# Improved insulin adherence after introduction of a smart connected insulin pen

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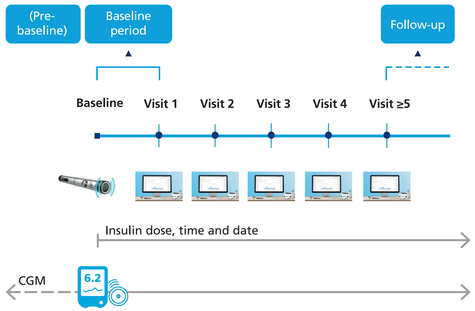
## Background

- The association between missed insulin injections and the impact on $HbA_{1c}$ levels in insulin-dependent diabetes is well established, with the unwanted effect of increasing the risk of diabetes-related complications.[1–4]
- The smart connected NovoPen® 6 collects and stores data on the date and time of insulin injections and the number of units administered. These data are then downloaded using near field connectivity to a centralised database. This allows healthcare professionals (HCPs) and patients to look at injection data together when discussing insulin treatment. If the injection data are further combined with glucose/continuous glucose monitoring (CGM) data the potential to improve patient-HCP dialogue is thought to be even greater.
- The possibility to have a combined view of insulin injections and CGM data and the potential for improved dialogue between patients and HCPs can eliminate any guessing about doses taken, missed doses and optimal injection time in relation to meals.
- An engaging and open patient-HCP dialogue has been identified as highly important for optimal disease management, and could reduce the number of missed insulin injections to improve treatment adherence.[5,6] It is therefore of interest to assess whether use of the NovoPen® 6 can reduce the number of missed injections in everyday clinical use.

**Figure 1**: Study design

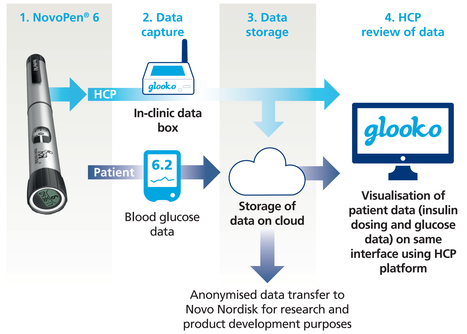



Pre-baseline was the period before study commencement where patients were already using CGM, but without concurrent use of the NovoPen® 6.
CGM, continuous glucose monitoring.

## Aim

- To investigate whether the use of NovoPen® 6 can influence the behaviour of patients with type 1 diabetes (T1D) in terms of change in numbers of missed bolus dose (MBD) injections.

**Figure 2**: Using NovoPen® 6 with the Glooko/Diasend® system

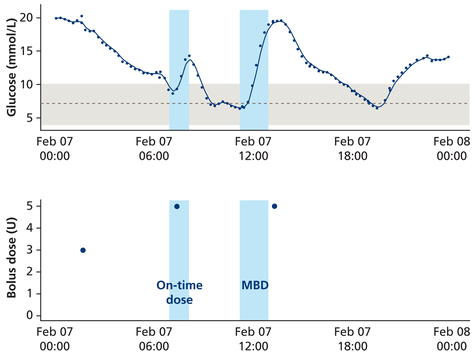



HCP, healthcare professional.

## Methods

- This pilot study was a prospective, non-interventional study running from May 2017–Nov 2018. Twelve diabetes clinics from different parts of Sweden participated. Patients with T1D using CGM were included if their treating physicians decided to offer them a NovoPen® 6.
- At baseline, patients received a NovoPen® 6 for basal and/or bolus insulin injections. Baseline was then followed by a baseline period between pen introduction and visit 1, during which the patient started to use the NovoPen® 6 but without access to downloads of injection data. The first data download occurred at visit 1, using the Glooko/Diasend® in-clinic system to transfer data from the pen to the Glooko/Diasend® server. From here the data were accessed via the Glooko/Diasend® HCP web portal and the patient and HCP had the first chance to look at the data together.
- Hereafter, the study continued with HCP visits according to clinical practice. At each visit, pen data were available for download and use by the patient and HCP during the consultation (Figures 1 and 2).
- With this study design, it was possible to compare the number of MBD injections between the baseline and follow-up periods. CGM and dosing data from the first 14 days following a clinic visit were used in the analyses. The 14-day time period was chosen to be in line with the international consensus on the use of CGM.[7] Visit 5 was chosen as the earliest point for follow-up, as patients would on average have been in the study for ≥180 days, allowing for sufficient interaction with HCPs and discussion of available pen data.
- MBDs were identified using the clinically validated Glucose Rate Increase Detector (GRID) algorithm[8] to detect meals from the CGM signal. An MBD was defined as an occasion where no bolus injection had occurred within –15 to +60 minutes from the start of a meal, as detected by the algorithm (Figure 3).

**Figure 3**: Detection of missed bolus insulin doses by the GRID algorithm




Example of a day with two meals detected. The solid dark blue line represents the CGM signal and the light blue shaded areas each represent a detected meal. The grey dashed line represents a glucose level of 7.2 mmol/L and the grey shaded area represents a target glycaemic range of 3.9–10.0 mmol/L, as previously reported.[8] Meals are detected when the CGM signal is ≥7.2 mmol/L and increases steeply over 30–45 minutes. A bolus dose within 15 minutes before to 60 minutes after a meal starts is considered 'on-time', whereas a dose outside of this time window is considered an MBD. Male patient, aged 30 at baseline.
CGM, continuous glucose monitoring; GRID, Glucose Rate Increase Detector; MBD, missed bolus dose.

### Statistical analyses

- Pen and CGM data for each patient were linked based on patient IDs. Data from days with unacceptable CGM coverage (<70%) or where bolus injections were not available, were excluded.
- Each day was aggregated to the number of MBD meals, the number of on-time meals and total number of meals.
- A generalised linear mixed model based on the Poisson distribution was applied with visit number (baseline, 1, 2, 3, 4, 5+) as fixed effect and patient and visit nested within patient as random effects. The model allows for unbalanced and missing data.
- The estimated difference between the follow-up period (visits ≥5) and the baseline period was obtained on the logarithmic-scale. Estimates and 95% confidence intervals were converted to the original scale.

## Results

- Eighty-one adults with T1D with a mean [min; max] age of 39.2 years [18; 83] were included in these analyses. A total of 1892 days were analysed.
- A significant decrease of 43.1% in the average daily number of MBD injections was observed from the baseline period to the follow-up period, from 0.74 (95% CI [0.62; 0.88]) to 0.42 (95% CI [0.30; 0.60]) ($p$=0.002) (Figure 4 and Table 1).
- Based on the assumption that patients have three main meals per day, this corresponded to a decrease from 24.7% (95% CI [20.8; 29.4]) to 14.1% (95% CI [9.9; 19.9]) in MBD injections (Table 1).

**Table 1**: Mean number of daily meals and dosing behaviours from the baseline period to the follow-up period

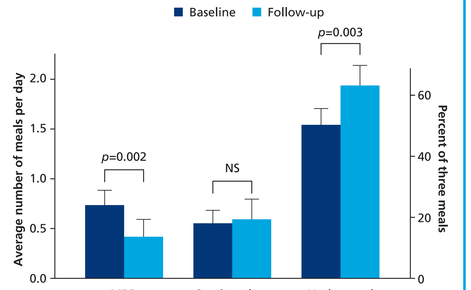
| | Estimated relative change [95% CI] | Baseline level [95% CI] | | Follow-up level [95% CI] | | *P* value |
|---|---|---|---|---|---|---|
| | | Daily meals (n) | Proportion of 3 meals | Daily meals (n) | Proportion of 3 meals | |
| MBD | –43.1% [–60.5; –18.0] | 0.74 [0.62; 0.88] | 24.7% [20.8; 29.4] | 0.42 [0.30; 0.60] | 14.1% [9.9; 19.9] | 0.002 |
| On-time dose | 2.7% [–24.7; 40.2] | 0.57 [0.48; 0.69] | 19.1% [15.9; 23.0] | 0.59 [0.43; 0.80] | 19.6% [14.5; 26.7] | 0.865 |
| Undetected meals* | 25.4% [8.7; 43.5] | 1.54 [1.37; 1.70] | 51.5% [45.6; 56.7] | 1.94 [1.69; 2.14] | 64.6% [56.4; 71.2] | 0.003 |

Mean and 95% CI based on a mixed Poisson model, with visit number (baseline, 1, 2, 3, 4, 5+) as fixed effect and patient and visit nested in patient as random effects.
*Assuming 3 meals per day on average. CI, confidence interval; MBD, missed bolus dose; n, number.

- A significant increase in the number of daily, undetected meals was observed from the baseline period to the follow-up period, from 1.54 (95% CI [1.37; 1.70]) to 1.94 (95% CI [1.69; 2.14]) (Figure 4 and Table 1).
- These results indicate that patients achieved more well-dosed meals, as indicated by the slight increase in the number of on-time doses observed in the follow-up period compared with the baseline period (Table 1). The increase was not statistically significant, however, because well-dosed meals tend to have a lower CGM response and are as such undetected by the GRID algorithm (Figure 3).

**Key result**

**Figure 4**: Mean number of daily meals and dosing behaviours from the baseline period to the follow-up period




Estimated mean number of daily meals with 95% confidence intervals. MBD are meals with missed bolus doses. On-time doses are meals where a bolus dose is taken. Undetected are meals that are not detected by the CGM signal, assuming an average of three meals per day.
CGM, continuous glucose monitoring; MBD, missed bolus dose; NS, not significant.

## Conclusions

- These real-world findings confirm that missed bolus dose injections are the reality for patients with T1D and that the smart connected NovoPen® 6 can support good injection behaviour, with fewer missed and more well-dosed mealtime injections.
- This could subsequently lead to better glycaemic control and thus lower the risk of diabetes-related complications.

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**References:** (**1**) The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993;329:977–86; (**2**) Nathan *et al. N Engl J Med* 2005;353:2643–53; (**3**) Holman *et al. N Engl J Med* 2008;359:1565–76; (**4**) Munshi *et al. Diabetes Care* 2013;36:543–9; (**5**) Heisler *et al. J Gen Intern Med* 2002;17:243–52; (**6**) Ritholz *et al. Chronic Illn* 2014;10:303–13; (**7**) Danne *et al. Diabetes Care* 2017;40:1631–40; (**8**) Harvey *et al. J Diabetes Sci Technol* 2014;8:307–20.