4 min earlier ($p < 0.001$) for faster aspart versus IAsp [20]. Likewise, $t_{\text{Early } 50\% \text{GIR}_{\text{max}}}$ occurred 11.1 min earlier ($p < 0.001$), $AUC_{\text{GIR},0-30\text{min}}$ was approximately two-fold greater ($p = 0.002$) and $t_{\text{Late } 50\% \text{GIR}_{\text{max}}}$ occurred 24.0 min earlier ($p = 0.002$) for faster aspart versus IAsp [20]. $AUC_{\text{IAsp},0-t}$ and $AUC_{\text{GIR},0-t}$ from the bolus dose were both similar for faster aspart and IAsp. The treatment ratios of faster aspart/IAsp were 0.97 (95% CI 0.90–1.05, $p = 0.477$) and 1.04 (95% CI 0.95–1.13, $p = 0.427$), respectively [20]. In conclusion, faster aspart administered via CSII provides accelerated onset, greater initial exposure and glucose-lowering effect, and earlier offset relative to IAsp. Thus, in a CSII setting, the faster aspart pharmacological profile better

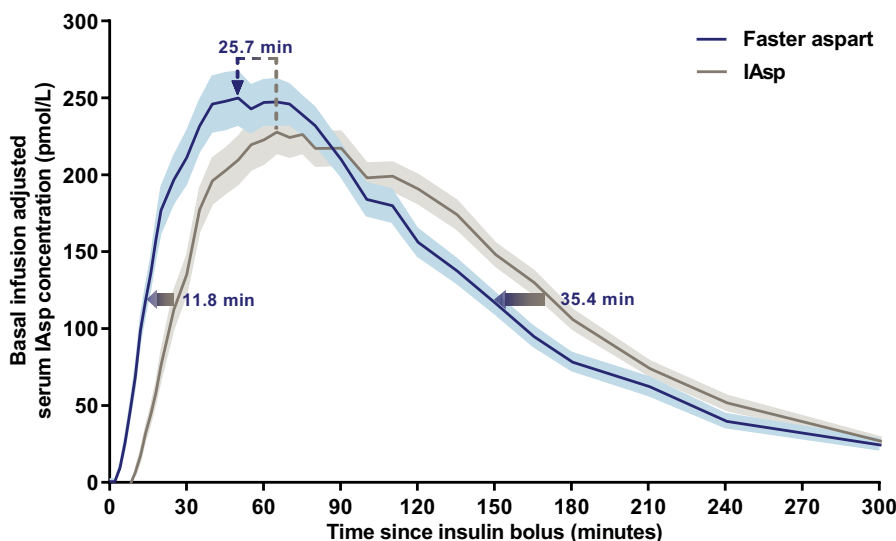


Fig. 7 Mean 5-h serum IAsp concentration–time profiles after a bolus dose of 0.15 U/kg faster aspart or IAsp administered by CSII on top of a basal infusion. Variability bands show the standard error of the mean. The blue/grey arrows indicate that the estimated onset and offset of exposure occurred earlier for faster aspart than for IAsp, as reflected by the endpoints $t_{\text{Early } 50\% C_{\text{max}}}$, t_{max} and $t_{\text{Late } 50\% C_{\text{max}}}$.

CSII continuous subcutaneous insulin infusion, *IAsp* insulin aspart, $t_{\text{Early } 50\% C_{\text{max}}}$ time to 50% of maximum concentration in the early part of the pharmacokinetic profile, t_{max} time to maximum concentration, $t_{\text{Late } 50\% C_{\text{max}}}$ time to 50% of maximum concentration in the late part of the pharmacokinetic profile, *U* units. Modified from Heise et al. [20]

approximates mealtime insulin secretion in healthy subjects, as observed after subcutaneous injection.

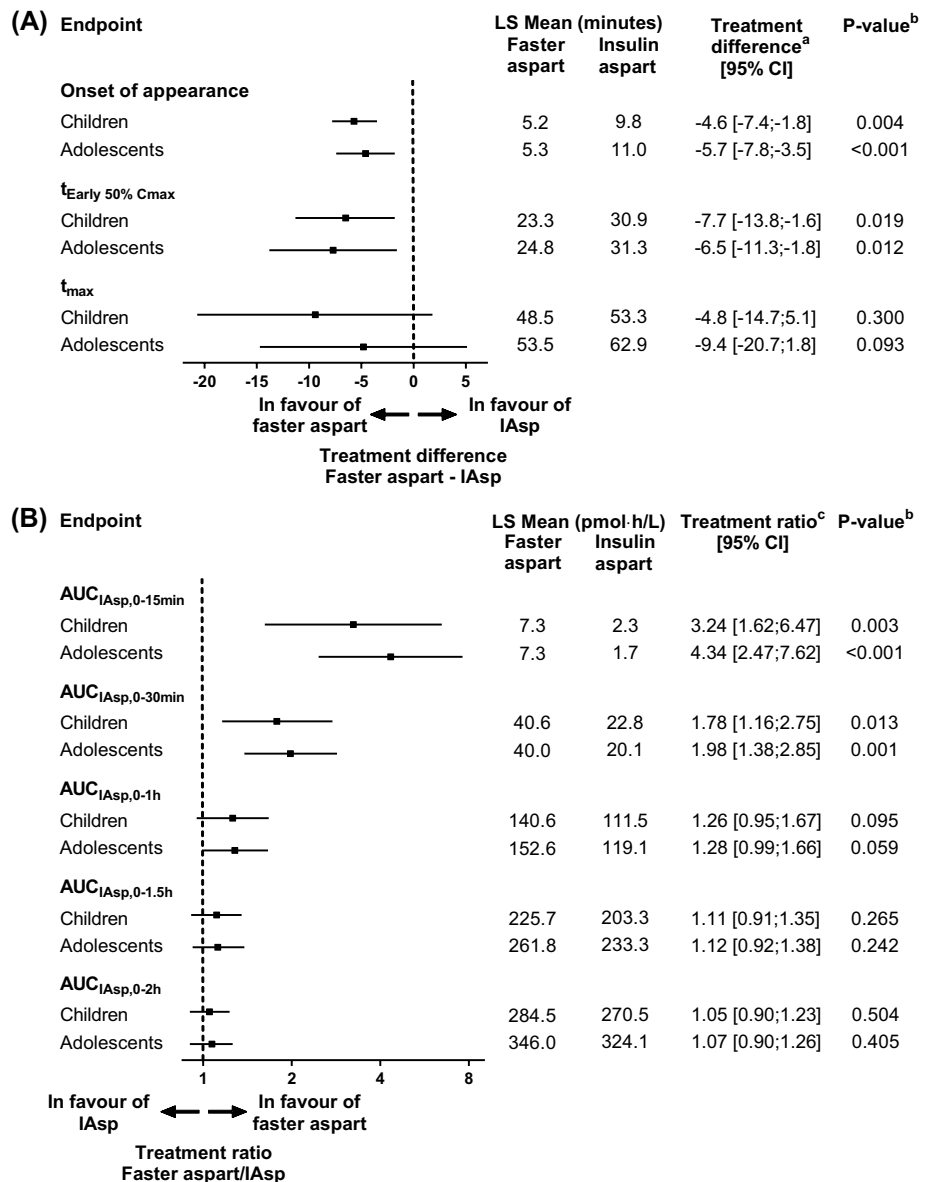
7 Different Patient Populations, Injection Regions and Insulin Antibody Levels

7.1 Children and Adolescents

Faster aspart was compared with IAsp in a pharmacokinetic and meal test trial in children (6–11 years), adolescents (12–17 years) and adults with T1D [23]. In children and adolescents, onset of appearance occurred approximately twice as fast, $t_{\text{Early } 50\% C_{\text{max}}}$ was ~7 min shorter and $AUC_{\text{IAsp},0-30\text{min}}$ was 78–98% greater for faster aspart versus IAsp (Fig. 8).

$AUC_{\text{IAsp},0-t}$ for faster aspart was 41% lower in children ($p < 0.001$) and 22% lower in adolescents ($p = 0.002$) versus adults. In a linear mixed model with period, age group, treatment, and interaction between age group and treatment as fixed effects, the p value for interaction between age group and treatment was 0.481 [23]. Thus, the age effect on $AUC_{\text{IAsp},0-t}$ did not differ statistically significantly between faster aspart and IAsp. Furthermore, the age effect on $AUC_{\text{IAsp},0-t}$ is not considered clinically important since individual titration of faster aspart must be carried out. Interestingly, all subjects received 0.2 U/kg body weight irrespective of age, and the age effect on $AUC_{\text{IAsp},0-t}$ largely followed the age group differences in absolute dose (mean of 8.3, 12.8 and 15.6 U in children, adolescents and adults, respectively). It was therefore speculated that the increased total exposure

Fig. 8 Onset of exposure (a) and early exposure (b) for faster aspart versus IAsp after a subcutaneous dose of 0.2 U/kg in children and adolescents with T1D. ^aFaster aspart—IAsp. ^bFor treatment comparison of faster aspart versus IAsp. ^cFaster aspart/IAsp. *AUC* area under the curve, *CI* confidence interval, *IAsp* insulin aspart, *LS Mean* least square mean, *T1D* type 1 diabetes, $t_{\text{Early } 50\% C_{\text{max}}}$ time to 50% of maximum concentration in the early part of the pharmacokinetic profile, t_{max} time to maximum concentration, *U* units. Data from Fath et al. [23]



with increasing age might reflect that the volume of distribution does not develop closely according to increases in body weight from childhood and adolescence to adulthood [23]. In response to a standardised liquid meal, the average glucose excursion during the first 1 and 2 h and the maximum glucose excursion were all reduced in children by 1.2–1.6 mmol/L for faster aspart versus IAsp ($p = 0.005$, $p = 0.028$ and $p = 0.044$, respectively). A trend in the same direction was seen in adolescents (0.2–0.6 mmol/L), which was not statistically significant [23].

7.2 Elderly

In a glucose clamp trial comparing faster aspart with IAsp in elderly subjects (≥ 65 years) and younger adults (18–35 years) with T1D, onset of appearance occurred approximately twice as fast (3 min earlier; $p < 0.001$), $t_{\text{Early } 50\% C_{\text{max}}}$ was 10 min shorter ($p < 0.001$) and initial exposure up to 2 h after dosing was greater for faster aspart versus IAsp in the elderly subjects [24]. Similarly, onset of action occurred 10 min earlier, $t_{\text{Early } 50\% \text{ GIR}_{\text{max}}}$ was 6 min shorter and initial glucose-lowering effect up to 2 h after dosing was greater for faster aspart versus IAsp (Fig. 9). The effect of faster aspart versus IAsp on the pharmacokinetic/pharmacodynamic endpoints did not differ statistically significantly between elderly and younger adults [24]. Thus, faster aspart should also be able to reduce PPG excursion compared with previously developed rapid-acting insulins in elderly patients with diabetes.

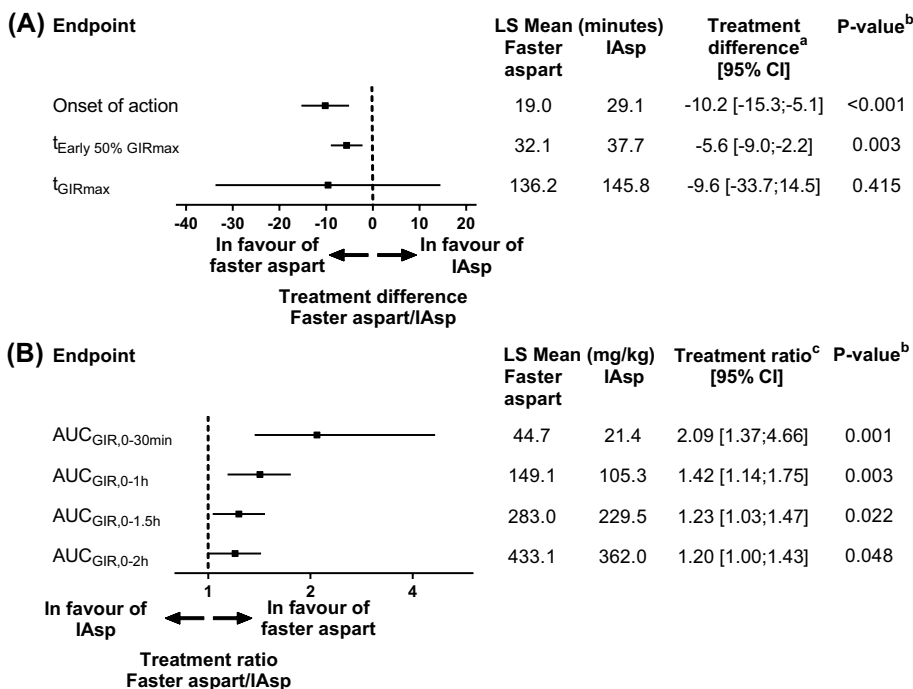
7.3 Individuals with Renal or Hepatic Impairment

Renal and hepatic impairment may potentially affect drug clearance and/or metabolism [61, 62]. The pharmacokinetic properties of faster aspart have not been investigated in subjects with renal or hepatic impairment. The only change in faster aspart versus IAsp relates to the subcutaneous absorption process, and the IAsp molecule in faster aspart has not been modified compared with the original IAsp formulation [13]. Furthermore, receptor-mediated clearance is the main pathway for clearance of IAsp molecules. Therefore, pharmacokinetic results on IAsp in renal and hepatic impairment can also be used as representative for faster aspart. It was shown that there is no impact of renal impairment (as assessed by creatinine clearance) or hepatic impairment (as assessed by Child–Pugh score) on the pharmacokinetics of IAsp [63]. Consequently, it is concluded that the pharmacokinetic characteristics of faster aspart are also not affected, to any clinically significant extent, by renal or hepatic impairment.

7.4 Japanese Individuals

Since race and ethnicity may affect the pharmacological characteristics of insulin products, the pharmacological properties of faster aspart were compared with IAsp in a glucose clamp trial in Japanese subjects with T1D [25, 64]. The pharmacokinetic/pharmacodynamic profiles were left-shifted for faster aspart versus IAsp (Fig. 10). For faster aspart relative to IAsp, onset of appearance occurred 4.1 min

Fig. 9 Onset of glucose-lowering effect (a) and early glucose-lowering effect (b) for faster aspart versus IAsp after a subcutaneous dose of 0.2 U/kg in elderly subjects with T1D. ^aFaster aspart—IAsp. ^bFor treatment comparison of faster aspart versus IAsp. ^cFaster aspart/IAsp. *AUC* area under the curve, *CI* confidence interval, *GIR* glucose infusion rate, *IAsp* insulin aspart, *LS Mean* least square mean, *T1D* type 1 diabetes, $t_{\text{Early } 50\% \text{ GIR}_{\text{max}}}$ time to 50% of maximum glucose infusion rate in the early part of the glucose infusion rate profile, $t_{\text{GIR}_{\text{max}}}$ time to maximum glucose infusion rate, *U* units. Data from Heise et al. [24]



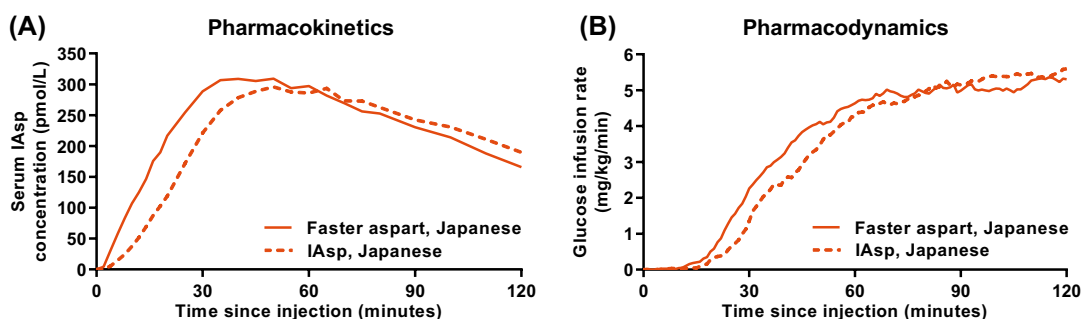


Fig. 10 Mean 2-h serum IAsp concentration–time profiles (a) and mean 2-h glucose-lowering effect profiles (b) for faster aspart versus IAsp after a subcutaneous dose of 0.2 U/kg in Japanese subjects with

T1D. IAsp insulin aspart, T1D type 1 diabetes, U units. From Shiramoto et al. [25]

earlier ($p < 0.001$), $t_{\text{Early } 50\% C_{\text{max}}}$ was 10.2 min shorter ($p < 0.001$) and $\text{AUC}_{\text{IAsp},0-30\text{min}}$ was 94% greater ($p < 0.001$) [25]. Likewise, onset of action occurred 5.3 min earlier ($p = 0.001$), $t_{\text{Early } 50\% \text{GIR}_{\text{max}}}$ was 10.0 min shorter ($p < 0.001$) and $\text{AUC}_{\text{GIR},0-30\text{min}}$ was 110% greater ($p = 0.002$) [25]. The corresponding differences for faster aspart relative to IAsp in Caucasians were 4.9 min earlier onset of appearance, 9.5 min shorter $t_{\text{Early } 50\% C_{\text{max}}}$, 101% greater $\text{AUC}_{\text{IAsp},0-30\text{min}}$, 4.9 min earlier onset of action, 9.5 min shorter $t_{\text{Early } 50\% \text{GIR}_{\text{max}}}$ and 74% greater $\text{AUC}_{\text{GIR},0-30\text{min}}$ (all $p < 0.001$). Thus, in accordance with results shown in Caucasian subjects, faster aspart in Japanese subjects also better resembles healthy postprandial insulin secretion compared with previously developed rapid-acting insulins.

7.5 Different Injection Regions

Insulin can be administered subcutaneously in various injection regions, however potentially with different pharmacokinetic profiles [65–67]. Therefore, a trial in healthy males investigated the pharmacokinetics of faster aspart administered subcutaneously in the abdomen, upper arm or thigh (Fig. 11) [26]. Onset of appearance was ~3 min, $t_{\text{Early } 50\% C_{\text{max}}}$ was ~20 min and t_{max} was ~55 min for faster aspart independent of injection region. Early exposure within the first 1 or 2 h after administration and C_{max} were 20–30% lower for the thigh versus the abdomen and upper arm. $\text{AUC}_{\text{IAsp},0-t}$ was comparable for all three injection regions [26]. Based on these results, the ultra-fast pharmacokinetic properties of faster aspart are most pronounced when administered in the abdomen or upper arm compared with the thigh.

7.6 Effect of Anti-Insulin Antibodies

The impact of anti-IAsp antibodies on the pharmacokinetics/pharmacodynamics of faster aspart and IAsp was investigated based on four clinical pharmacology trials supplemented with results from a phase III trial [21]. For both

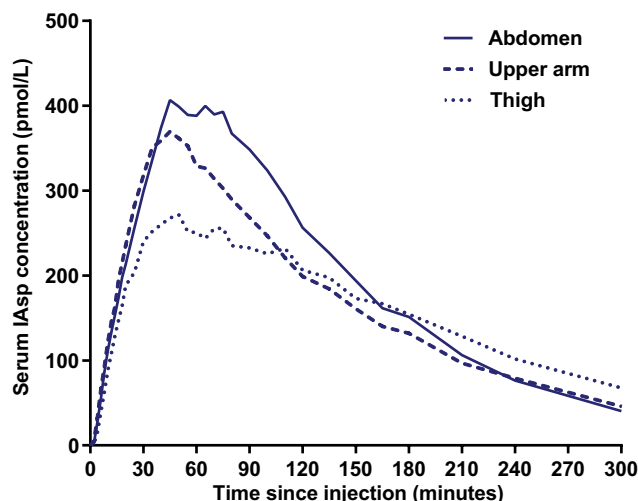


Fig. 11 Mean 5-h serum IAsp concentration–time profiles for 0.2 U/kg faster aspart administered subcutaneously in the abdomen, upper arm or thigh in healthy male subjects. IAsp insulin aspart, U units. From Hövelmann et al. [26]

faster aspart and IAsp, overall exposure was approximately twofold greater for total versus free IAsp, which could at least partly be explained by the presence of anti-IAsp antibodies. Thus, higher anti-IAsp antibody levels were associated with lower ratio of free/total IAsp for $\text{AUC}_{\text{IAsp},0-t}$ [21]. It was also shown that initial glucose-lowering effect within 1 h post-dose was consistently greater for faster aspart versus IAsp irrespective of anti-IAsp antibody levels, and there was essentially no correlation between anti-IAsp antibody level and PPG increment at 1 h in a meal test [21]. Based on these findings, it is concluded that faster aspart provides accelerated pharmacological properties versus IAsp independent of the anti-IAsp antibody level. This is in line with several other trials showing no clinically significant impact of anti-insulin antibodies on insulin pharmacodynamics, efficacy or safety [21, 68–70].

8 Clinical Consequences of Faster Aspart Pharmacological Properties

8.1 Multiple Daily Injection Therapy

The improved pharmacological properties of faster aspart have been shown in several phase III trials to result in better PPG control and at least as efficient overall glycaemic control with similar or reduced overall risk of hypoglycaemia compared with IAsp when used as multiple daily injection therapy and administered at meal initiation (Table 1).

In subjects with T1D, the efficacy and safety of faster aspart were compared with IAsp in a basal-bolus regimen in a 52-week trial with insulin detemir and in a 26-week trial with insulin degludec [28, 30, 31]. PPG increment

in a meal test was consistently reduced by faster aspart versus IAsp at 1 h post-meal in both trials, and also at 30 min post-meal in the 26-week trial and at 2 h post-meal after 26 weeks of the 52-week trial (Fig. 12a) [28, 30, 31]. In the 52-week trial, HbA_{1c} was reduced, for faster aspart versus IAsp, by 0.15% after 26 weeks and 0.10% after 52 weeks, while non-inferiority in HbA_{1c} was demonstrated for faster aspart versus IAsp in the 26-week trial (Table 1). The rate of overall severe or BG-confirmed hypoglycaemia was comparable for faster aspart and IAsp in both trials (Table 1).

In subjects with T2D, a 26-week trial and a 16-week trial both compared faster aspart with IAsp in a basal-bolus regimen and showed that PPG increment in a meal test was reduced by faster aspart versus IAsp at 1 h post-meal with non-inferiority in HbA_{1c}, i.e. essentially similar results as shown in T1D (Table 1) [32, 33]. While the rate of overall

Table 1 Summary of efficacy and hypoglycaemia results in phase III trials with faster aspart

Study name	Study population	Treatment duration; treatment regimen	Comparator	Difference in efficacy with faster aspart vs. comparator (estimated treatment difference)			Difference in rate of hypoglycaemia with faster aspart vs. comparator (% difference)	
				HbA _{1c} (%)	ΔPPG _{1h} (mmol/L)	ΔPPG _{2h} (mmol/L)	Severe hypoglycaemia	Severe or BG-confirmed hypoglycaemia
MDI therapy								
Onset 1 [30]	T1D	26 weeks; BB IDet	IAsp	-0.15 ; non-inferior; significant	-1.18	-0.67	ND	1↑
Onset 1 [28]	T1D	52 weeks; BB IDet	IAsp	-0.10 ; significant	-0.91	-0.42	21↓	1↑
Onset 8 [31]	T1D	26 weeks; BB IDeg	IAsp	-0.02; non-inferior	-0.90	-0.35	ND	NS
Onset 2 [32]	T2D; treated with basal insulin + OAD(s)	26 weeks; BB IGLar + OAD(s)	IAsp	-0.02; non-inferior	-0.59	-0.36	25↑	9↑
Onset 9 [33]	T2D; treated with BB	16 weeks; BB IDeg ± metformin	IAsp	-0.04; non-inferior	-0.40	ND	ND	19 ↓
Onset 3 [34]	T2D; treated with basal insulin + OAD(s)	18 weeks; BB + metformin	Basal only + metformin	-0.94 ; superior	ND	ND	789↑	724 ↑
CSII therapy								
Onset 5 [29]	T1D; treated via CSII	26 weeks	IAsp	0.09 ; non-inferior; significant	-0.91	-0.90	ND	0↔

Results shown in bold indicate a statistically significant difference between faster aspart and comparator. Arrows for hypoglycaemia indicate the numerical direction of the treatment difference

BB basal-bolus, BG blood glucose, CSII continuous subcutaneous insulin infusion, ΔPPG_{1h} 1-h postprandial glucose increment, ΔPPG_{2h} 2-h postprandial glucose increment, HbA_{1c} glycosylated haemoglobin, IAsp insulin aspart, IDeg insulin degludec, IDet insulin detemir, IGLar insulin glargine, MDI multiple daily injection, ND not determined, NS not significant (but no estimate provided), OAD oral antidiabetic drug, T1D type 1 diabetes, T2D type 2 diabetes

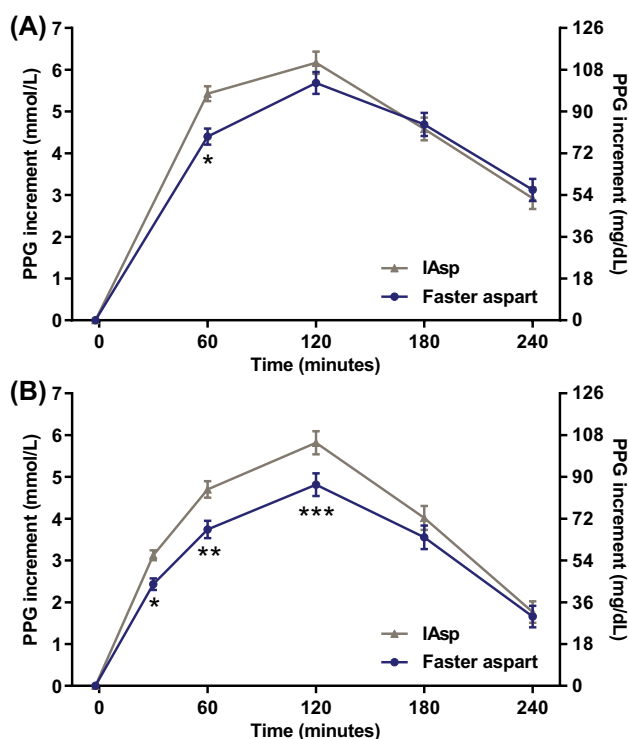


Fig. 12 PPG increment for faster aspart versus IAsp in subjects with T1D during a 4-h meal test conducted after 52 weeks of multiple daily injection therapy (a) or after 16 weeks of CSII treatment (b). Subjects received a bolus dose of 0.1 U/kg followed by a standardised liquid meal (approx. 80 g carbohydrate) consumed within 12 min. Error bars show \pm standard error of the mean. * $p < 0.001$, ** $p = 0.001$, *** $p = 0.01$. CSII continuous subcutaneous insulin infusion, IAsp insulin aspart, PPG postprandial glucose, T1D type 1 diabetes, U units. From Mathieu et al. [28] and Klonoff et al. [29]

severe or BG-confirmed hypoglycaemia was comparable for faster aspart and IAsp in the 26-week trial, a significantly lower hypoglycaemia rate was observed for faster aspart in the 16-week trial [32, 33]. An 18-week trial investigated the addition of faster aspart to basal insulin and metformin in subjects with T2D [34]. Expectedly, superiority in HbA_{1c} reduction (Table 1) and improvement of 2.48 mmol/L in average self-measured 2-h PPG for all meals were shown for faster aspart versus basal-only therapy, with a several-fold higher rate of severe or BG-confirmed hypoglycaemia when adding faster aspart to basal insulin (Table 1).

The efficacy and safety of faster aspart were also evaluated in children and adolescents (1–17 years) with T1D in a 26-week trial with faster aspart or IAsp in a basal-bolus regimen with insulin degludec [35]. PPG increment at 1 h, based on self-measured BG, was reduced for faster aspart versus IAsp at breakfast, dinner and across all meals, and HbA_{1c} was reduced by 0.17% for faster aspart versus IAsp, with a comparable overall rate of severe or BG-confirmed hypoglycaemia [35]. These results suggest that also in children and adolescents, the accelerated absorption of faster

aspart leads to improved PPG control, and at least as efficient overall glycaemic control with similar overall risk of hypoglycaemia compared with IAsp.

The ultra-fast pharmacological characteristics of faster aspart may also allow for post-meal dosing. Faster aspart administered 20 min after meal initiation was investigated in several phase III trials including children, adolescents and adults with T1D [30, 31, 35]. PPG increment in a meal test was higher with post-meal faster aspart versus meal-time IAsp up to 1 h post-meal. Nonetheless, post-meal faster aspart provided a non-inferior HbA_{1c} reduction and comparable overall rate of severe or BG-confirmed hypoglycaemia versus mealtime IAsp [30, 31, 35]. These findings suggest that post-meal administration of faster aspart could be an alternative in children, who often have irregular eating patterns, and in other situations where actual food intake is difficult to estimate in advance.

8.2 CSII

With accelerated insulin pharmacokinetics, as seen for faster aspart, it may be possible to further utilise the features of insulin pumps [71]. Pump compatibility of faster aspart versus IAsp over 6 weeks was investigated in 37 subjects with T1D. There were no observations of microscopically confirmed occlusions of the infusion set, suggesting comparable compatibility of faster aspart and IAsp in CSII [42]. An exploratory trial in 43 subjects with T1D showed that in a meal test following 2 weeks of CSII with faster aspart or IAsp, the average BG increment across the first 2 h after meal ingestion was 0.99 mmol/L lower with faster aspart versus IAsp [43]. Finally, in a 16-week phase III trial in adults with T1D investigating the efficacy and safety of faster aspart in CSII, the PPG increment in a meal test at the end of treatment was reduced by faster aspart versus IAsp at 30 min, 1 and 2 h post-meal (Fig. 12b) [29]. HbA_{1c} was non-inferior for faster aspart versus IAsp, although the 0.09% difference in favour of IAsp was statistically significant, and the rate of overall severe or BG-confirmed hypoglycaemia was similar for faster aspart and IAsp (Table 1) [29]. Thus, it appears that the improved PPG control with faster aspart versus previously developed rapid-acting insulin seen after subcutaneous injection also pertains to treatment via CSII. As more advanced insulin pump systems become available, it is possible that the accelerated absorption of faster aspart will be even more important for future insulin application systems, including closed-loop and artificial pancreas systems [71, 72]. Still, given the relatively limited clinical experience with the use of faster aspart in pumps, larger-scale clinical trials and/or accumulated real-world experience are needed to fully unravel both the safety profile and the clinical potential of faster aspart in pump use [73].

9 Potential Risk Factors and Limitations Associated with Faster Aspart

In all clinical trials, faster aspart was safe and well tolerated, which was expected since the IAsp molecule is unchanged in the faster aspart formulation and the two added excipients in faster aspart versus the original IAsp formulation are also assessed to be safe (see Sect. 2).

With an ultra-fast-acting insulin, there is a risk that the glucose-lowering effect profile may become too fast to match the glucose absorption from the meal, particularly in case of large and/or high-fat meals [5, 11]. In some trials, faster aspart has been associated with a slightly increased risk of hypoglycaemia during the first 1–2 h after meal initiation, although this time period is characterised by a generally low frequency of hypoglycaemia [28–30, 32]. Another potential concern could be the risk of late under-insulinisation and resulting hyperglycaemia. However, this seems not to be an issue with faster aspart, at least up to 4 h post-meal (Fig. 12). Rather, a reduced risk of hypoglycaemia from 3 to 4 h post-meal was shown with faster aspart versus IAsp, indicating that the faster aspart action profile better matches the need for glucose disposal during the late postprandial period [31]. Nevertheless, a given duration of insulin action cannot fit all types and sizes of meals. In the majority of trials investigating the PPG excursion with faster aspart versus IAsp in a meal test, subjects ingested a standard liquid meal [23, 28–33]. It is also important to establish the best dosing schedules of faster aspart for mixed, high-fat or high-carbohydrate meals with respect to injection-meal interval and the potential need for additional doses. Interestingly, several trials have investigated PPG control with mealtime faster aspart versus mealtime IAsp following subjects' own individual meals. In subjects with T2D, change from baseline in self-measured 1-h PPG increment was statistically significantly in favour of faster aspart versus IAsp at lunch, main evening meal and across all meals [33]. In children and adolescents with T1D, changes from baseline in 1- and 2-h interstitial glucose increments assessed by continuous glucose monitoring were statistically significantly in favour of faster aspart versus IAsp at breakfast, main evening meal and across all meals [35]. Furthermore, in adults with T1D using CSII, changes from baseline in mean interstitial glucose increment over 1 or 2 h were statistically significantly in favour of faster aspart versus IAsp at all individual meals and across meals [29]. As meal composition and timing may vary considerably between individuals and between different regions and countries, studies to investigate dosing schedules for faster aspart in relation to meal types will not be able to cover all meal regimens. Therefore, it is always important to take an individual

approach to ensure the best match between insulin dosing regimen and meal habits.

The earlier onset and shorter duration of action of faster aspart should also be considered when using faster aspart via CSII. In a double-blind trial investigating faster aspart versus IAsp administered via CSII, continuous glucose monitoring showed higher nocturnal and pre-meal interstitial glucose concentrations with faster aspart than with IAsp [29]. It was hypothesized that the pump settings for both the basal rate and the bolus characteristics may have favoured IAsp and that adjustments might have been needed to adapt to the specific pharmacokinetics of faster aspart [29]. Thus, with faster aspart used in CSII, it must be considered in clinical practice if a different distribution between basal rate and bolus doses is needed and whether adjustments to the various bolus types are required compared with current practice for rapid-acting insulins [73].

10 Conclusions

Faster aspart is an ultra-fast-acting formulation of IAsp developed to provide accelerated absorption after subcutaneous administration. Faster aspart has consistently provided overall left-shifts of the pharmacokinetic/pharmacodynamic profiles compared with IAsp across different populations (adults with T1D or T2D, children and adolescents, the elderly and Japanese individuals) as well as in CSII. The improved pharmacological characteristics of faster aspart translate into superior PPG control and at least as efficient overall glycaemic control with a similar risk of hypoglycaemia compared with IAsp. Altogether, faster aspart may partly address the unmet need in patients with diabetes for mealtime insulins, with a pharmacokinetic profile that approaches healthy endogenous prandial insulin secretion.

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Compliance with Ethical Standards

Conflict of interest This article was funded by Novo Nordisk. Hanne Haahr is an employee and shareholder of Novo Nordisk. Tim Heise is shareholder of Profil, which has received research funds from Adocia, Boehringer Ingelheim, Dance Pharmaceuticals, Eli Lilly, Gan & Lee Pharmaceuticals, Johnson & Johnson, Mars, MedImmune, Mylan, Nordic Bioscience, Novo Nordisk, Pfizer, Poxel, Saniona, Sanofi, Wockhardt and Zealand Pharma. In addition, Tim Heise is member of advisory panels for Mylan and Novo Nordisk and received speaker honoraria and travel grants from Eli Lilly and Novo Nordisk.

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