Use of fast-acting insulin aspart in insulin pump therapy in clinical practice

Mark Evans, Antonio Ceriello, Thomas Danne, Christophe de Block, J. Hans Devries, Marcus Lind, Chantal Mathieu, Kirsten Nørgaard, Eric Renard, Emma Wilmot

To cite this version:
Mark Evans, Antonio Ceriello, Thomas Danne, Christophe de Block, J. Hans Devries, et al.. Use of fast-acting insulin aspart in insulin pump therapy in clinical practice. Diabetes, Obesity and Metabolism, Wiley, 2019, 21 (9), pp.2039-2047. 10.1111/dom.13798. hal-02860446
Use of fast-acting insulin aspart in insulin pump therapy in clinical practice

Mark Evans,1 Antonio Ceriello,2 Thomas Danne,3 Christophe De Block,4 J. Hans DeVries,5 Marcus Lind,6 Chantal Mathieu,7 Kirsten Nørgaard,8 Eric Renard,9 Emma G. Wilmot10

1. Wellcome Trust/MRC Institute of Metabolic Science and Department of Medicine, University of Cambridge, Cambridge, UK
2. IRCCS MultiMedica, Milan, Italy; Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Spain; Department of Cardiovascular and Metabolic Diseases, IRCCS MultiMedica, Sesto San Giovanni, Italy
3. Diabeteszentrum für Kinder und Jugendliche, Kinderkrankenhaus auf der Bult, Hannover, Germany
4. Department of Endocrinology-Diabetology-Metabolism, Antwerp University Hospital, Edegem, Belgium
5. Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; Profil Institute of Metabolic Research, Neuss, Germany
6. Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden; Department of Medicine, NU - Hospital Group, Trollhättan/Uddevalla, Sweden
7. Clinical and Experimental Endocrinology, University Hospital Leuven, KU Leuven, Leuven, Belgium
8. Steno Diabetes Center Copenhagen, Gentofte, Denmark
9. Montpellier University Hospital, Department of Endocrinology, Diabetes, Nutrition, and Institute of Functional Genomics, University of Montpellier, CNRS, INSERM, Montpellier, France
10. University Hospitals of Derby and Burton NHS Foundation Trust, Derby, United Kingdom

Corresponding author: Mark Evans, Wellcome Trust/MRC Institute of Metabolic Science and Department of Medicine, University of Cambridge, Box 289 Addenbrooke’s Hospital, Hills Road, Cambridge CB2 0QQ, UK. Email: mle24@cam.ac.uk

Word count (5000 max): 3009

References (100 max): 52

Tables/Figures (5 max): 3
Abstract:

Fast-acting insulin aspart (faster aspart) is a novel formulation of insulin aspart (IAsp) containing the additional excipients niacinamide and L-arginine. The improved pharmacological profile and greater early glucose-lowering action of faster aspart compared with IAsp suggests that faster aspart may be advantageous for people with diabetes using continuous subcutaneous insulin infusion (CSII). The recent onset 5 trial was the first to evaluate the efficacy and safety of an ultra-fast-acting insulin in CSII therapy in a large number of participants with type 1 diabetes (T1D). Faster aspart was confirmed to be non-inferior to IAsp in terms of HbA1c reduction and demonstrated significantly improved postprandial glucose control after a standardized meal test without an increased risk of overall severe or blood glucose-confirmed hypoglycaemia. This review summarizes the available clinical evidence for faster aspart administered via CSII and highlights practical considerations based on clinical experience that may help healthcare providers and people with T1D successfully initiate and adjust faster aspart in CSII.
Introduction

Continuous subcutaneous insulin infusion (CSII) using an insulin pump is an increasingly popular treatment option for children and adults with type 1 diabetes (T1D). \(^1\)\(^3\) In meta-analyses of randomized controlled trials, CSII is associated with improved glycaemic control and lower risk of severe hypoglycaemia compared with multiple daily injection (MDI) therapy. \(^4\)\(^6\) CSII aims to mimic the physiological basal and prandial insulin profile, with basal infusion rates set to cover varying requirements during the night and between meals, and user-activated bolus doses at mealtimes.

Most insulin pumps offer a range of preprogrammed bolus infusion types to provide coverage at mealtimes, including infusion of an entire bolus at once (standard bolus), infusion of small quantities over an extended period of time (delayed/extended bolus) or a combination of a standard and delayed bolus (dual/multi-wave). \(^7\)\(^9\) Insulin pumps also have integrated bolus calculators enabling insulin dose calculation based on carbohydrate counting, personalized carbohydrate:insulin ratios, duration of insulin action and insulin sensitivity factors, and they allow insulin doses to be adjusted by a tenth of a unit or less (compared with one unit or half a unit with pen injectors).

Despite developments in insulin pump technology, there are a number of challenges in optimizing glycaemic control with CSII. These include optimization of basal and bolus infusion rates, selection of bolus type, time of meal bolus programming, variability of insulin action, and type of insulin used. Calculation of appropriate insulin doses requires users to perform frequent blood glucose testing (self-measured blood glucose [SMBG]) at correct times, or use continuous glucose monitoring (CGM), \(^3\)\(^10\)\(^11\) and make accurate estimations of meal composition and carbohydrate content. \(^12\)\(^13\) Conventional insulin pumps use an external infusion set to deliver insulin from the insulin reservoir in the pump housing into the subcutaneous tissue, while recently developed patch pumps deliver insulin via a very short internal infusion set. \(^14\) Pump failure, and infusion set malfunctions or occlusions, can cause unexplained hyperglycaemia, ketosis and diabetic ketoacidosis. \(^15\) The infusion site and the duration of infusion site usage can also impact the rate of insulin absorption and consequently the glucose-lowering action. \(^16\)

In normal physiology, insulin is secreted very rapidly from the \(\beta\)-cell in response to, and even anticipation of, a meal. Despite advances in insulin formulations, subcutaneously administered insulins have a delayed onset and a longer duration of action compared with endogenously secreted insulin. A recent study found a positive correlation between time-to-peak insulin action and HbA1c level in studies of closed-loop insulin delivery and sensor-augmented pump therapy, indicating the need for insulins with rapid and consistent absorption properties that are more able to reproduce physiological insulin responses. \(^17\) Current rapid-acting insulin analogues (RAIAs) — insulin aspart


(IAsp), insulin lispro and insulin glulisine — have faster absorption kinetics than regular human insulin\(^1\); however, postprandial glucose (PPG) control with pump therapy remains limited by the pharmacokinetics of RAIAs.\(^1\)

A new generation of ultra-fast-acting insulins, such as BioChaperone Lispro,\(^2\) treprostinil lispro,\(^3\) and fast-acting insulin aspart (faster aspart), is under development. Faster aspart is the first of these to be approved for pump use in adults with T1D and type 2 diabetes (T2D), and is now available in several countries. This review summarizes the available clinical data for faster aspart administered via CSII and highlights some practical considerations for its use in insulin pumps based on this evidence, as well as observations from clinical practice.

**Fast-acting insulin aspart (faster aspart)**

Faster aspart is a novel formulation of IAsp containing the additional excipients niacinamide and L-arginine.\(^4\) This novel formulation builds on the safety studies of conventional IAsp,\(^5,6\) and both excipients are listed by the US Food and Drug Administration (FDA) as ‘generally recognized as safe’ (Gingras, \#16).\(^7\) Niacinamide mediates a faster initial absorption into the bloodstream by both increasing the initial abundance of IAsp monomers in the subcutaneous depot, and mediating a transient, local vasodilatory effect;\(^8\) L-arginine functions as a stabilizing agent.

In a pooled analysis of six clinical studies in adults with T1D, faster aspart administered by subcutaneous injection demonstrated an accelerated pharmacological profile compared with IAsp.\(^2,8\) Faster aspart had a ~5-min earlier onset of appearance in the circulation, ~two-fold higher early insulin exposure and ~74% greater early glucose-lowering effect within the first 30 min compared with IAsp.\(^8\) In addition, offset of exposure and glucose-lowering effect occurred 12–14 min earlier with faster aspart than with IAsp. Similar pharmacological properties after subcutaneous injection have been observed in elderly adults and in a Japanese population,\(^9,10\) as well as in children and adolescents with T1D.\(^11\)

When delivered through CSII, the left-shift in the pharmacological profile of faster aspart versus IAsp appears to be even greater compared with that seen after subcutaneous injection (Figure 1). In adults with T1D using CSII, faster aspart demonstrated ~three-fold higher early insulin exposure and ~100% greater glucose-lowering effect within the first 30 min compared with IAsp.\(^2,12\) In addition, offset of exposure and offset of glucose-lowering effect occurred 35 min and 24 min earlier, respectively, with faster aspart than with IAsp. The reason for the differences between subcutaneous and CSII administration is not completely understood, and comparisons across trials
should always be done with caution; however, one hypothesis is that the continuous supply of niacinamide in a CSII setting further augments the rate of insulin monomer dissociation, thereby further increasing the early absorption rate of faster aspart compared with conventional IAsp. It is also possible that the smaller size of the CSII subcutaneous insulin depot (versus a bolus injection) contributes to the accelerated kinetics of faster aspart versus IAsp.

**Clinical evidence for faster aspart**

*Multiple daily injection (MDI) regimens*

Several clinical trials comparing faster aspart and IAsp in MDI regimens demonstrate that the improved pharmacological properties of faster aspart translate into clinical benefits.33-35 The onset 1 and onset 8 trials in people with T1D reported non-inferiority of MDI with mealtime faster aspart (administered 0–2 min before a meal) and post-meal faster aspart (administered within 20 min after a meal) versus IAsp in terms of HbA1c reduction 26 weeks after randomization, with a statistically significantly greater reduction for mealtime faster aspart in onset 1 (onset 1: estimated treatment difference [ETD] −0.15% [95% CI −0.23; −0.07], −1.62 mmol/mol [−2.50; −0.73]; onset 8: ETD [95% CI] −0.02% [−0.11; 0.07], −0.24 mmol/mol [−1.24; 0.76]). Mealtime faster aspart was also effective in reducing PPG excursions in both trials, and superiority to IAsp was confirmed (onset 1: 2-hour PPG increment: −0.67 mmol/L [−1.29; −0.04], −12.01 mg/dL [−23.33; −0.70]; onset 8: 1-hour PPG increment: ETD −0.90 mmol/L [−1.36; −0.45], −16.24 mg/dL [−24.42; −8.05]). In both trials, the overall rate of severe or blood glucose (BG)-confirmed hypoglycaemia (plasma equivalent glucose value <3.1 mmol/L [56 mg/dL]) was not statistically significantly different between mealtime or post-meal faster aspart and IAsp, and the overall safety profiles were similar between treatments. A pooled post hoc analysis across both onset 1 and onset 8 demonstrated a lower rate of nocturnal hypoglycaemia with mealtime faster aspart versus IAsp (estimated treatment ratio: 0.84 [95% CI: 0.72; 0.98]).36

*Continuous subcutaneous insulin infusion (CSII) setting*

A small, exploratory, crossover trial demonstrated improvements in glycaemic control with faster aspart versus IAsp in adults with T1D using CSII,37 with a ~25% greater glucose-lowering effect during the first 2 hours following a standardized meal test (ETD −0.99 mmol/L [95% CI −1.95; −0.03], −17.84 mg/dL [−35.21; −0.46]). This was supported by 2 weeks of CGM data, which indicated improvements in PPG control after all regular meals with faster aspart versus IAsp, with the largest
difference at breakfast (1-hour interstitial glucose [IG] increment, 1.12 vs 2.04 mmol/L [20.19 vs 36.69 mg/dL], respectively).

Insulin preparation formulation type can influence the risk of infusion set failure\textsuperscript{38}; however, results of the 6-week onset 4 trial indicated a similar compatibility of faster aspart and IAsp in CSII.\textsuperscript{39} No microscopically-confirmed infusion set occlusions were observed for faster aspart or IAsp, and after adjusting for an imbalance during the run-in period, the rate of severe or BG-confirmed hypoglycaemia was similar for bothinsulins. A higher number of premature infusion set changes was observed with faster aspart versus IAsp (21 changes reported by 11 participants versus four reported by two participants, respectively), with technical issues being the most commonly cited reason. As this was a relatively small trial of short duration, further studies may be needed to get a true feel for insulin pump compatibility.

The recent double-blind, treat-to-target, randomized, 16-week trial on set 5 trial evaluated the efficacy and safety of faster aspart administered via CSII in 472 adults with T1D.\textsuperscript{40} During the 4-week run-in, participants received reinforcement of training in pump use, diabetes education and trial procedures, and mean HbA1c decreased from 7.79 and 7.80% in the faster aspart and IAsp treatment arms respectively, to 7.49% in both arms. Participants remained on their pre-trial insulin (3% insulin glulisine, 40% insulin lispro and 57% IAsp), and basal pump rates and bolus dose calculator settings were not adjusted unless for safety reasons. At randomization, participants switched to double-blinded treatment with faster aspart or IAsp on a unit-for-unit basis. Basal rates were adjusted to target a fasting and pre-prandial SMBG between 4.0 and 6.0 mmol/L (71–108 mg/dL) (plasma equivalent glucose values) and to ensure that fasting plasma glucose was kept in a stable range (within 2 mmol/L [35 mg/dL]), and mealtime insulin (administered 0–2 min before a meal) was titrated based on carbohydrate counting. Participants continued using their own insulin pump, and approximately 25% of participants in each treatment arm used their own real-time CGM device. During the treatment period, HbA1c decreased further to 7.44% in the faster aspart arm and 7.35% in the IAsp arm. As expected with a treat-to-target design, non-inferiority between treatments was confirmed with regard to the change in HbA1c; however, the ETD was statistically significant in favour of IAsp (Table 1).\textsuperscript{40} In contrast, PPG increments at 30 min, 1 hour and 2 hours after a standardized meal test were statistically significantly reduced with faster aspart compared with IAsp. This was corroborated by lower postprandial IG increments after 1 and 2 hours with faster aspart versus IAsp measured during three ~2-week periods of blinded CGM (Table 1).\textsuperscript{40}

The reasons for the discrepancy between the impact on HbA1c levels and PPG control are not fully clear. Participants did not change their pump settings during the double-blinded trial period unless
deemed necessary by an investigator, and so pump parameters were optimized for RAIAs rather than faster aspart use. Nocturnal and pre-meal levels of IG were slightly higher for participants receiving faster aspart compared with IAsp. Elevated nocturnal IG in the faster aspart treatment arm may have been due to a suboptimal bolus type (i.e. dual-/multi-wave versus standard bolus) for the composition of the evening meal (e.g. fat content), a lack of basal insulin compensation owing to the shorter bolus insulin action, or suboptimal basal insulin rates during the night.

The rate of overall severe or BG-confirmed hypoglycaemia was not different between treatments; although, consistent with its faster pharmacokinetic/pharmacodynamic (PK/PD) profile, the rate for the small proportion of episodes that occurred during the first hour after a meal was higher for faster aspart versus IAsp (Table 1). While the trial was not powered to assess differences in severe hypoglycaemia, the number of episodes was numerically higher for faster aspart versus IAsp. Eleven participants treated with faster aspart reported 21 episodes and five participants treated with IAsp reported seven episodes. This imbalance was also observed in the run-in period, with four episodes reported by three participants later randomized to faster aspart. Unlike many clinical trials of CSII, it is important to note that people with hypoglycaemia unawareness or preceding severe hypoglycaemia were not excluded from this trial, and there was no stratification for these parameters. A similar rate of infusion set changes (routine and non-routine) was reported with both treatments, although a numerically higher number of infusion site reactions (a cited reason for non-routine changes) was reported with faster aspart versus IAsp (Table 1).

Closed-loop automated insulin delivery systems

Many hybrid and fully closed-loop insulin delivery systems have been limited by how aggressively RAIAs can be used to control PPG due to the risk of late hypoglycaemia. The use of a faster-acting insulin in these systems is expected to be of great interest, and trials of faster aspart are in progress. Indeed the observed elevated nocturnal IG reported with faster aspart in the onset 5 study could potentially be minimized by the automated basal insulin delivery offered by closed-loop systems. An initial study suggests that faster aspart provides a modestly greater glucose-lowering effect compared with IAsp in a fully closed-loop delivery system ($\Delta AUC_{0-1h}$ after breakfast, $-3782$ mmol/L*min; $\Delta AUC_{0-5h}$ after dinner, $-1158$ mmol/L*min). At present closed-loop glucose control algorithms are designed for use with RAIAs and the more rapid onset of faster aspart may require adaptations of these algorithms. Clinical trials will need to provide an answer to this important question.
**Faster aspart in CSII: practical considerations**

The accelerated absorption kinetics of faster aspart suggest that it would provide clinical benefits with CSII use. Despite improvements in PPG control, it is surprising that faster aspart did not improve HbA1c to a greater extent than IAsp in the onset 5 trial. The double-blind design of onset 5 prevented tailored adjustments according to the pharmacological profile of faster aspart, and conventional CSII practices may require optimisation for faster aspart to fully realize its potential benefits. Faster aspart has been approved for use in insulin pumps for CSII by the European Medicines Agency and is available in several counties. However, practical guidance on the use of faster aspart in CSII is lacking. Herein we highlight important considerations that may help healthcare providers (HCPs) and people with diabetes successfully initiate and adjust faster aspart in CSII.

As in the onset 5 trial, a 1:1 unit dose conversion is recommended when switching to faster aspart. However, while pump settings may have been ideal for the previously used insulin, given the difference in pharmacology, a review and guided change in all pump settings should be expected over the weeks and months following the switch. Differences in bolus delivery between different insulin pumps should also be considered as these can affect the pharmacological characteristics of mealtime insulin, and also influence the ‘insulin on board’ or active insulin estimation (the residual glucose-lowering activity from prior boluses) and therefore correction bolus dosing.

Due to the accelerated absorption kinetics of faster aspart, bolus dosing will need to be addressed to reduce the risk of early postprandial hypoglycaemia or late postprandial hyperglycaemia. Early postprandial hypoglycaemia is uncommon, but may be an issue after unexpectedly delayed meals or meals with a high fat content, errors in carbohydrate counting, or in patients with gastroparesis. Data suggest that administering a pre-prandial bolus of ultra-rapid-acting insulin 15 min before a meal compared with immediately before can improve postprandial hyperglycaemia. While this was not examined in the onset 5 trial, clinical experience suggests that pre-meal bolus dosing can be beneficial for pump users with faster aspart, especially when consuming food with a high glycaemic index. Adjustments to the basal insulin dose (potentially using a basal rate test) will also need to be considered for optimal use of faster aspart, although HCPs should be aware that some pump users will not be accustomed to changing basal rate parameters without support from their treatment team.

Pump users should be performing sufficient BG monitoring and may need to increase the frequency of SMBG testing to enable this optimization. The use of CGM or flash glucose monitoring (FGM)
could enable optimization of dosing for each individual user when switching to faster aspart. If long-term use of CGM or FGM is not possible, short-term use over 8–12 weeks would likely be helpful. Monitoring the insulin on board/active insulin function on their pump could help pump users understand and tailor their dosing needs.

A good understanding of meal content and glycaemic index is likely to be important for pump users to fully benefit from the effect of faster aspart. Although the use of faster aspart in the context of high or low glycaemic index meals has not been addressed in clinical trials, there may be more need for different bolus types, such as a delayed/extended bolus with larger meals or a dual- or multi-wave bolus for high-fat and high-protein meals (Figure 2). As a starting point for high-fat and high-protein meals, 30% of the total insulin dose can be administered immediately and 70% delayed over the 2–4 hours following the meal. It should also be noted that more insulin may be needed than that calculated by carbohydrate counting alone.

The occurrence of a burning sensation around the infusion site has been reported in some people using faster aspart in clinical practice. Some users also report needing to change their infusion set more frequently after switching to faster aspart to avoid hyperglycaemia, and others have found that correction doses do not work as expected. There are likely to be other, currently unknown factors involved in determining the success of faster aspart treatment in CSII, and HCPs may find that glycaemic improvements are seen in some, but not necessarily all users.

**Summary**

Faster aspart use in insulin pump therapy provides potential benefits for glucose control. The improved PK/PD profile of faster aspart compared with IAsp suggests that faster aspart may be advantageous for people with diabetes using CSII. While the large, double-blind onset 5 trial demonstrated that faster aspart is effective in glycaemic control, superiority of faster aspart over IAsp in terms of HbA1c reduction was not confirmed, although meal test and CGM results suggest that faster aspart is especially beneficial for PPG control. Experience from clinical practice indicates that starting faster aspart in CSII should not be viewed as a simple switch of insulin. All pump settings will need to be reviewed and tailored to the individual patient. The use of CGM or FGM, along with a good understanding of meal content and bolus type, may also facilitate optimal use of faster aspart in CSII. There is currently limited evidence on the optimal clinical use of faster aspart in CSII, and further studies are required to maximize its potential benefits in pump therapy.
Acknowledgements: The authors are grateful to Helen Parker PhD and Erin Slobodian of Watermeadow Medical, an Ashfield company, part of UDG Healthcare plc, for medical writing and editorial assistance in the development of this manuscript. This assistance was funded by Novo Nordisk, who also had a role in the review of the manuscript for scientific accuracy.

Author contributions: All authors discussed the concept, worked on the outline, commented in detail on the first iteration, made critical revisions on later drafts and approved the final draft for submission.

Disclosures

ME has participated in advisory boards for Novo Nordisk, Abbott Diabetes Care, Roche, Medtronic, CellNovo and Dexcom; has received speakers’ fees from Novo Nordisk, Abbott Diabetes Care, Eli Lilly, MSD and Astra Zeneca; has received travel support from Novo Nordisk; and participated in research collaborations/trial list with MedImmune, Boehringer Ingelheim, Novo Nordisk and Sanofi.

AC received research grants from AstraZeneca, Novartis, and Mitsubishi; personal fees from AstraZeneca, Boehringer Ingelheim, DOC Generici, Eli Lilly, Janssen, Novo Nordisk, OM Pharma, Novartis, Sanofi, and Takeda. TD received research support or has consulted for Abbott, AstraZeneca, Bayer, Boehringer, DexCom, Insulet Corp., Eli Lilly, Medtronic, Novo Nordisk, Roche and Sanofi, and is a shareholder of DreaMed. CDB reports personal fees from Abbott, AstraZeneca, A. Menarini Diagnostics, Johnson & Johnson Lilly, Medtronic, MSD, Novartis, Novo Nordisk, Roche Diagnostics and Sanofi. JHVD serves on advisory panels for Insulet, Novo Nordisk, Roche, Sanofi and Zealand Research; and has received research support from Dexcom, Medtronic, Novo Nordisk and Senseonics, and speaker fees from Novo Nordisk, Roche and Senseonics.

ML has received research grants from AstraZeneca, DexCom and Novo Nordisk, and has received honoraria or consulted for AstraZeneca, DexCom, Eli Lilly, MSD and Novo Nordisk.

CM has participated in advisory panels for Novo Nordisk, Sanofi-Aventis, Merck Sharp & Dohme Ltd., Eli Lilly and Company, Novartis, AstraZeneca LP, Jansen Pharmaceuticals, Hanmi Pharmaceuticals, Intrexon, Boehringer Ingelheim; received research support from Novo Nordisk, Sanofi-Aventis, Merck Sharp & Dohme Ltd., Boehringer Ingelheim; and has participated in speakers’ bureaus for Novo Nordisk, Sanofi-Aventis, Merck Sharp & Dohme, Eli Lilly and Company, Novartis, AstraZeneca. KN serves as an adviser at Medtronic, Abbott and Novo Nordisk, owns shares in Novo Nordisk, has received research grants from Novo Nordisk, Zealand Pharma and Roche, and has received fees for speaking from Medtronic, Roche, Rubin Medical, Sanofi, Zealand Pharma, Novo Nordisk and Bayer.

ER serves as a consultant/advisor for Abbott, Air Liquide, Cellnovo, Dexcom, Eli Lilly, Insulet, Johnson & Johnson
(Animas, LifeScan), Medtronic, Novo Nordisk, Roche Diagnostics and Sanofi-Aventis, and has received research grant/material support from Abbott, Dexcom, Insulet, Roche Diagnostics and Tandem Diabetes Care. EW has received personal fees from Abbott Diabetes Care, Dexcom, Eli Lilly, Medtronic, Novo Nordisk, and Sanofi-Aventis.
References


Figure 1: Key pharmacokinetic and pharmacodynamic properties of faster aspart administered via continuous subcutaneous insulin infusion

A) Mean serum insulin aspart concentration after a bolus dose of 0.15 U/kg faster aspart or insulin aspart. The arrows indicate that the estimated onset and offset of exposure occurred earlier for faster aspart versus insulin aspart, and show the left-shift of the time of maximum insulin aspart concentration observed for faster aspart versus insulin aspart. B) Mean glucose-lowering effect after a bolus dose of 0.15 U/kg faster aspart or insulin aspart. Variability bands show the SEM.

Faster aspart, fast-acting insulin aspart; SEM, standard error of the mean.

Figure reproduced and adapted from Heise et al. Diabetes Obes Metab 2017;19:208–215, under the terms of Creative Commons Attribution-NonCommercial-License, © 2016.
Consideration should be given to matching the type of bolus insulin administered via a pump with the expected glucose profile of a meal.
Table 1: Faster aspart in continuous subcutaneous insulin infusion: key efficacy and safety endpoints from the onset 5 trial

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Faster aspart</th>
<th>Insulin aspart</th>
<th>Estimated treatment difference [95% CI], P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c 16 weeks after randomization</td>
<td>7.44</td>
<td>7.35</td>
<td>0.09 [0.01; 0.17], P = 0.022 (non-inferiority confirmed, P &lt; 0.001†)</td>
</tr>
<tr>
<td>(primary endpoint), %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline 16 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>after randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-min PPG increment (meal test), mmol/L</td>
<td>−0.53</td>
<td>0.11</td>
<td>−0.66 [−1.00; −0.31], P &lt; 0.001</td>
</tr>
<tr>
<td>1-hour PPG increment (meal test), mmol/L</td>
<td>−0.89</td>
<td>0.05</td>
<td>−0.91 [−1.43; −0.39], P = 0.001</td>
</tr>
<tr>
<td>(confirmatory secondary endpoint)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-hour PPG increment (meal test), mmol/L</td>
<td>−0.82</td>
<td>0.09</td>
<td>−0.90 [−1.58; −0.22], P = 0.01</td>
</tr>
<tr>
<td>0–1 hour IG increment (CGM), mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breakfast</td>
<td>−0.13</td>
<td>0.14</td>
<td>−0.27 [−0.44; −0.11], P = 0.001</td>
</tr>
<tr>
<td>Lunch</td>
<td>−0.02</td>
<td>0.15</td>
<td>−0.20 [−0.35; −0.06], P = 0.004</td>
</tr>
<tr>
<td>Main evening meal</td>
<td>−0.16</td>
<td>0.04</td>
<td>−0.15 [−0.28; −0.01], P = 0.032</td>
</tr>
<tr>
<td>All meals</td>
<td>−0.10</td>
<td>0.11</td>
<td>−0.21 [−0.31; −0.11], P &lt; 0.001</td>
</tr>
<tr>
<td>0–2 hour IG increment (CGM), mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breakfast</td>
<td>−0.28</td>
<td>0.16</td>
<td>−0.43 [−0.67; −0.18], P = 0.001</td>
</tr>
<tr>
<td>Lunch</td>
<td>−0.24</td>
<td>0.22</td>
<td>−0.44 [−0.65; −0.23], P &lt; 0.001</td>
</tr>
<tr>
<td>Main evening meal</td>
<td>−0.29</td>
<td>−0.03</td>
<td>−0.23 [−0.43; −0.04], P = 0.018</td>
</tr>
<tr>
<td>All meals</td>
<td>−0.25</td>
<td>0.12</td>
<td>−0.38 [−0.52; −0.23], P &lt; 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety</th>
<th>Faster aspart</th>
<th>Insulin aspart</th>
<th>Estimated treatment ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycaemic episodes, PYE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe or BG-confirmed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>45.07</td>
<td>45.29</td>
<td>1.00 [0.85; 1.16], NS</td>
</tr>
<tr>
<td>Within 1 hour</td>
<td>1.26</td>
<td>0.71</td>
<td>1.78 [1.15; 2.75], P = 0.009</td>
</tr>
<tr>
<td>&gt;1–2 hours</td>
<td>5.36</td>
<td>5.05</td>
<td>1.05 [0.82; 1.35], NS</td>
</tr>
<tr>
<td>&gt;2–3 hours</td>
<td>6.78</td>
<td>7.76</td>
<td>0.86 [0.70; 1.06], NS</td>
</tr>
<tr>
<td>&gt;3–4 hours</td>
<td>5.95</td>
<td>6.03</td>
<td>0.98 [0.77; 1.24], NS</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment period</td>
<td>0.29</td>
<td>0.10</td>
<td>2.78 [0.78; 9.94], NS</td>
</tr>
<tr>
<td>Run-in</td>
<td>0.21</td>
<td>0.00</td>
<td>-</td>
</tr>
<tr>
<td>Infusion site reactions, PYE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.61</td>
<td>0.45</td>
<td>-</td>
</tr>
<tr>
<td>Possibly or probably related to trial product</td>
<td>0.29</td>
<td>0.18</td>
<td>-</td>
</tr>
<tr>
<td>Infusion set changes, PYE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>132.67</td>
<td>130.57</td>
<td>-</td>
</tr>
<tr>
<td>Non-routine changes</td>
<td>6.97</td>
<td>6.68</td>
<td>-</td>
</tr>
</tbody>
</table>

*P-values from a two-sided test for treatment difference evaluated at the 5% level. †P-values from a 1-sided test for non-inferiority and superiority evaluated at the 2.5% level.

BG-confirmed: recorded plasma equivalent glucose value <3.1 mmol/L (56 mg/dL).
CGM, continuous glucose monitoring; CI, confidence interval; faster aspart, fast-acting insulin aspart;
IG, interstitial glucose; NS, not significant; PPG, postprandial glucose; PYE, number of events per patient-year of exposure.