



BRIEF REPORT

Survival assessment of the extended-wear insulin infusion set featuring lantern technology in adults with type 1 diabetes by the glucose clamp technique

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Abstract

Maintaining good glycaemic control with the same infusion set for longer than 3 days may improve the quality of life of insulin pump users. The aim of the current study was to assess the efficacy and safety of the novel, extended-wear infusion set over 7 days of wear in adults with type 1 diabetes. Sixteen participants completed three identical 8-hour euglycaemic clamp experiments on Days 1, 4 and 7 of infusion set wear. Between the experiments, the participants were discharged home for routine diabetes management while wearing the same extended-wear infusion set throughout the study. Time to reach the maximum glucose infusion rate (T_{GIRmax}) on Day 7 was reduced by 67% compared with Day 1 ($p < .001$). The corresponding area under the glucose infusion rate curve (AUC_{GIR}) was comparable for the first 2 h of the clamp ($p = .891$) but decreased by 28% over time ($p < .008$). While the extent of insulin absorption decreased with prolonged wear, it was accompanied by an increase in insulin absorption rate. The infusion set survival rate was 100% without leakages, occlusion alarms, severe hypoglycaemia or ketoacidosis. The extended-wear infusion set proved safe and effective during prolonged wear in real-life conditions.

KEYWORDS

clinical trial, CSII, insulin pump therapy, pharmacodynamics, pharmacokinetics, type 1 diabetes

1 | INTRODUCTION

Modern insulin therapy aims to establish good glycaemic control without causing clinically relevant hypoglycaemia. Currently, continuous subcutaneous insulin infusion (CSII) therapy comes closest to achieving that goal.¹⁻⁴ However, because of physiological and mechanical effects occurring at the infusion site, CSII may be associated with non-metabolic complications^{5,6} (i.e. local tissue inflammation, the effect of insulin solution preservatives on the infusion site, infusion

set-related events) that affect insulin delivery leading to fluctuations in insulin absorption and eventually to deterioration of glycaemic control. Because the incidence and frequency of CSII complications increase over time, manufacturers of insulin pumps and infusion sets recommend changing the infusion set and rotating the infusion site every 2-3 days to ensure reliable insulin delivery.⁷⁻¹¹ However, in practice, most individuals prefer to use one infusion set and one insertion site longer than recommended to avoid experiencing frequent insertion-related pain, but also to keep the cost of treatment down.

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We investigated the efficacy and safety of the novel, extended-wear insulin infusion set featuring patented Lantern technology over 7 days of wear. The set includes a soft cannula with anti-inflammatory coating and additional openings in the form of multiple longitudinal perforations in the cannula shaft. The cannula coating is designed to suppress the foreign body response, while the shaft perforations compensate for fluctuations in insulin delivery because of kinking/ crimping, or a partial/full cannula tip occlusion (Figure 1). Owing to the cannula design, the extended-wear infusion set may reduce the likelihood of non-metabolic CSII complications, thus enabling prolonged wear, consistent with patients' wishes.

2 | METHODS

This open, single-centre, single-arm, controlled pilot study assessed the efficacy and safety of the novel, extended-wear insulin infusion set featuring Lantern technology in 16 experienced insulin pump users with type 1 diabetes over 7 days of wear. The study was approved by the Medical University of Graz ethics committee (EC number 29-566 ex 16/17) and the Austrian national health authority, and was entered into the German Clinical Trials Register (DRKS00013263). Signed informed consent was obtained prior to any study-related activities. The participants (five females and 11 males, age 44.2 ± 15.4 years, body mass index 24.5 ± 2.3 kg/m², diabetes duration 20.0 ± 9.0 years, HbA1c $7.2\% \pm 0.7\%$ [55.3 ± 7.8 mmol/mol]) underwent a total of four identical 8-h long euglycaemic clamp experiments following bolus administration of 0.15 IU/kg body weight of insulin lispro (Humalog, Eli Lilly, Indianapolis, IN, USA) with the study-specific insulin pump (MiniMed 640G, Medtronic, Northridge, CA, USA). The first clamp experiment was performed with the standard infusion set (Inset II, Unomedical, Osted, Denmark) on the first day of infusion set wear to serve as baseline, while the remaining three clamp experiments were performed with the extended-wear infusion set on Days 1, 4, and 7 of infusion set wear. The participants spent the days between the experiments (Days 2, 3, 5 and 6) at home routinely managing their diabetes while wearing the same extended-wear infusion set in combination with the study-specific insulin pump and the flash glucose monitor (FGM; FreeStyle Libre, Abbott Diabetes Care, Alameda, CA, USA).

2.1 | Euglycaemic clamp experiment protocol

The participants were required to spend each clamp experiment fasting and on bed rest. Upon arrival at the research centre, they were fitted with the FGM (Day 1 only) and intravenous lines for frequent blood sampling and infusion of insulin and glucose. Prior to clamp start, the standard infusion set was primed with insulin lispro and inserted into the periumbilical subcutaneous adipose tissue to deliver insulin at a constant flow rate of 0.10 IU/h for the duration of the clamp. A variable intravenous infusion of human insulin (Actrapid, Novo Nordisk, Bagsvaerd, Denmark) in saline was started immediately thereafter and continued for 3 to 5 h to obtain a stable plasma glucose level of 5.6 ± 0.6 mmol/L 30 min prior to administering the subcutaneous insulin bolus (0.15 IU/kg body weight). Following bolus administration, the plasma glucose target concentration was maintained by tapering off the insulin infusion and discontinuing it when the plasma glucose dropped by 0.28 mmol/L relative to baseline. At this time, a variable intravenous glucose infusion (20% glucose; Fresenius Kabi, Bad Homburg, Germany) was started to maintain the plasma glucose target concentration for the rest of the clamp. The clamp was terminated 8 h after bolus administration or earlier if the plasma glucose level exceeded 8.3 mmol/L in the absence of glucose infusion. The plasma glucose concentration was determined at the bedside in 5–30-min intervals using a glucose-oxidase method (Super GL 2; Dr. Müller Gerätebau GmbH, Freital, Germany) with a coefficient of variation (CV) of less than 2%, while the plasma insulin concentration was determined as previously described,¹² using radioimmunoassay (Lispro Insulin RIA, Merck Millipore, Burlington, MA, USA) with intra-assay CVs of 6.1%–19%.

Following the end of clamp, the participants switched to routinely managing their diabetes with the study-specific insulin pump while being observed overnight. The described clamp experiment was repeated the next day using the extended-wear infusion set. Upon completing the experiment, the participants were observed overnight again, and were discharged the next morning to spend the days between the remaining clamp experiments at home routinely managing their diabetes with the extended-wear infusion set while following their daily routine. While at home, the participants documented insulin doses and carbohydrate intake in a diary and frequently monitored their glucose with the FGM system along with performing seven capillary blood glucose measurements per day using the integrated blood glucose meter. If the measured blood glucose concentration consistently exceeded 16.7 mmol/L, the participants were instructed to test

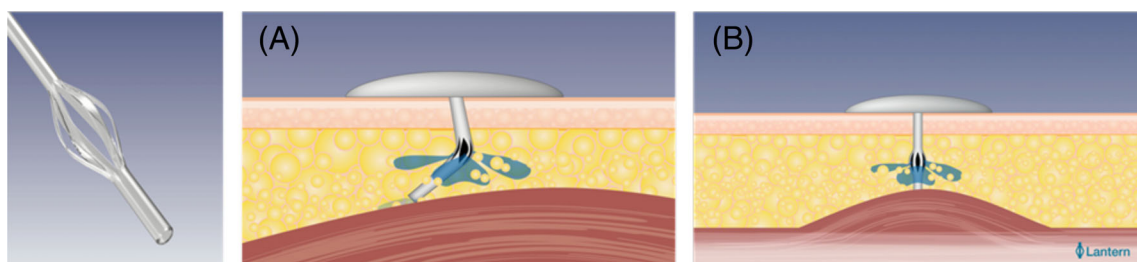


FIGURE 1 Extended-wear infusion set cannula with additional openings in the form of multiple longitudinal perforations in the cannula shaft: because of the cannula design, uninterrupted insulin flow is facilitated if A, the cannula is kinked, and B, when the cannula tip is occluded

the capillary blood for ketones and administer a correction bolus with an insulin pen (Humalog KwikPen). The two remaining clamp experiments were performed with the extended-wear infusion set on Days 4 and 7 of infusion-set wear following the described clamp protocol.

2.2 | Data analysis

The data were checked for normality with the Shapiro–Wilk test. Depending on normality distribution, the variables were analysed using the mixed-effect model, the repeated measures ANOVA, or the Friedman test. In case of a significant result ($p < .05$), the data were compared by means of the paired t-test or the Wilcoxon signed rank test with an adjusted level of significance ($p = .0083$, for all pharmacodynamic endpoints, and the total daily insulin dose). All data are presented as median (25th–75th percentiles) or mean \pm standard deviation.

3 | RESULTS

3.1 | Pharmacodynamics

Figure 2A shows glucose infusion rate profiles obtained following bolus administration of 0.15 IU/kg body weight of insulin lispro when using the standard and the extended-wear infusion set on Day 1 of infusion set wear. Although time to reach the maximum glucose infusion rate (T_{GIRmax}) was numerically considerably shorter with the standard compared with the extended-wear infusion set (67.5 [45–115] vs. 137.5 [72.5–147.5] min; $p = .046$), the numerical difference did not reach statistical significance, and the total area under the glucose infusion rate curve ($AUC_{GIR\ total}$) was similar between the sets (1042.3 [692.5–1311.5] vs. 874.2 [711.2–1130.1] mg/kg; $p = .197$) (Table 1).

Figure 2B shows glucose infusion rate profiles obtained following bolus administration of 0.15 IU/kg body weight of insulin lispro when using the extended-wear infusion set on Days 1, 4 and 7 of infusion-

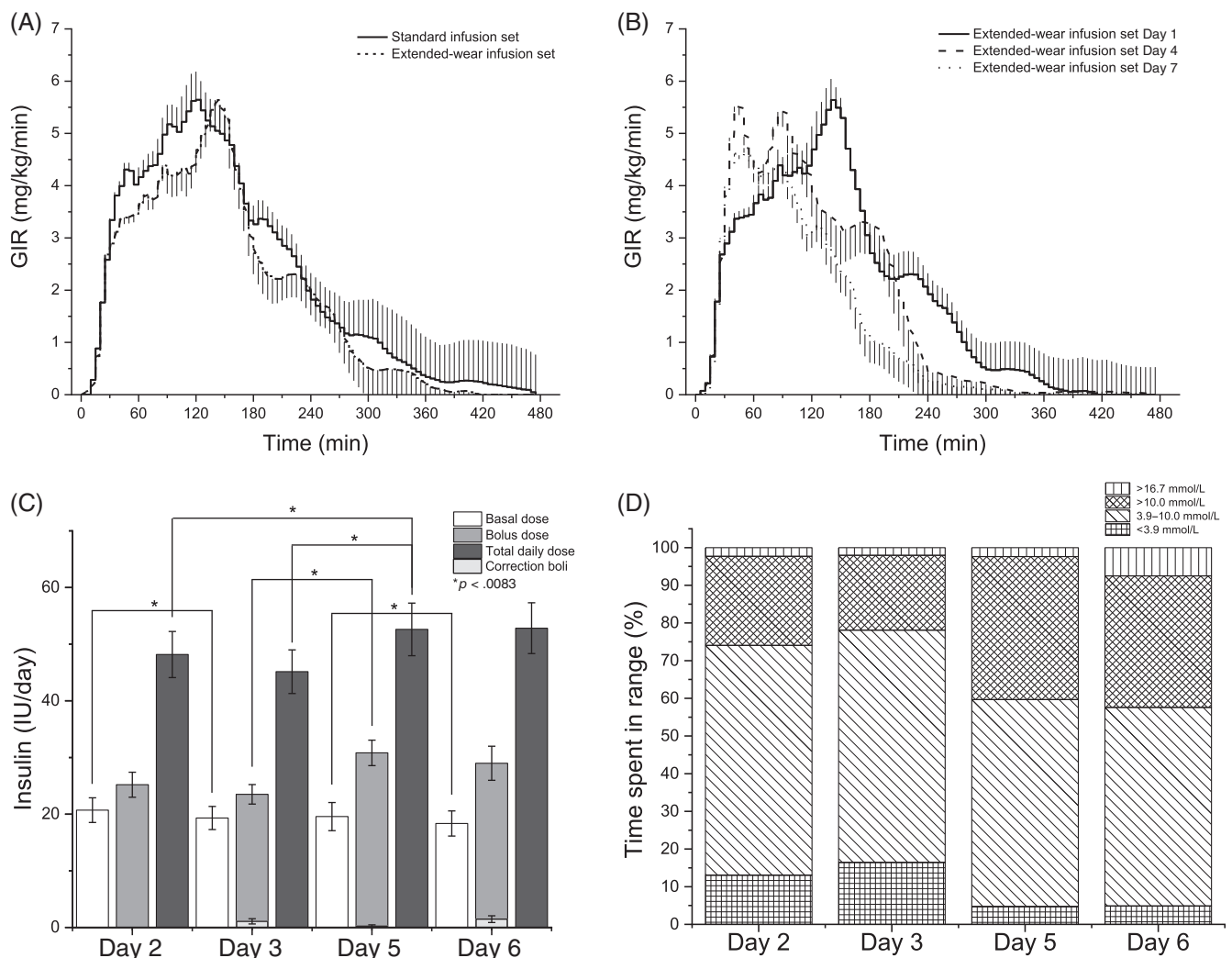


FIGURE 2 A, Glucose infusion rate (GIR) profiles ($n = 16$, mean \pm SEM) obtained following bolus administration of 0.15 IU/kg body weight of insulin lispro when using the standard and the extended-wear infusion set on Day 1 of infusion set wear. B, GIR profiles ($n = 16$, mean \pm SEM) obtained following bolus administration of 0.15 IU/kg body weight of insulin lispro when using the extended-wear infusion set on Days 1, 4 and 7 of infusion set wear. C, Total daily insulin dose ($n = 13$, mean \pm SEM) administered at home. D, Average percentage of time spent in different glycaemic ranges at home

set wear. While the area under the glucose infusion rate curve (AUC_{GIR}) was comparable for the first 2 h of each clamp experiment (Day 1: 339.8 [250.9–458.5] mg/kg vs. Day 4: 458.8 [280.4–592.7] mg/kg vs. Day 7: 414.8 [228.2–540.8] mg/kg; $p = .142$), it significantly decreased throughout the rest of the experiment with prolonged infusion-set wear (Day 1: 874.2 [711.2–1130.1] mg/kg vs. Day 4: 856.3 [509–1074.4] mg/kg vs. Day 7: 630.3 [328.3–814] mg/kg; $p = .03$). The reduction in the extent of insulin effect observed on Day 7 was accompanied by a substantial increase in the insulin absorption rate, with T_{GIRmax} reduced by 67% compared with Day 1 (Day 1: 137.5 [72.5–147.5] vs. Day 7: 45 [35–62.5] min; $p < .001$). Additionally, the plasma glucose concentration variability, as expressed by the CV, did not significantly differ during the four clamp experiments (standard infusion set, Day 1: 5.7% \pm 2.1%; extended-wear infusion set, Day 1: 5.0% \pm 1.1%; Day 4: 5.8% \pm 1.5%; Day 7: 5.2% \pm 1.4%; $p = .371$) (Figure 3 and Table 2).

3.2 | Pharmacokinetics

Both time to reach 50% of the maximum insulin concentration ($T_{CINSmax50\%}$) (Day 1: 23.3 [18.4–27.7] vs. Day 7: 12.8 [11.6–15.5] min; $p = .011$) and time to reach the maximum insulin concentration ($T_{CINSmax}$) (Day 1: 60 [35–80] vs. Day 7: 27.5 [20–35] min; $p = .016$)

were significantly shorter with prolonged infusion-set wear. There were no statistically significant differences in the maximum insulin concentration (C_{INSmax}) and the area under the insulin concentration

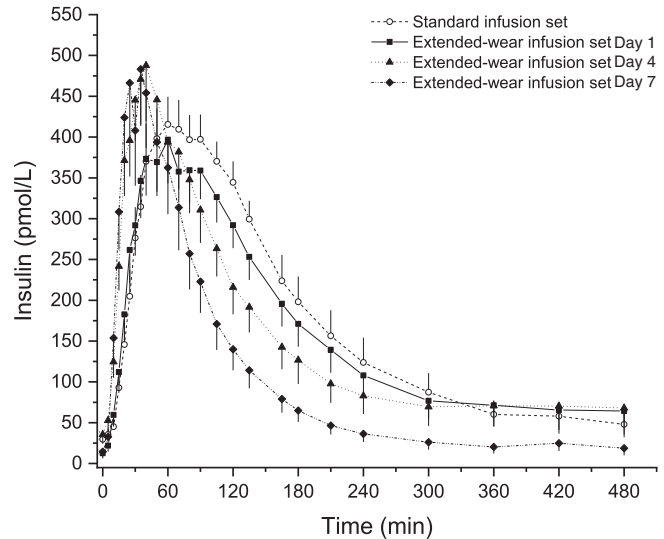


FIGURE 3 Plasma insulin concentration profiles ($n = 14$, mean \pm SEM) obtained following bolus administration of 0.15 IU/kg body weight of insulin lispro when using the standard and the extended-wear infusion set

TABLE 1 Summary of pharmacokinetic and pharmacodynamic variables of the standard and the extended-wear infusion set

Variable	Standard infusion set Day 1 Median (25th–75th)	Extended-wear infusion set Day 1 Median (25th–75th)	<i>p</i>
Pharmacodynamics			
GIR_{max} [mg/(kg*min)]	7.3 (5.2–8.8)	6.6 (4.1–8.4)	.482
T_{GIRmax} (min)	67.5 (45–115)	137.5 (72.5–147.5)	.046
$T_{GIRmax 10\%}$ (min)	20 (15–25)	20 (15–25)	.957
$T_{GIRmax 50\%}$ (min)	32.5 (25–37.5)	27.5 (22.5–45)	.971
$AUC_{GIR 0-60 min}$ (mg/kg)	152.9 (109.5–183)	122.2 (84.5–172.7)	.276
$AUC_{GIR 0-120 min}$ (mg/kg)	396.7 (272.8–579.8)	339.8 (250.9–458.5)	.279
$AUC_{GIR 0-240 min}$ (mg/kg)	809.5 (567.5–1140.5)	734 (603.3–1009.1)	.377
$AUC_{GIR 0-360 min}$ (mg/kg)	1036 (692.5–1280.2)	872.1 (709.1–1122.4)	.242
$AUC_{GIR total}$ (mg/kg)	1042.3 (692.5–1311.5)	874.2 (711.2–1130.1)	.197
Pharmacokinetics			
$T_{CINSmax 10\%}$ (min)	8.2 (2.9–15.9)	9.4 (6.2–18.1)	.052
$T_{CINSmax 50\%}$ (min)	28.8 (23.4–35.2)	23.3 (18.4–27.7)	.728
$T_{CINSmax}$ (min)	60 (40–70)	60 (35–80)	1.000
C_{INSmax} (pmol/L)	461.4 (385.4–544.2)	482.7 (384.4–561.3)	1.000
$AUC_{INS 0-60 min}$ (min*pmol/L)	15,512 (9677–18,770)	15,153 (12,901–19,803)	1.000
$AUC_{INS 0-120 min}$ (min*pmol/L)	36,667 (29,719–46,196)	36,944 (29,795–45,289)	1.000
$AUC_{INS total}$ (min*pmol/L)	81,245 (49,308–96,847)	69,063 (48,224–87,585)	.242

Abbreviations: $AUC_{GIR 0-tmin}$, area under the GIR curve from 0 min until specified time point; $AUC_{GIR total}$, area under the GIR curve from 0 min until clamp end; $AUC_{INS 0-tmin}$, area under the insulin concentration curve from 0 min until specified time point; $AUC_{INS total}$, area under the insulin concentration curve from 0 min until clamp end; C_{INSmax} , maximum insulin concentration; GIR_{max} , maximum glucose infusion rate; $T_{CINSmax 10\%}$, time to reach 10% of C_{INSmax} ; $T_{CINSmax 50\%}$, time to reach 50% of C_{INSmax} ; $T_{CINSmax}$, time to reach C_{INSmax} ; T_{GIRmax} , time to reach GIR_{max} ; $T_{GIRmax 10\%}$, time to reach 10% of GIR_{max} ; $T_{GIRmax 50\%}$, time to reach 50% of GIR_{max} .

TABLE 2 Summary of pharmacokinetic and pharmacodynamic variables of the extended-wear infusion set

Variable	Extended-wear infusion set Day 1 median (25th–75th)	Extended-wear infusion set Day 4 median (25th–75th)	Extended-wear infusion set Day 7 median (25th–75th)	<i>p</i> d1 vs. d4	<i>p</i> d1 vs. d7	<i>p</i> d4 vs. d7
Pharmacodynamics						
GIR _{max} [mg/(kg*min)]	6.6 (4.1–8.4)	7.5 (5.7–8.5)	6.7 (4–7.2)	.151	.595	.065
T _{GIRmax} (min)	137.5 (72.5–147.5)	50 (40–80)	45 (35–62.5)	.002	<.001	.215
T _{GIRmax 10%} (min)	20 (15–25)	20 (15–25)	20 (15–20)	.948	.755	.709
T _{GIRmax 50%} (min)	27.5 (22.5–45)	30 (25–35)	30 (22.5–30)	.610	.305	.425
AUC _{GIR 0–60 min} (mg/kg)	122.2 (84.5–172.7)	163.6 (136.1–210.2)	156.6 (113.3–200.6)	.027	.102	.508
AUC _{GIR 0–120 min} (mg/kg)	339.8 (250.9–458.5)	458.8 (280.4–592.7)	414.8 (228.2–540.8)	.060	.891	.223
AUC _{GIR 0–240 min} (mg/kg)	734 (603.3–1009.1)	815.8 (501–1017.9)	630.3 (328.3–811)	.533	.021	.037
AUC _{GIR 0–360 min} (mg/kg)	872.1 (709.1–1122.4)	856.3 (509–1074.4)	630.3 (328.3–814)	.173	<.008	.034
AUC _{GIR total} (mg/kg)	874.2 (711.2–1130.1)	856.3 (509–1074.4)	630.3 (328.3–814)	.177	<.008	.033
Pharmacokinetics						
T _{CINSmax 10%} (min)	9.4 (6.2–18.1)	4.5 (0–7.9)	6.2 (5.8–7.2)	.052	.052	.052
T _{CINSmax 50%} (min)	23.3 (18.4–27.7)	14.9 (13.5–17.5)	12.8 (11.6–15.5)	.011	<.001	.193
T _{CINSmax} (min)	60 (35–80)	35.5 (30–40)	27.5 (20–35)	.243	.016	.000
C _{INSmax} (pmol/L)	482.7 (384.4–561.3)	553 (352–699)	517.8 (290.7–763.8)	.521	.000	.000
AUC _{INS 0–60min} (min*pmol/L)	15,153 (12,901–19,803)	21,979 (13,580–28,960)	21,173 (10,838–30,405)	.040	.802	.000
AUC _{INS 0–120min} (min*pmol/L)	36,944 (29,795–45,289)	40,941 (24,079–56,289)	41,248 (14,294–48,145)	.000	.000	.766
AUC _{INS total} (min*pmol/L)	69,063 (48,224–87,585)	63,685 (43,857–86,341)	50,770 (28,792–70,679)	.770	.040	.019

Abbreviations: AUC_{GIR 0-tmin}, area under the GIR curve from 0 min until specified time point; AUC_{GIR total}, area under the GIR curve from 0 min until clamp end; AUC_{INS 0-tmin}, area under the insulin concentration curve from 0 min until specified time point; AUC_{INS total}, area under the insulin concentration curve from 0 min until clamp end; C_{INSmax}, maximum insulin concentration; GIR_{max}, maximum glucose infusion rate; T_{CINSmax 10%}, time to reach 10% of C_{INSmax}; T_{CINSmax 50%}, time to reach 50% of C_{INSmax}; T_{CINSmax}, time to reach C_{INSmax}; T_{GIRmax}, time to reach GIR_{max}; T_{GIRmax 10%}, time to reach 10% of GIR_{max}; T_{GIRmax 50%}, time to reach 50% of GIR_{max}.

curve from min 0 to min 120 (AUC_{INS 0–120 min}) between the different study days, or between the two infusion sets, while the total area under the insulin concentration curve (AUC_{INS total}) was slightly but significantly reduced with prolonged infusion-set wear (Day 1: 69,063.1 [48,223.6–87,584.9] vs. Day 7: 50,769.5 [28,791.9–70,679.4] min*pmol/L; *p* = .040).

The total daily insulin dose at home (Figure 2C) slightly increased over time (Day 2: 48.2 ± 14.7 vs. Day 3: 45.2 ± 13.9 vs. Day 5: 52.6 ± 16.7 vs. Day 6: 52.8 ± 16.2 IU; *p* = .045), while the percentage of time spent in hypoglycaemia (Figure 2D) significantly decreased (Day 2: 13.5% ± 11.3% vs. Day 3: 9.7% ± 11.2% vs. Day 5: 5.2% ± 6.8% vs. Day 6: 4.9% ± 7.8%; *P* = .038). The infusion set survival rate was 100% without reported infusion set failure, change of infusion site, leakage or occlusion alarms throughout the 7-day study period. None of the participants experienced severe hypoglycaemia or ketoacidosis during the study period.

4 | DISCUSSION

In this study we assessed the efficacy and safety of the novel, extended-wear insulin infusion set featuring Lantern technology over

7 days of wear. We used the euglycaemic clamp technique to determine the pharmacokinetic and the pharmacodynamic properties of the extended-wear infusion set in adults with type 1 diabetes following subcutaneous bolus administration of 0.15 IU/kg of rapid-acting insulin on Days 1, 4 and 7 of infusion-set wear. We observed a reduction in the extent of insulin absorption that was accompanied by an increase in the insulin absorption rate with prolonged infusion-set wear.

Our findings are consistent with those of previous studies that investigated the effects of prolonged infusion-set wear on insulin sensitivity in humans and swine.^{13,14} The study in humans examined the pharmacodynamics of two rapid-acting insulins over 4 days of standard infusion-set wear and observed a significant increase in the speed of insulin absorption on the last compared with the first study day. The study in swine compared a standard with an investigational infusion set over 5 days of wear and also found that the fastest insulin absorption occurred on the last study day. In addition, histological analysis of the infusion site tissue showed that the cannula-induced tissue damage caused by both the commercial and the investigational infusion set on Day 5 of infusion-set wear was similar to the damage observed in clean surgical wounds. The observed reduction in the extent of insulin absorption may be offset by the accompanying

increase in the insulin absorption rate. Furthermore, the increased absorption rate may also facilitate better postprandial glycaemic control (i.e. 2 h postmeal) during routine care, especially because the extent of insulin absorption observed during the postprandial time period was comparable with prolonged infusion-set wear. Finally, although the onset of insulin action was slower with the extended wear compared with the standard infusion set at the beginning of the study, the observed difference was not significant. The initially slower onset of insulin action may be attributed to the participants being mostly on bed rest during the first two study days, because prolonged bed rest is associated with increased insulin resistance.¹⁵

Being able to safely use the same insulin infusion set beyond the currently recommended 3 days would provide a number of benefits to individuals on CSII therapy: by changing infusion sets less frequently, the insertion-related pain experienced may be reduced, as well as the time and effort required to change the set, which in turn may increase treatment compliance and lead to an improved quality of life. Furthermore, individuals using hybrid closed-loop systems would presumably benefit most from the extended-wear infusion set because, in addition to being mitigated by the faster onset of insulin action, the somewhat reduced extent of insulin absorption may also be mitigated by automated basal insulin delivery.

In summary, although this pilot study is limited because of its small population size, the non-randomized design and the lack of a control group, the data presented suggest that the novel, extended-wear insulin infusion set featuring Lantern technology safely maintains glycaemic control during prolonged wear.

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CONFLICT OF INTEREST

PKS, MH and TS are ConvaTec employees. TRP is an advisory board member of Novo Nordisk A/S, consultant for Roche Diabetes Care, Novo Nordisk A/S, Eli Lilly & Co, Infineon, Carnegie Bank, shareholder of decide Clinical Software GmbH, and is on speaker's bureau of Novo Nordisk A/S and Astra Zeneca. JKM is an advisory board member of Abbott Diabetes Care, Boehringer Ingelheim, Becton-Dickinson, Eli Lilly, Medtronic, Merck Sharp & Dohme GesmbH, Roche Diabetes Care and Sanofi-Aventis GmbH, a shareholder of decide Clinical Software GmbH, and has received speaker honoraria from Abbott Diabetes Care, Astra Zeneca, Dexcom, Eli Lilly, Medtronic, Novo Nordisk A/S, Roche Diabetes Care, Sanofi-Aventis GmbH, Servier and Takeda. The other authors declare no competing interests.

AUTHOR CONTRIBUTIONS

AS, TP and DN performed the study, interpreted data and contributed to discussions. AS, JKM and TA drafted the manuscript. WR, TRP, MH, TS and PKS contributed to discussions and interpreted data. TA, AGS and AS performed statistical analysis and interpreted data. JKM

designed the study, interpreted data, contributed to discussions, supervised the project and is the guarantor of this work. All the authors critically revised and approved the final version of the manuscript.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14337>.

DATA AVAILABILITY STATEMENT

Data are available with the authors upon request.

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