BRIEF REPORT

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Patient-reported outcomes in a study of human regular U-500 insulin delivered by continuous subcutaneous insulin infusion or multiple daily injections in patients with type 2 diabetes

Jieling Chen PhD[1] | Ludi Fan PhD[1] | Xiaomei Peng MD[1] | Liza Ilag MD[1] | Trang Ly MBBS[2] | Jennal Johnson MS[1]

[1]Eli Lilly and Company, Indianapolis, Indiana

[2]Insulet Corporation, Billerica, Massachusetts

Correspondence
Jieling Chen, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA.
Email: chen_jieling@lilly.com

Abstract

Human regular U-500 insulin (U-500R) provides both basal and prandial coverage to people with diabetes. As part of the VIVID study, we studied patient-reported outcomes (PRO) of U-500R delivered by multiple daily injections (MDI, n = 211) and continuous subcutaneous infusion using a novel U-500R pump (CSII, n = 209). Treatment-Related Impact Measure for Diabetes (TRIM-D) for Diabetes Device (TRIM-DD) questionnaires were administered at weeks 0, 14 and 26. TRIM scores with effect sizes (ES) for within-group and between-group change were reported. All TRIM-D scores significantly improved from baseline for both groups ($P < .001$). The Diabetes Management domain had the greatest improvement, 16.3 (ES = 0.85) and 10.6 (ES = 0.51) for CSII and MDI, respectively. At the study end, the CSII group had significantly higher TRIM-D scores than the MDI group ($P < .05$). Most TRIM-DD scores had small within-group improvements and were not different between groups. People with type 2 diabetes on U-500R by either CSII or MDI reported improvement in PRO, particularly in Diabetes Management, Treatment Burden and Psychological Health domains, with greater improvement in the CSII group. In terms of delivery device and function, the CSII and MDI methods were similarly acceptable.

KEYWORDS

CSII, MDI, patient-reported outcomes, TRIM-D, TRIM-DD, type 2 diabetes

1 | INTRODUCTION

Human regular U-500 insulin (U-500R) monotherapy is indicated for patients requiring high insulin doses (>200 units/day).[1] U-500R has unique pharmacokinetics and pharmacodynamics properties that provide both basal insulin coverage and post-prandial glucose-lowering effects.[2] Although not an approved route of administration, continuous subcutaneous insulin infusion (CSII) of U-500R may confer benefits of pump delivery such as flexible lifestyle, precise dosing and frequent dose calculations.[3]

In the Evaluating U-500R Infusion vs Injection in Type 2 Diabetes (T2D) mellitus (VIVID) study (NCT02561078), U-500R treatment by CSII (using the investigational Omnipod DASH™ U-500 Insulin

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Management System) was compared with that by multiple daily injection (MDI) for assessing their efficacy and safety in participants with T2D. As an exploratory analysis within the VIVID study, we assessed patient-reported outcomes (PRO) to capture patient functioning and well-being factors impacted by U-500R treatment with CSII compared with MDI.

2 | METHODS

2.1 | Study design and measures

Participants with T2D and inadequate glycaemic control were randomized to receive U-500R treatment by CSII (using the investigational Omnipod DASH™ U-500 Insulin Management System; n = 209) or MDI (n = 211). The study design is described elsewhere[4] and in Supporting Information. The study protocol was approved by local ethics review boards. All participants provided informed consent before participation.

Two validated PRO measures, Treatment-Related Impact Measure for Diabetes (TRIM-D) and for Diabetes Device (TRIM-DD),[5] were administered at weeks 0 (at randomization/baseline), 14 and 26, or at the time of early termination. TRIM-D consists of five domains: Treatment Burden, Daily Life, Diabetes Management, Compliance, and Psychological Health. TRIM-DD consists of two domains: Device Function and Bother of Device. TRIM scores (TRIM-D and TRIM-DD) range from 0 to 100 with a higher score indicating a better health state (see Supporting Information).

As TRIMs are devised as instruments for PROs with abstract scores, effect sizes (ES) were measured by Cohen's d to contextualize the difference in scores.[6] ES for within-patient change score was calculated by dividing mean change in score by standard deviation (SD) of the mean baseline score; whereas ES for between-group change score difference was calculated by dividing mean change difference of the two groups by pooled SD.[7] ES was categorized as: trivial (<0.2), small (≥0.2-0.4), moderate (≥0.4-<0.8), and large (≥0.8).[6]

2.2 | Statistics

All TRIM scores and their changes from baseline to weeks 14 and 26 were analysed using a mixed-effects model for repeated measures (MMRM) approach. Besides baseline measures, the MMRM model included the following fixed effects: treatment device, weeks on treatment, interaction between treatment and weeks, and stratification factors [U-500R at entry vs. other insulins, entry glycated haemoglobin (HbA1c) ≥8.5% or <8.5%, and non-users vs. users of glucagon-like peptide-1 receptor agonists or sodium-glucose cotransporter-2 inhibitors].[4] ES were estimated for TRIM change scores within and between MDI and CSII groups with the 95% confidence intervals (CIs) estimated using a bootstrapping procedure. Statistical testing was performed at the .05 significance level with no adjustments for multiplicity. All analyses were performed using SAS version 9.2 or higher (SAS Institute, Inc., Cary, NC, USA).

3 | RESULTS

Baseline demographics, clinical characteristics and TRIM scores were comparable between the CSII and the MDI groups (Table 1, Table S1, Figures S1 and S2). However, regardless of the therapy groups, baseline scores for TRIM-DD were higher than those for the TRIM-D (78.7-80.4 vs. 47.5-71.2, respectively). Among all baseline scores, Diabetes Management had the lowest score (mean ± SD: 47.5 ± 20.8 for CSII and 49.1 ± 19.6 for MDI).

3.1 | TRIM-D

Patients in both groups had a statistically significant improvement in all TRIM-D scores from baseline to week 26 (Table 1, Figure S1), with the CSII group scoring significantly higher than the MDI group in all five domains. The least-squares mean ± standard error (LSM ± SE) change from baseline score in overall score was 11.0 ± 0.9 for the CSII group with a large ES (0.82) and 6.1 ± 0.9 for the MDI group with a moderate ES (0.42; Table 1). For individual domains, all the within-treatment changes were statistically significant with moderate ES, except for the Compliance domain. The greatest change was observed in the Diabetes Management domain (16.3 ± 1.4 and 10.6 ± 1.4, for CSII and MDI groups, respectively), with large ES (0.85) in the CSII group and moderate ES (0.51) in the MDI group. The between-group difference was statistically significant (P = .005) with a small ES of 0.35 (CI: 0.10, 0.61). The next largest changes were observed in the Treatment Burden and Psychological Health domains with statistically significant LSM ± SE changes from baseline of 12.5 ± 1.3 (ES = 0.59) and 10.1 ± 1.2 (ES = 0.58) in the CSII group and statistically significant changes from baseline in the MDI group of 6.7 ± 1.3 (ES = 0.27) and 6.7 ± 1.2 (ES = 0.37), respectively. For the Daily Life domain and Compliance domain in the CSII group, LSM ± SE score changes were 8.8 ± 1.4 (moderate ES = 0.50) and 6.7 ± 1.3 (small ES = 0.39), respectively. The MDI group showed smaller LSM ± SE score changes with small ES [2.6 ± 1.3 (ES = 0.13) and 3.0 ± 1.2 (ES = 0.12), respectively].

The overall week 26 score in the CSII group was significantly higher than that in the MDI group with a moderate between-group difference in ES (0.43, CI: 0.21, 0.66). Individual week 26 domain scores were all statistically higher in the CSII group than in the MDI group, but the between-group differences in ES were small (0.20-0.39).

3.2 | TRIM-DD

The CSII and MDI groups showed significant improvements in TRIM-DD overall and all domain scores from baseline to week 26 (P < .05; Table 1), except for the Device Function domain in the CSII group.

TABLE 1 Change from baseline in patient reported outcomes (TRIM-D and TRIM-DD)

TRIM domains	U-500R CSII				U-500R MDI				Between-group difference at week 26	
	Baseline (mean ± SD)	Week 14 CFB (LSM ± SE)	Week 26 CFB (LSM ± SE)	Effect size for CFB at week 26 (CI)	Baseline (mean ± SD)	Week 14 CFB (LSM ± SE)	Week 26 CFB (LSM ± SE)	Effect size for CFB at week 26 (CI)	LSM difference	Effect size for LSM (CI)
TRIM-D										
Overall score	64.1 ± 14.22	9.8 ± 0.8#,*	11.0 ± 0.9#,*	0.82(0.65, 1.00)	65.4 ± 13.30	6.7 ± 0.8#,*	6.1 ± 0.9#,*	0.42(0.26, 0.57)	5.0(2.5, 7.4)*	0.43(0.21, 0.66)
Treatment burden	64.8 ± 22.08	11.7 ± 1.2#,*	12.5 ± 1.3#,*	0.59(0.43, 0.75)	67.0 ± 21.11	6.3 ± 1.2#,*	6.7 ± 1.3#,*	0.27(0.13, 0.40)	5.8(2.2, 9.4)*	0.34(0.12, 0.57)
Daily life	65.9 ± 19.30	6.3 ± 1.2#	8.8 ± 1.4#,*	0.50(0.34, 0.66)	67.0 ± 17.87	4.8 ± 1.2#	2.6 ± 1.3#,*	0.13(−0.08, 0.32)	6.2(2.5, 9.9)*	0.39(0.14, 0.65)
Diabetes management	47.5 ± 20.77	12.6 ± 1.2#	16.3 ± 1.4#,*	0.85(0.65, 1.07)	49.1 ± 19.60	10.6 ± 1.2#	10.6 ± 1.4#,*	0.51(0.33, 0.69)	5.7(1.7, 9.6)*	0.35(0.10, 0.61)
Compliance	68.4 ± 19.17	9.3 ± 1.1#,*	6.7 ± 1.3#,*	0.39(0.23, 0.55)	69.9 ± 17.94	5.8 ± 1.1#,*	3.0 ± 1.2#,*	0.12(−0.05, 0.28)	3.7(0.2, 7.2)*	0.29(0.06, 0.52)
Psychological health	70.7 ± 18.03	9.0 ± 1.1#	10.1 ± 1.2#,*	0.58(0.43, 0.74)	71.2 ± 17.57	6.3 ± 1.1#	6.7 ± 1.2#,*	0.37(0.22, 0.52)	3.3(0.1, 6.6)*	0.20(−0.02, 0.43)
TRIM-DD										
Overall score	79.6 ± 14.82	2.9 ± 0.9#	4.3 ± 0.9#	0.32(0.16, 0.47)	80.4 ± 15.53	5.3 ± 0.9#	3.6 ± 0.9#	0.19(0.05, 0.32)	0.7(−1.9, 3.2)	0.12(−0.08, 0.34)
Bother of device	80.0 ± 23.47	5.6 ± 1.4#	7.6 ± 1.5#	0.39(0.24, 0.53)	83.1 ± 21.26	5.2 ± 1.4#	3.6 ± 1.4#	0.09(−0.09, 0.25)	4.0(0.0, 8.0)	0.32(0.08, 0.57)
Device function	79.3 ± 17.29	1.1 ± 1.1*	2.1 ± 1.1	0.12(−0.05, 0.27)	78.7 ± 18.82	5.5 ± 1.0#,*	3.8 ± 1.1#	0.19(0.05, 0.31)	−1.7(−4.8, 1.3)	−0.08(−0.29, 0.13)

Abbreviations: CFB, change from baseline; CI, confidence interval; CSII, continuous subcutaneous insulin infusion; LSM, least squares mean; MDI, multiple daily injection; SD, standard deviation; SE, standard error; TRIM-D, Treatment Related Impact Measure for Diabetes; TRIM-DD, Treatment Related Impact Measure for Diabetes Device; U-500R, human regular U-500 insulin.

#$P < .05$ within-treatment change from baseline.

*$P < .05$ between-treatment change from baseline. Number of patients (n) in the population with baseline and postbaseline value varied at different time points due to dropouts. For CSII group: n = 197 at baseline, n = 186 at week 14, and n = 171 at week 26; for MDI group: n = 197 at baseline, n = 191 at week 14, and n = 181 at week 26.

The ES for within-treatment changes was small/trivial for the CSII group and trivial for the MDI group (Table 1).

No statistically significant differences were observed between the CSII and MDI groups on the TRIM-DD scores at week 26 (Table 1, Figure S2). The Overall Score and Device Function domain showed no effect difference between groups, but the Bother of Device domain had a small effect difference favouring the CSII group (0.32, CI: 0.08, 0.57).

4 | DISCUSSION

In the VIVID study, U-500R treatment by both CSII and MDI had a positive effect on treatment-related well-being and patient functioning, with a greater improvement in the CSII group. For either group, all domain and overall scores in both TRIM-D and TRIM-DD were significantly higher at the study end compared with baseline, except for Device Function in the CSII group. All TRIM-D scores were significantly higher in the CSII group compared with the MDI group. From a PRO perspective, this study adds much-needed evidence for the CSII benefits in people with T2D.

This study highlights that PROs could capture the broad treatment effect on a patient's well-being and functioning, some of which were mediated through changes in clinical outcomes and some directly impacted by treatment. TRIMs are designed to capture clinical outcomes as part of the Diabetes Management and Psychological Health domain. A post hoc analysis confirmed that, among the TRIM measures, the Diabetes Management domain and the overall TRIM score were significantly related to improvement in HbA1c after adjusting for confounders (P = .007 and P = .026, respectively). Equally important is that TRIMs captured the direct effect of U-500R on aspects such as patients' social activities, energy level, medication storage and depression, with patients' well-being improving comprehensively in all TRIM domains. The U-500R results contrast with a wide range of diabetes treatment studies with TRIM application,[8-11] wherein the scores appeared to be consistent with the reported clinical outcomes, yet none showed broad improvement in all TRIM-D domains and overall scores. The low baseline scores in this study compared with those studies[9,10] reflect the poor health state and low treatment satisfaction[12,13] of patients requiring high insulin doses.

Results from the MDI group are consistent with the results from a previous study[13] in patients with T2D requiring high dose insulin and transitioning from U-100 MDI to U-500R in which the TRIM-D scores demonstrated clinically relevant and significant improvements. In both studies, the Diabetes Management domain, which captures treatment efficacy and the impact of side effects on PRO,[5] had the lowest baseline score and the greatest improvement at study end. This implies that diabetes management was a major challenge for patients requiring high-dose insulin and demonstrated that U-500R MDI as an insulin monotherapy improved the ability of patients to manage their disease.

U-500R CSII treatment could further augment patients' well-being (Figure 1). Improvement in the Diabetes Management domain in the CSII group over the MDI group was prominent, consistent with the fact that the CSII group showed statistically significant improvement in HbA1c and fasting plasma glucose levels compared with the MDI group,
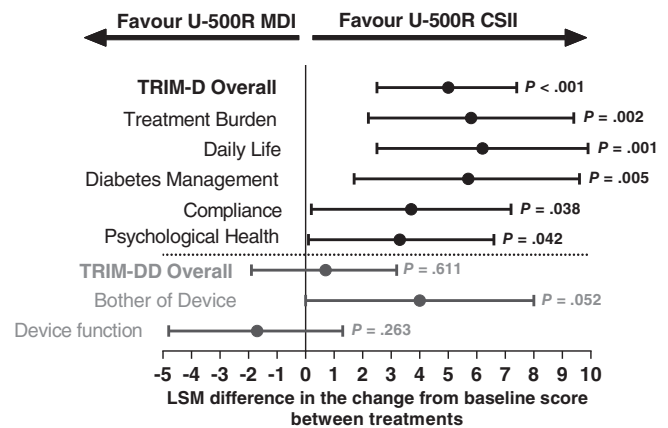

FIGURE 1 Forest plot depicting patient response on U-500R treatment by CSII or MDI. CSII, continuous subcutaneous insulin infusion; LSM, least squares mean; MDI, multiple daily injection; TRIM-D, Treatment Related Impact Measure for Diabetes; TRIM-DD, Treatment Related Impact Measure for Diabetes Device; U-500R, human regular U-500 insulin

as well as a statistically greater percentage of patients reaching the HbA1c target of <7% and <7.5%.[4] Also consistent with better glycaemic control in the CSII group[4] was the small to moderately higher Psychological Health score change compared with the MDI group, as the psychological component of treatment is often driven by efficacy.[6,14] The CSII group also showed a moderate magnitude of improvement over the MDI group in the Treatment Burden domain, which is probably a reflection of pump therapy benefits such as flexibility, discretion, convenience, embedded dose calculation and dosing precision.

Although the CSII group scored higher on TRIM-D, the TRIM-DD scores were similar between groups. These findings suggest that insulin itself, more than the insulin delivery method, played a major role in PRO improvement. The observed ES were smaller for TRIM-DD than for TRIM-D in general. The unremarkable ES in within-group change for Device Function indicate that studied patients with an average 17 years of diabetes, did not have a steep learning curve for pump use and adapted quickly to U-500R administered through either CSII or MDI. The continued MDI use by a fraction of the 28% of participants who were already administering U-500R using U-100 syringes before their transition to MDI, may have also caused the unremarkable change in TRIM-DD scores. The significantly improved score in the CSII group for the Bother of Device domain with a moderate ES may be attributed to the increased acceptability of insulin pumps among obese or severely insulin-resistant patients.[15] The tubeless U-500R CSII device may further add to the patients' convenience.

Strengths of the study include its prospective design as part of the randomized trial with a large number of participants and its focus on PROs for insulin delivery via CSII and MDI. One weakness is the open label design. The favourable CSII results over MDI found in this study may be limited to people with T2D who are able to manage diabetes with CSII, given that seven patients allocated to the CSII group discontinued the treatment for various reasons.

In conclusion, all the TRIM-D and TRIM-DD scores for both CSII and MDI groups demonstrated clinically and statistically significant

improvements during the study period, except for the Device Function score in the CSII group. U-500R treatment administered via either CSII or MDI increased overall patient satisfaction, ameliorated treatment burden, improved daily life and diabetes management, and promoted psychological health. When comparing score changes between delivery methods, the CSII group scored higher than the MDI group on TRIM-D, indicating U-500R CSII treatment further enhanced patients' well-being. The CSII delivery for U-500R was perceived to be as acceptable as the MDI delivery in terms of device burden.

AUTHOR CONTRIBUTIONS

All authors were involved in the preparation and critical review of this manuscript and gave their approval to publish this version of the manuscript. Jieling Chen was involved in the design of the work and interpretation of data. Xiaomei Peng was involved in the design of the work. Ludi Fan, Liza Ilag and Trang Ly were involved in the interpretation of the data. Jennal Johnson was involved in the conception and design of the work and interpretation of data.

DATA AVAILABILITY STATEMENT

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

ORCID

Trang Ly ![ORCID] https://orcid.org/0000-0002-5995-1447

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.