Outcomes of using flash glucose monitoring technology by children and young people with type 1 diabetes in a single arm study

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Background and Objective: Outcomes of using flash glucose monitoring have been reported in adults. This trial evaluated use in children and teenagers with type 1 diabetes.

Methods: Prospective, single arm, non-inferiority multicenter study to demonstrate equivalence of time in range (TIR [70-180 mg/dL]) by comparing 14-day masked sensor wear (baseline) with self-monitored blood glucose (SMBG) testing to the final 14-days of 8-week open-label system use for diabetes self-management including insulin dosing.

Results: A total of 76 children and teenagers (46.1% male; age 10.3 ± 4.0 years, type 1 diabetes duration 5.4 ± 3.7 years; mean ± SD) from 10 sites participated. TIR improved significantly by 0.9 ± 2.8 h/d (P = 0.005) vs SMBG baseline. Time in hyperglycemia (>180 mg/dL) reduced by −1.2 ± 3.3 h/d (P = 0.004). HbA1c reduced by −0.4% (−4.4 mmol/mol), from 7.9 ± 1.0% (62.9 ± 11.2 mmol/mol) baseline to 7.5 ± 0.9% (58.5 ± 9.8 mmol/mol) study end (P < 0.0001) with reductions across all age-subgroups (4-6, 7-12 and 13-17 years). Time in hypoglycemia (<70 mg/dL) was unaffected. Throughout the treatment phase system utilization was 91% ± 9%; sensor scanning was 12.9 ± 5.7/d with SMBG dropping to 1.6 ± 1.9 from 7.7 ± 2.5/d. Diabetes Treatment Satisfaction Questionnaire “Total Treatment Satisfaction” score improved for parents (P < 0.0001) and teenagers (P < 0.0001).

No adverse events (n = 121) were associated with sensor accuracy, 42 participants experienced sensor insertion signs and symptoms. Three participants experienced three mild device-related (sensor wear) symptoms, resolving quickly (without treatment [n = 2], non-prescription antihistamines [n = 1]).

Conclusions: Children with diabetes improved glycemic control safely and effectively with short-term flash glucose monitoring compared to use of SMBG in a single arm study.

KEYWORDS
children, glycated hemoglobin A1c, self-monitoring, technology

1 INTRODUCTION

Glucose monitoring is recognized as an essential element of diabetes management for children with diabetes and their caregivers or families. Use of standard continuous glucose monitoring (CGM) is increasingly recognized to be of benefit in pediatric individuals with diabetes. However, published data demonstrating the glycemic benefit of standard CGM use in pediatrics is less certain. The change in glycated hemoglobin (HbA1c) levels between the pediatric participants in the intervention and control groups in the Juvenile Diabetes Research Foundation (JDRF) trial in CGM did not reach significance. Other studies have reported improved HbA1c levels in mixed cohorts

Abbreviations: CGM, continuous glucose monitoring; DTSQ, diabetes treatment satisfaction questionnaire; MDI, multiple daily injection; PLGM, predictive low glucose management; SMBG, self-monitoring of blood glucose; TDD, total daily dose

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of adults and children or restricted inclusion to insulin pump users. More recently the value of standardizing reports of CGM data in addition to HbA1c has gained momentum, focusing on time in target range results can be invaluable to expedite understanding of the obstacles to improving glucose control. The aim of this study was to demonstrate the equivalence (non-inferiority) of time in range using the flash glucose monitoring system compared to self-monitoring of blood glucose (SMBG) in children and young people (4-17 years) with type 1 diabetes.

2 | METHODS

This prospective, multicenter, open-label, non-inferiority, single arm treatment study (ClinicalTrials.gov NCT 02821117) was conducted at 10 European diabetes centers (seven in United Kingdom, two in Republic of Ireland, and one in Germany). Eligible patients were: aged 4 to 17 years with type 1 diabetes for a year or more, on their current insulin regimen for at least 2 months, and performing self-monitoring regularly (equivalent to ≥2 times per day). Patients not included were: allergic to medical-grade adhesives, currently using FreeStyle Libre or CGM or used in the previous 3 months, pregnant, breast feeding, or allergic to medical-grade adhesives, currently using FreeStyle Libre or CGM or used in the previous 3 months, pregnant, breast feeding, or receiving oral steroid therapy for any condition. Non-inferiority was confirmed if the lower limit of the two-sided confidence interval (CI) for the mean change in time in range was ≥−1.2 h/d, to correspond to a change of +0.3% (3.3 mmol/mol) HbA1c. Prior to starting the study, independent ethics approval was obtained for all centers and each participant’s written informed consent. The study was conducted in compliance with the protocol, International Conference on Harmonisation Guidelines, Good Clinical Practice, and Declaration of Helsinki.

Following consent, screening for eligibility, and enrolment, all participants had baseline HbA1c (local laboratory tested) and physical measurements taken. Subsequently, all participants wore the system in masked mode for the 14-day baseline period and were asked to scan their sensor when performing blood glucose fingerstick tests and at least every 8 hours. Sensor glucose measurements were not visible to the first reading returning within the range. System utilization (defined as the percentage of data collected, relative to continuous device wear) and insulin dose decisions for participants ≥13 years were also analyzed.

Sub-group analysis included: age, gender, and insulin administration method. Sensor glucose analysis was daytime (6:00 AM-10:00 PM), nighttime (10:00 PM-6:00 AM) and per day (24 hours).

Patient-reported outcome measures assessment (baseline and study end [day 70]) used the Diabetes Treatment Satisfaction Questionnaire (teens and parent versions) for participants aged ≥13 years and all caregivers. User questionnaires (participant, caregiver, and health care professional) results were assessed at the end of the study.

Adverse events (including symptomatic hypoglycemia, severe hypoglycemia, and diabetic ketoacidosis) and sensor insertion-site symptoms were monitored throughout the study.

2.2 | Statistical analysis

Time in range, other glycemic measures, HbA1c, TDD of insulin, and BMI were considered using a paired t-test. Since the study did demonstrate superiority in the primary endpoint, it is appropriate to switch the hypothesis from non-inferiority to superiority. A one-sample t-test was used to compare Diabetes Treatment Satisfaction Questionnaire scores to zero change. Glycemic measures were compared between different insulin dose decision groups using analysis of covariance on baseline values. Data analysis was performed by Abbott Diabetes Care using SAS version 9.2 (SAS Institute, Cary, NC) or higher for all analyses.

3 | RESULTS

3.1 | Participants

A total of 76 participants were enrolled between June 27, 2016 and November 30, 2016 (Table 1); one participant withdrew before completing the baseline phase. The full analysis set (FAS) included 75 participants, average age was 10.3 ± 4.0 years (mean ± SD). The per protocol (PP) analysis set included 66 participants, 4 participants (5, 8, 12, and 17 years) did not complete the study. Protocol deviations affected data integrity for five participants. The primary endpoint is presented for the PP and FAS. All other results presented are for the FAS (Figure 1).
3.2 | Glycemic measures

The lower confidence limit for change in time in range (70-180 mg/dL) exceeded the non-inferiority margin, −1.2 h/d, demonstrating non-inferiority. Moreover, time in range improved by 1.0 (0.30-1.65) h/d (mean [95% CI]) from 10.1 ± 3.0 (mean ± SD) at baseline to 11.1 ± 3.2 h/d at study end (PP set, Table 2). Similarly, time in range in the FAS improved by 0.9 ± 2.8 h/d (mean ± SD) from 10.1 ± 3.0 h/d to 11.1 ± 3.3, P = 0.005 (Table 2), demonstrating superiority.

Time spent above all hyperglycemic thresholds reduced (Table 2). Time spent in glucose >180 mg/dL reduced by −1.2 ± 3.3 h/d (mean ± SD, P = 0.004) and the number of events increased by 0.2 ± 0.6 h/d (P = 0.04). Time spent in sensor glucose >240 mg/dL reduced by −1.0 ± 3.0 h/d (P = 0.008). The change in events at >240 mg/dL by −0.1 ± 0.7, from 2.3 ± 0.7 to 2.2 ± 0.8, did not reach significance (P = 0.32). Time spent in sensor glucose >300 mg/dL reduced by −0.6 ± 2.1 (P = 0.02) and events reduced by −0.2 ± 0.7 (P = 0.03).

TABLE 1 Baseline characteristics

| Baseline characteristics | Participants (N = 76) |
|--------------------------|----------------------|
| Gender                   |                      |
| Girls                    | 41/76 (53.9%)        |
| Boys                     | 35/76 (46.1%)        |
| Race                     |                      |
| Asian                    | 3/76 (3.9%)          |
| Black                    | 3/76 (3.9%)          |
| White                    | 67/76 (88.2%)        |
| Mixed                    | 2/76 (2.6%)          |
| Pakistani                | 1/76 (1.3%)          |
| Age (years)              |                      |
| 4 to 6                   | 14/76 (18.4%)        |
| 7 to 12                  | 37/76 (48.7%)        |
| 13 to 17                 | 25/76 (32.9%)        |
| Height (m)               | 1.42 (0.22)          |
| Height (inches)          | 55.8 (8.8)           |
| Weight (kg)              | 41.6 (19.3)          |
| Weight (lbs)             | 91.8 (42.4)          |
| BMI (kg/m²)              | 19.5 (3.9)           |
| Years since diagnosis    | 5.4 (3.7)            |
| Baseline A1c (%)         | 7.9 (1.0)            |
| Baseline A1c (mmol/mol)  | 62.9 (11.1)          |
| Insulin administration method |                |
| CSII                     | 44/76 (57.9%)        |
| MDI                      | 32/76 (42.1%)        |
| Insulin, total daily dose (units) |     |
| Overall (n = 71)         | 35.8 (25.6)          |
| Basal                    | 16.8 (12.2)          |
| Bolus                    | 23.6 (18.3)          |
| CSII                     | 32.8 (23.9)          |
| Self-reported blood glucose frequency per day | 7.3 (2.7) |

Abbreviations: CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injection. Data are n/N (%) or mean (SD).

Time spent in hypoglycemia (<70 mg/dL) was unchanged (from 1.1 ± 1.2 to 1.4 ± 1.2, P = 0.09). There was a small increase in the number of events (<70 mg/dL) by 0.2 ± 0.6 from 0.8 ± 0.7 to 1.0 ± 0.7 (P = 0.01, Table 2).

HbA1c measurements were improved from 7.9 ± 1.0% (62.9 ± 11.2 mmol/mol) at baseline to 7.5 ± 0.9% (58.5 ± 9.8 mmol/mol) at 8 weeks, decreasing by −0.4 ± 0.6% (4.4 ± 5.9 mmol/mol, mean ± SD, P < 0.0001).

Mean glucose reduced by −10 ± 30 mg/dL (P = 0.005, Table 2). Glycemic variability improvements were: SD (P = 0.004), high blood glucose index (P = 0.004), and blood glucose risk index (BGRI) (P = 0.005). Change for low blood glucose index did not reach statistical significance (P = 0.06, [Table 2]).

3.3 | Insulin use and BMI

Self-reported TDD of insulin (71 participants) increased by 4% (1.4 ± 3.5 units) from 35.8 ± 25.6 to 37.2 ± 25.6 units (mean ± SD, [P < 0.001]). TDD for multiple daily injection (MDI) users (n = 28) increased by 4% (1.5 ± 4.3 units) from 40.4 ± 27.8 to 41.9 ± 27.8 units (P = 0.08) and for insulin pumps users (n = 43) by 4% (1.4 ± 2.9 units) from 32.8 ± 23.9 to 34.2 ± 23.8 units (P = 0.003). Insulin pump upload data (n = 38) showed more variation in the change between participants, resulting in an overall (71 participants) 3% change (P = 0.24 [Table S1 in Supporting Information]).

BMI is expected to change with age and increased during the study (0.28 ± 0.68 kg/m² [mean ± SD], P < 0.001). BMI adjusted for age15 increased by 0.13 ± 0.40 SDS (P = 0.006).

3.4 | Sensor scanning frequency

With unmasked system use, mean daily frequency of SMBG testing immediately reduced from 7.7 ± 2.5 per day (mean ± SD) during baseline to 1.6 ± 1.9 per day during the treatment phase and frequency of sensor scans was 12.9 ± 5.7 per day (Figure 2).
System utilization was 91% ± 9 (median 95%) overall, 95% ± 4 (median 97%) in participants aged 4-6 years (n = 13); 93% ± 6 (median 95%), in 7 to 12 year olds (n = 35), and 87% ± 12 (median 89%) in teenagers (n = 23, [Table S2 in Supporting Information]).

Further analysis of the final 14 days (days 57-70) showed that participants with a higher time in range scanned the sensor more often (P = 0.05) and change in time in range was also positively associated with scanning frequency (P = 0.05).

### 3.5 | Sub-group analysis

Time in range rose in each age group; improving for participants aged 4 to 6 years (P = 0.035) and for 13 to 17 year olds (P = 0.025). The rise in time in range for participants aged 7 to 12 years did not reach significance (P = 0.3 [Tables S3-S5 and Figures S2 and S3 in Supporting Information]).

HbA1c reduced in each age group (Table S6 in Supporting Information) with the greatest improvement observed in teenagers.
(n = 24) by -0.7 ± 0.6% (-7.2 ± 5.9 mmol/mol, mean ± SD) from 8.3 ± 1.4% (67.0 ± 15.4 mmol/mol) to 7.6 ± 1.2% (59.8 ± 13.1 mmol/mol, P < 0.0001). In participants aged 7 to 12 years (n = 37), a reduction of -0.3 ± 0.5% (-2.8 ± 5.7 mmol/mol) was observed (from 7.7 ± 0.8% (60.5 ± 8.5 mmol/mol) to 7.4 ± 0.7% (57.7 ± 7.8 mmol/mol, P = 0.005) and in the youngest children (n = 14) a -0.3 ± 0.5% (-3.6 ± 5.2 mmol/mol) reduction from 7.8 ± 0.6% (61.9 ± 6.8 mmol/mol) to 7.5 ± 0.8% (58.3 ± 8.6 mmol/mol, P = 0.02).

Time spent in hyperglycemia improved in teenage participants at all thresholds. For participants aged 7 to 12 years, time spent in hyperglycemia fell at all thresholds without reaching statistical significance. For participants aged 4 to 6 years time spent in glucose >180 mg/dL and >300 mg/dL reduced. The fall in time spent >240 mg/dL did not reach statistical significance (Tables S3-S5 in Supporting Information).

For participants using MDI (n = 31), HbA1c improved by -0.3 ± 0.6% (-3.8 ± 6.6 mmol/mol, mean ± SD) from 8.0 ± 1.2% (64.4 ± 13.4 mmol/mol) to 7.7 ± 1.1% (60.6 ± 11.5 mmol/mol, P = 0.003). Time in range rose by 0.7 ± 2.8 h/d, failing to reach statistical significance (P = 0.2). Time spent in hyperglycemia fell at all thresholds without reaching statistical significance (P = 0.2). SD glucose improved by -7.1 ± 13.1 mg/dL (P = 0.005). For insulin pump users (n = 44), HbA1c improved by -0.4 ± 0.5% (-4.8 ± 5.5 mmol/mol) from 7.8 ± 0.9% (61.8 ± 9.4 mmol/mol) to 7.4 ± 0.8% (57.0 ± 8.3 mmol/mol, P < 0.0001). Time in range improved by 1.1 ± 2.8 h/d (mean ± SD, P = 0.016) while time spent >180 and >240 mg/dL reduced (P = 0.007, P = 0.016, respectively). Time spent >300 mg/dL reduced without reaching statistical significance (P = 0.051). SD glucose was unchanged (P = 0.2).

Time in range increased during waking hours (6:00 AM-10:00 PM [16 hours]) and rose without reaching statistical significance at night (10:00 PM-6:00 AM [8 hours]). Time spent above all hyperglycemic thresholds reduced during the daytime and fell without reaching significance at nighttime. Time spent below all hypoglycemic thresholds was unchanged during both waking hours and at night (Tables S7 and S8 in Supporting Information).

### 3.6 | Patient-reported outcomes

The Diabetes Treatment Satisfaction Questionnaire (parent version) score for caregivers (n = 70) improved for overall satisfaction with treatment (P < 0.0001) and perceived diabetes control (P < 0.0001). Perceived hyperglycemia for caregivers increased (P = 0.02). Diabetes Treatment Satisfaction Questionnaire (teen version) score for teenagers (≥13 years) demonstrated an improvement in overall satisfaction with treatment (P < 0.0001). Changes to perceived diabetes control were nearing significance (P = 0.05) [Table S9 and Figures S4 and S5 in Supporting Information]. User and caregiver questionnaire responses were equally positive as were healthcare professional questionnaire responses (Figures S6 and S7 in Supporting Information).

### 3.7 | Insulin dose decision making

During the final 14-day phase, 18 of 23 teenage participants recorded their insulin dose decisions in a diary. Eight teenagers (44%) calculated/decided insulin doses on all (100%) occasions, 16 (89%) on >90% of occasions, and 17 (94%) on >80% of occasions. One 6-year 13-year-old female participant, with a baseline HbA1c of 11.1% (98 mmol/mol), reported making less than 20% of dosing decisions. Comparing glycemic measures for decision makers on <80%, 80% to 99%, and 100% of occasions with younger children, there was no difference between these subgroups for time in range, hyperglycemia, and the BGRI. For time in hypoglycemia (<70 mg/dL), there was no difference in the subgroups making 100% (P = 0.89) and those making <80% of decisions (P = 0.56). For the 80% to 99% sub-group, time in hypoglycemia increased by 1.2 h/d compared to younger participants (P = 0.002).

### 3.8 | Adverse events

There were no serious adverse events for severe hypoglycemia, hyperglycemia, or diabetic ketoacidosis. One participant withdrew after experiencing moderate erythema which resolved without treatment and was reported as sensor-wear related; an anticipated device effect. In total, there were 121 adverse events or serious adverse
events experienced by 54 participants. Two serious adverse events were reported for two participants (gastroenteritis and bruised back; Table S10 in Supporting Information) which were unrelated to the study device or procedure. There were three mild device-related (sensor wear) adverse events (dry flaky skin, dry yellow/white collection, and non-itchy, redness) for three participants (aged 8, 6, and 15 years [Table S11 in Supporting Information]).

Sensor insertion signs and symptoms ($n = 96$) experienced by 42 participants were associated with sensor insertion (bleeding [27 occurrences], pain [24], induration [7], and bruising [4]) or sensor wear (erythema [23], itching [5], rash [5], and infection [1], reported as mild, resolved without treatment). See Table S12 in Supporting Information.

4 | DISCUSSION

This study shows improved time in the range of 56 min/d, an almost 10% increase compared with SMBG use during baseline. An earlier study in pediatric CGM use demonstrated less improvement while other published data have not included findings for this glucose parameter in children with diabetes. More recently, a short (14-day) study in predictive low glucose management (PLGM) integrated with insulin suspend technology use by children with diabetes (8-18 years) demonstrated an improvement in a narrower range of 3.9 to 7.8 mmol/L. In the present study, time in range increased almost immediately sensor results could be utilized (ie, following the masked sensor wear at baseline) which was before clinical review with a healthcare professional. Speculatively, sensor information may have encouraged proactive reactions for glucose self-management. The improvement in daytime glucose control and changes in total insulin doses support this rationale. Benefit was maintained until study end, indicating rapid acceptance of the device by participants and confidence in sensor data use. This result supports findings from studies of flash glucose monitoring use in adults with type 1 diabetes, national guidance, and experiential observations from clinicians. The observed benefit was largely due to reduced hyperglycemia at all thresholds in addition to less glycemic variability. These results contrast with improved time in range resulting from reduced hypoglycemia with an analogous rise in hyperglycemia above 7.8 mmol/L reported for PLGM technology in a similar population.

Notably, time in range and HbA1c improved without impacting clinical concern on hypoglycemic risk; all clinicians agreed that the sensor glucose reports provided insight into hypoglycemia (Figure S7 in Supporting Information). To the best of our knowledge, improved time in the range associated with reduced HbA1c was last reported in a population (aged 8, 6, and 15 years [Table S11 in Supporting Information]).

Sensor-wear adverse events were similar to the reported prevalence in this population for sensor use over 2 weeks. Symptoms were primarily mild and do not appear to have impacted on the high level of device acceptability, as demonstrated by the user questionnaire results which support findings from a shorter study.

The improvement in HbA1c is especially notable in the teenage participants as a reduction may not always be achieved with SAP technology. Teenagers can confound expectations of improved glucose from technology use with high attrition rates from trials and a weaker association of sensor use with improved glycemic control. Commonly, teens favor accessing current glucose results discreetly and may not share assumed benefits, such as the streaming of glucose data, seeing it as disruptive, visually obvious, and differentiating them from their peers. These issues may explain the high sensor system utility observed in this sub-group which add to findings in flash sensor use for young adults.

Glycemic improvements for teenagers making all/most insulin dose decisions were broadly similar to those observed for younger children. The reasons for increased time spent in hypoglycemia in nine teenagers nearing full independence (80-99% insulin decisions), who also showed the biggest improvement in hyperglycemia, are not clear. Sensor-wear adverse events were similar to the reported prevalence in this population for sensor use over 2 weeks. Symptoms were primarily mild and do not appear to have impacted on the high level of device acceptability, as demonstrated by the user questionnaire results which support findings from a shorter study.

The strength of the study was its reflection of the real-world in demonstrating safe home-use of the system without device training or a mandated insulin adjustment algorithm. Limitations include short-term use of the system in a cohort with reasonable glycemic control for this population, relatively small participant numbers in each age sub-group and no control group for comparison. The study duration was designed to evaluate the effect of starting use of FreeStyle Libre, allowing time for a clinical review of the sensor glucose data generated and for the outcome of that review to have an effect on outcomes. The study was of sufficient duration to evaluate the effect on glycemic control. Whether further improvement, maintenance, or weakening of glycemic benefit would occur with longer device use is unknown. No adjustment was made for multiple testing of secondary endpoints and as many of these are highly inter-related they should not be considered in isolation. Future studies over a longer period
with a larger cohort and control arm are now required to further assess the long-term impact of flash technology in this population.

In summary, non-inferiority, and superiority, of flash glucose monitoring over self-monitoring of blood glucose for glycemic control were demonstrated in this short-term, single arm study. Use of flash glucose technology in children and young people with type 1 diabetes using insulin pump or multiple injection therapy resulted in improved time in range, reduced HbA1c, and better treatment satisfaction.

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Disclosure of interests

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Authors’ contributions

All authors were; involved in planning the study protocol, investigators for the study, and collected data. F.C. wrote the first draft and together with the co-authors worked collaboratively to write, discuss, and review the manuscript. All authors collectively took the decision to submit for publication. F.C. is the guarantor of this work, had full access to all the study data, and takes responsibility for the integrity of the data and accuracy of the analysis.

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

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