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ORIGINAL ARTICLE

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A novel glucose beta-hydroxybutyrate combination improves hypoglycaemia recovery and patient-reported outcomes in type 1 diabetes

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Abstract

Aims: Hypoglycaemia remains a major barrier to optimal diabetes management. Current treatments based on simple sugars have limitations, including rapid glucose fluctuations and persistent neuroglycopenic symptoms. We investigated FLO23011, a novel multi-substrate energy formulation containing glucose and beta-hydroxybutyrate, as a superior hypoglycaemia treatment.

Methods: Two studies were conducted: Study A, a randomised, crossover pharmacokinetic investigation in six healthy adults comparing FLO23011 versus standard glucose treatment over 180 min; and Study B, a 12-week randomised, open-label, crossover clinical trial in 12 adults with type 1 diabetes comparing FLO23011 to standard of care. Study B evaluated glycaemic control using continuous glucose monitoring and assessed patient experience through structured questionnaires across 14 domains.

Results: Study A demonstrated a comparable glucose response between FLO23011 and standard of care (Cmax 7.4 ± 0.3 vs. 7.9 ± 0.2 mmol/L, $p = 0.122$), but FLO23011 resulted in sustained beta-hydroxybutyrate elevation (Cmax 0.6–1.2 mmol/L). Study B participants experienced 1032 hypoglycaemic episodes, as recorded by continuous glucose monitoring. FLO23011 significantly improved post-hypoglycaemia time in range (82.5% vs. 77.0%, $p = 0.019$) and reduced recurrent episodes by 27% ($p = 0.031$). Patient-reported outcomes favoured FLO23011 in 13 of 14 domains.

Conclusions: FLO23011 provides superior hypoglycaemia management through improved glycaemic stability, reduced recurrence, and enhanced patient experience compared to current glucose-only treatments.

KEYWORDS

glycaemic control, hypoglycaemia, patient reported outcomes, pharmacokinetics, randomised trial, type 1 diabetes

Plain Language Summary

Why was this study done?

This study tested an innovative product for treating low blood sugar (hypoglycaemia) in adults with type 1 diabetes and found that it gave a steadier recovery and fewer repeat lows than standard glucose treatments, while also helping people feel better and more in control after episodes. Many people with type 1 diabetes have frequent hypos each year, which can be frightening and exhausting, and can undermine confidence in managing glucose levels. Standard treatments use fast-acting sugar, which usually corrects the low but can cause blood sugar swings and leave people feeling wiped out or foggy afterwards.

What did the researchers do?

The team developed a novel drink formulation that combines usual fast sugar with BHB, an energy source that acts as extra fuel for the brain - sometimes called adaptive energy – when glucose use is limited. They first studied how the product was handled by the body in six healthy adults, then ran a 12-week trial in 12 adults with type 1 diabetes, comparing the drink with their usual glucose treatment whenever they had a low, using continuous glucose monitors and questionnaires.

What did they find?

In healthy adults, the innovative product raised blood sugar to similar levels to standard treatment but also increased BHB levels for several hours, providing an additional energy source. In people with type 1 diabetes, over 1000 hypos were analysed and the novel combination formula led to more time in the target range in the two hours after a low, fewer repeat lows in that period, and no loss of overall glucose control. Participants rated the new option better than their usual treatment on most questionnaire measures, including speed of symptom relief, ability to get back to normal activities, and confidence in managing hypos.

What does this mean for patients and families?

These results suggest that a drink combining glucose with an extra brain fuel may offer a better and more sustained recovery from hypos than glucose alone. These findings highlight the potential for this approach to become a meaningful addition to everyday self-care for low blood sugar.

1 | INTRODUCTION

Hypoglycaemia represents a critical therapeutic challenge in diabetes management: people with type 1 diabetes may experience 100–200 treatment-related episodes annually.[1–3] Current recommended therapeutic interventions using glucose-only treatments frequently result in suboptimal outcomes, including rapid glucose fluctuations, persistent neuroglycopenic symptoms and fear-driven non-adherence to medication that compromises long-term glycaemic control.[2,4]

Clinical practice guidelines consistently recommend 15–20 g of rapidly absorbed carbohydrates for acute hypoglycaemia management, with 15 g glucose established as the standard therapeutic dose by major diabetes organisations, including the American Diabetes Association, European Association for the Study of Diabetes, and Joint British Diabetes Societies.[5–7] While fast-acting carbohydrates restore plasma glucose concentration, utilisation of glucose by neurons may be limited by inhibition of glycolysis due to poly(ADP-ribose) polymerase-1 (PARP-1) activation and nicotinamide adenine dinucleotide (NAD+) depletion by the hypoglycaemic episode.[8] The human brain's capacity to utilise alternative, adaptive energy substrates that bypass glycolysis, such as beta-hydroxybutyrate (BHB), presents a novel therapeutic opportunity.[9,10] BHB crosses the blood–brain barrier efficiently via monocarboxylate transporters, which are upregulated in diabetes and hypoglycaemia. BHB is then able to enter the tricarboxylic acid (TCA) cycle, bypassing glycolysis and generating ATP. BHB therefore provides metabolically efficient energy delivery when glycolysis is compromised.[10–12] It is hypothesised that better energy provision to the brain supports improved recovery from hypoglycaemia.

FLO23011 (FLO), a novel multi-substrate energy formulation, combining glucose with BHB, was designed to achieve more rapid and complete hypoglycaemia recovery: the product raises both glucose and BHB levels acutely, improves glycaemic control in the immediate post-treatment period, and provides rapid, sustained neuroglycopenic recovery, transforming hypoglycaemia treatment outcomes.

2 | MATERIALS AND METHODS

Study A was a randomised, open-label, crossover pharmacokinetic investigation involving six healthy adults. Participants completed three fasted visits (7 days apart) receiving: FLO (15 g fast-acting carbohydrates +10 g BHB), two-dose FLO (2-FLO) and standard of care (glucose gel) containing 15 g glucose (SoC). Concentrations of plasma glucose (glucose oxidase method), BHB (enzymatic assay), insulin, and glucagon (radioimmunoassay) were analysed. Treatment effects were evaluated using one-way repeated measures analysis of variance and paired *t* tests. Area under the curve (AUC) and incremental AUC (iAUC) were calculated.

Study B was a randomised, open-label, 12-week, crossover clinical effectiveness trial in 12 adults with type 1 diabetes on insulin therapy (6 on multi-daily injection, 6 on standard insulin pump delivered therapy). Inclusion criteria were diagnosis >12 months and HbA1c 40–86 mmol/L. Power analysis indicated 12 participants would provide 80% power to detect clinically significant differences ($p < 0.05$). Participants were randomly assigned to SoC or FLO and managed episodes of hypoglycaemia in their normal manner, consuming as much of the assigned product as they determined necessary, during two periods of 6 weeks in randomised order. Following acute treatment of hypoglycaemia, participants were permitted to consume additional carbohydrates, in line with clinical practice guidelines.

Continuous glucose monitoring (CGM) data were collected from participants' personal devices, including Dexcom G6, Freestyle Libre 2, Freestyle Libre 3 and Medtronic Guardian 4 systems. Data were stored and collected after the assessment period. Data from CGM were recorded every 15 min over the study period. Selected measures of glucose control were calculated and compared between treatments using paired *t* tests with Bonferroni correction. Hypoglycaemia was defined as CGM glucose <4 mmol/L (70 mg/dL) sustained for ≥15 min, consistent with international consensus definitions. The 2-h post-hypoglycaemia recovery analysis window commenced when CGM glucose returned to 4 mmol/L and was sustained above this threshold for ≥15 min. Time-in-range (TIR) was calculated as the percentage of time with glucose 4–10.0 mmol/L. Analysis was performed using automated software (ScienceMachine.com) with manual verification of episode boundaries and recovery timepoints. Episode identification and analysis were based solely on CGM data parameters, independent of patient treatment decisions or subjective symptom reporting. This approach ensured objective, standardised assessment of hypoglycaemic episodes and recovery patterns, avoiding potential bias from varying patient treatment behaviours or symptom recognition.

Patient experience and reported outcomes were evaluated using structured questionnaires administered by trained staff. Participants rated each product independently using a 10-point Likert scale (1 = strongly favours SoC, 5 = equal, 10 = strongly favours FLO) for 14 parameters in 4 domains comprising: Clinical effectiveness (hypoglycaemia reversal, headache relief, speed of action, after-effects improvement), Functional recovery (return to daily activities, rebound prevention), Product characteristics (taste, palatability, pack usability, portability), Psychological outcomes (sense of control, worry about hypoglycaemia, dosing confidence, overall glucose management). Data for each product were collected and evaluated; results were compared using linear mixed-effects models (statsmodels, Python), controlling for participant and period effects. *p*-Values were corrected using the Benjamini–Hochberg procedure; significance was defined as false discovery rate <0.05. Cohen's d was used to report effect sizes.

Ethics approval was obtained from Leicester Central Research Committee.

3 | RESULTS

3.1 | Study A: Pharmacokinetic profile

Six healthy adults (3M/3F; mean age 46.5 ± 8.2 years; body mass index 24.7 ± 2.1 kg/m^2) completed all three study visits. FLO demonstrated bioequivalent glucose absorption compared to SoC, with comparable peak glucose concentrations (Cmax: 7.4 ± 0.3 vs. 7.9 ± 0.2 mmol/L, $p = 0.122$) and similar glucose exposure as measured by AUC (1170.9 ± 43.6 vs. 1110.3 ± 37.3 mmol/L·min, $p = 0.138$). FLO demonstrated a more gradual return to baseline, reaching euglycemia at approximately 150 min compared to <120 min for SoC (Figure 1).

After single FLO ingestion, there was a rapid elevation of plasma BHB levels with T_{max} at 30 min and C_{max} ranging from 0.4 to 1.1 mmol/L, which remained above baseline throughout the 180-min period. There was a significant difference between FLO and SoC ($p < 0.01$) (Figure 1). BHB levels were higher following 2-FLO compared to the single dose of FLO ($p < 0.001$) and sustained for a longer period (Figure 1). SoC produced no detectable BHB elevation and in fact fell slightly at 60 min, confirming the unique metabolic profile of the novel formulation (Figure 1).

Measured insulin is shown in Figure 2. As expected, insulin levels were higher following 2-FLO compared to SoC ($p < 0.04$) and FLO ($p < 0.024$). Glucagon levels did not differ between groups (Figure 2).

3.2 | Study B: Clinical effectiveness outcomes

All 12 participants with type 1 diabetes (8M/4F; mean age 49.2 ± 12.8 years; diabetes duration 28.6 ± 15.3 years; baseline HbA1c 61.5 ± 18.2 mmol/mol) completed both 6-week crossover periods. Over the 12-week study duration, 1032 hypoglycaemic episodes, identified from CGM data according to the defined criteria, were analysed across 232 607 CGM readings, representing 122 total days of monitoring time.

3.3 | Overall glycaemic control

Overall glycaemic parameters demonstrated equivalent control between treatment arms during the study period (Table 1): TIR was comparable between FLO and standard care (71.5% ± 7.9%

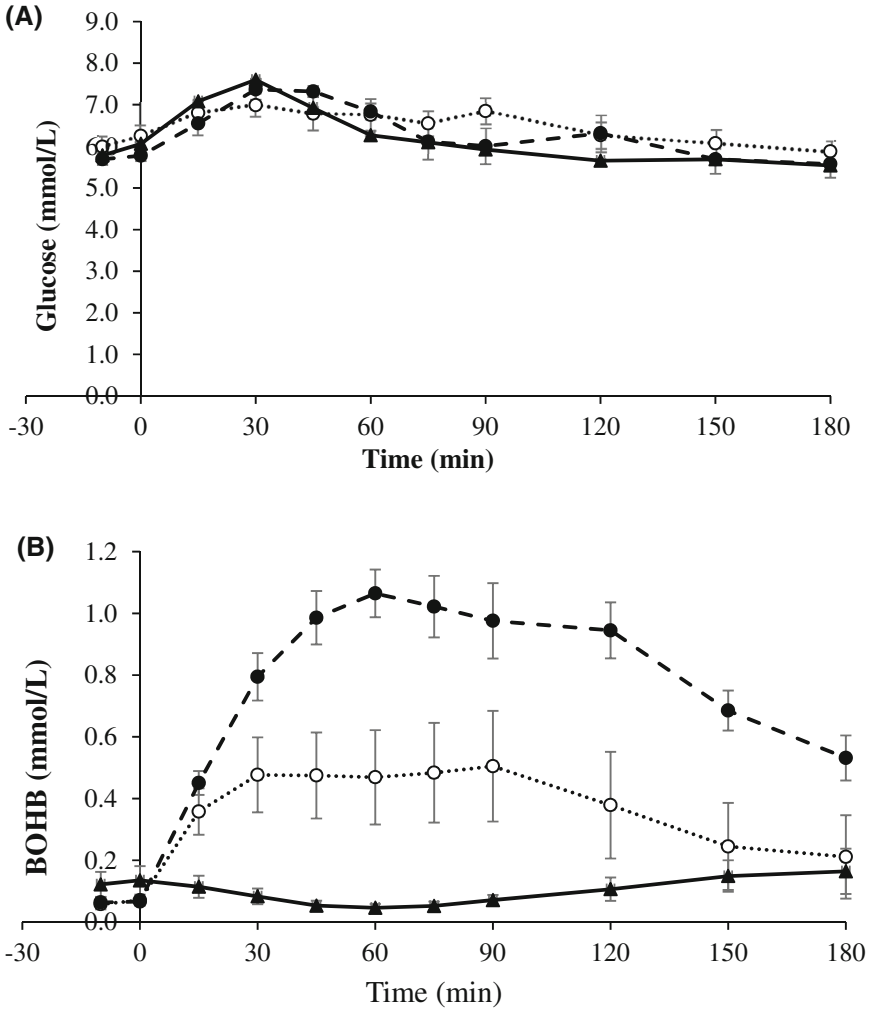

FIGURE 1 Plasma concentrations of (A) glucose and (B) BHB following the intake of FLO (open circle dotted line) or 2-FLO (closed circle dashed line) or SoC (closed triangle solid lines). Data are means ± SEM. There was no significant difference in glucose Cmax or AUC between treatments. AUC, area under the curve; BHB, beta-hydroxybutyrate.

vs. 71.6% ± 8.2%, difference −0.1%, 95% confidence interval [CI] −2.3% to 2.1%, $p = 0.934$). Similarly, time in hypoglycaemia (<4 mmol/L) showed a non-significant trend towards improvement with FLO (4.4% ± 2.8% vs. 5.1% ± 3.2%, $p = 0.186$). Mean glucose levels remained equivalent between treatments over the study duration (8.21 ± 1.18 vs. 8.04 ± 1.23 mmol/L, $p = 0.276$).

3.4 | Post-hypoglycaemia recovery analysis

The primary efficacy signal is evident in the critical 2-h post-hypoglycaemic recovery period. FLO significantly improved post-hypoglycaemia TIR (82.5% ± 10.1% vs. 77.0% ± 12.3%, absolute difference +5.5%, 95% CI 1.2% to 9.8%, $p = 0.019$) with a medium effect size (Cohen's d = 0.49). This 7.1% relative improvement in glycaemic stability during the vulnerable post-hypoglycaemic period represents a clinically meaningful enhancement in recovery quality.

Recurrent hypoglycaemia within 2 h was less frequent with FLO (6.3% vs. 8.6%), an absolute reduction of 2.3 percentage points ($p = 0.031$; 95% CI −4.3 to −0.3 pp), corresponding to a 27% relative reduction. This finding indicates superior therapeutic durability and reduced hypoglycaemic recurrence risk (Table 1).

3.5 | Glucose variability assessment

Glucose variability, as measured by CONGA-1 (1-h continuous overall net glycaemic action), showed a small but non-significant improvement with FLO (1.38 ± 0.29 vs. 1.42 ± 0.31 mmol/L, $p = 0.412$), following hypoglycaemia (Table 1). Analysis of CONGA-2 and 4 (2 and 4-h continuous overall net glycaemic action) showed similar non-significant patterns.

3.6 | Patient-reported outcomes

Patient experience assessments across 14 validated domains demonstrated consistent superiority of FLO. Ten of 14 patient experience assessment domains showed statistically significant improvement (Figure 3), notably speed of symptom resolution (mean difference + 0.67 units, $p = 0.025$), reduction in post-treatment effects (mean

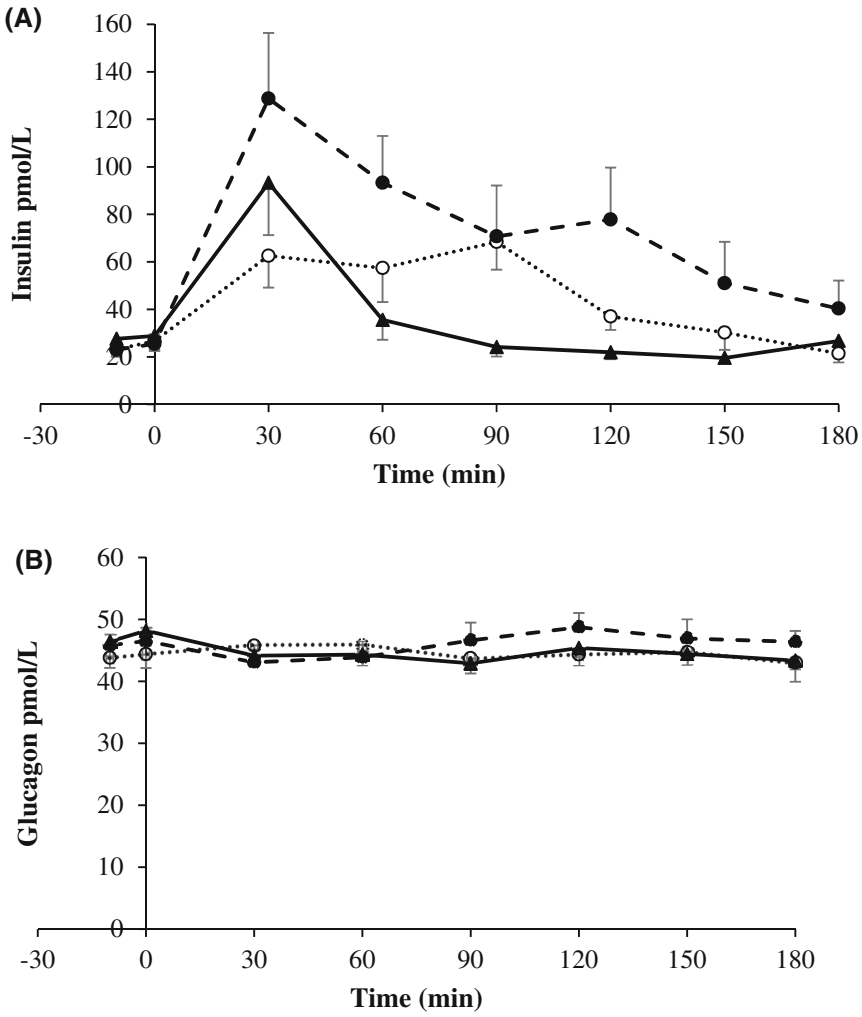

FIGURE 2 Plasma concentrations of (A) insulin and (B) glucagon following the intake of FLO (open circle dotted line) or 2-FLO (closed circle dashed line) or SoC (closed triangle solid lines). Data are means ± SEM.

TABLE 1 Analysis of 1032 episodes of hypoglycaemia assessed: time in range (2 h period post event) significantly improved and relative risk of recurrent episodes reduced with FLO versus SoC; other measures did not show a difference.

Parameter	FLO	SoC	Difference (95% CI)	*p*-Value	Effect size/RRR
Overall time in range (4–10 mmol/L)	71.5% ± 7.9%	71.6% ± 8.2%	−0.1% (−2.3% to 2.1%)	0.934	NS
Time in hypoglycaemia (<4 mmol/L)	4.4% ± 2.8%	5.1% ± 3.2%	−0.7% (−1.8% to 0.4%)	0.186	Trend
Mean glucose	8.21 ± 1.18 mmol/L	8.04 ± 1.23 mmol/L	+0.17 (−0.15 to 0.49) mmol/L	0.276	NS
Post-hypoglycaemia TIR (2 h)	82.5% ± 10.1%	77.0% ± 12.3%	+5.5% (1.2% to 9.8%)	0.019*	Medium (d = 0.49)
Recurrent hypoglycaemia (2 h)	6.3% ± 4.1%	8.6% ± 5.2%	−2.3% (−4.3% to −0.3%)	0.031*	27% RRR
CONGA-1 variability	1.38 ± 0.29 mmol/L	1.42 ± 0.31 mmol/L	−0.04 mmol/L	0.412	NS

Abbreviations: CI, confidence interval; NS, non-significant; RRR, relative risk reduction; TIR, time-in-range.
*$p < 0.05$.

difference +1.83, $p = 0.014$), and overall hypoglycaemia management ability (mean difference +1.08, $p = 0.019$). Comparative evaluation revealed patient preference for FLO in 13 of 14 assessed domains, indicating comprehensive improvement in treatment experience and satisfaction. Treatment-related confidence and reduced hypoglycaemia-associated anxiety were prominent themes in patient feedback, with participants reporting enhanced ability to maintain normal activities following hypoglycaemic episodes and reduced fear of recurrent events. Participants rated FLO effectiveness at 4.33 ± 0.65 compared to 3.58 ± 0.90 for SoC (difference +0.75, $p < 0.05$). Post-treatment "hangover" effects were substantially reduced with FLO, with FLO scoring 4.33 ± 0.89 versus 3.25 ± 1.29 for SoC (difference +1.08, $p < 0.05$). Participants described FLO as providing "clearer thinking" and "better focus" compared to SoC, which often left them feeling "lethargic" and finding it "difficult to concentrate" for extended periods.[13]

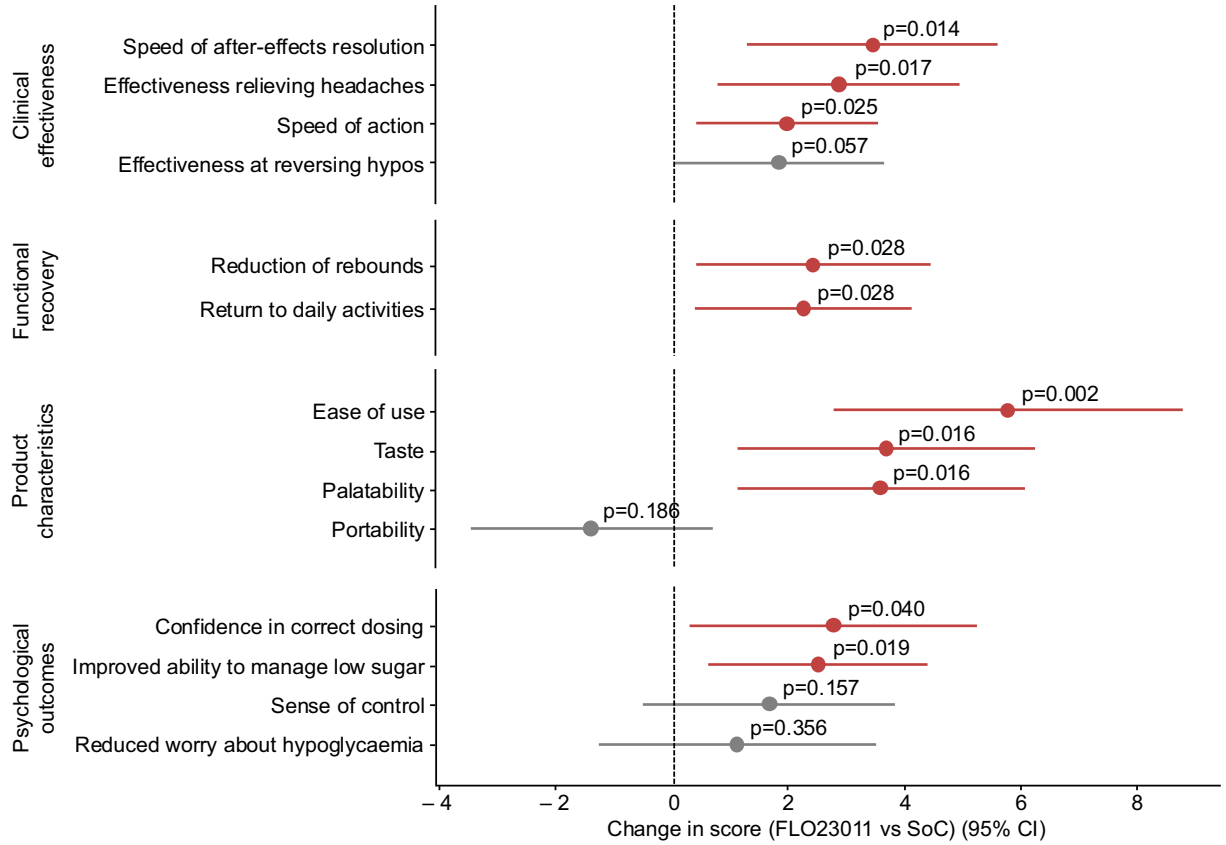

FIGURE 3 Estimated treatment effects for FLO versus standard of care across 14 assessed patient-reported outcome domains in 12 adults with type 1 diabetes. Points represent mean difference between treatments with 95% confidence intervals. Values to the right of zero indicate a preference for FLO. Red-shaded items indicate statistical significance ($p < 0.05$) after Benjamini–Hochberg correction for multiple comparisons. FLO demonstrated statistical superiority in 10 of 14 domains, including clinical effectiveness, functional recovery and product characteristics.

4 | DISCUSSION

These findings represent the first clinical evidence that combining glucose with BHB may provide superior hypoglycaemia management compared to glucose-only treatments, addressing both immediate glycaemic correction and faster, sustained neuroglycopenic recovery. The product delivers a more stable glucose profile, sustained elevation of circulating BHB for at least 3 h, and significantly improved patient-reported outcomes. These include faster symptom resolution, reduced fatigue, and quicker return to daily functions. The product also showed significant benefits for key usability factors, with markedly superior ease of use during hypoglycaemic episodes, better taste and enhanced palatability compared to SoC. FLO improved psychological outcomes related to hypoglycaemia management, including an enhanced sense of control during treatment and increased confidence in appropriate glucose dosing. CGM demonstrated that FLO significantly improves glycaemic stability in the immediate hypoglycaemia recovery period, increasing TIR and reducing the frequency of recurrent events. The significant improvements in post-hypoglycaemic glycaemic stability and patient-reported outcomes demonstrate the clinical potential of multi-substrate energy delivery during hypoglycaemia.

The observed clinical effects are consistent with the current understanding of disrupted brain energy metabolism during hypoglycaemia. The sustained elevation of plasma BHB concentrations provided by FLO addresses a fundamental limitation of current hypoglycaemia treatments. While glucose rapidly corrects plasma glucose levels, neuronal glucose utilisation remains compromised due to hypoglycaemia-induced metabolic disruption, specifically PARP-1 activation and NAD+ depletion that inhibits glycolysis.[8,14,15] In contrast, BHB, which is rapidly taken up by neurons via monocarboxylate transporters, enters the TCA cycle directly and restores ATP generation.[10,12,16] The ability of BHB to function as an alternative adaptive energy substrate that bypasses the glycolytic bottleneck enables neuronal energy production when glucose-dependent pathways are impaired. This avoids delayed cognitive recovery from prolonged neuroglycopenia, and may also reduce oxidative stress, and neuroinflammation.[8,17,18] BHB can also address these risks by acting as a direct antioxidant, suppressing the activation of the NLRP3 inflammasome and activating HCA2 receptors, which mediate anti-inflammatory and neuroprotective effects.[9,19–21]

These findings have important clinical implications. While tight glycaemic control reduces microvascular complications, this is associated with an increased frequency of hypoglycaemic episodes[22]; the overall effect on quality of life is highly detrimental and a long-term source of

anxiety, resulting in maladaptive tolerance of increased glucose levels and fear of exercise.[23,24] Moreover, severe hypoglycaemia causes neuronal death raising the concern of long-term damage to cognitive ability as well as impairing response to further hypoglycaemic episodes.[25–28]

The significant improvement in post-hypoglycaemic TIR and the 27% relative reduction in recurrent hypoglycaemia within 2 h of a hypoglycaemic episode represent a substantial improvement in treatment durability and recovery quality. Previous research has demonstrated that hyperglycaemic recovery from hypoglycaemia induces ischemia–reperfusion-like effects with increased oxidative stress, endothelial dysfunction, and inflammatory markers that persist for hours after glucose normalisation.[18,29] Recurrent hypoglycaemia following initial treatment affects many individuals, contributing to treatment burden, healthcare utilisation, and patient anxiety.[24,30] The sustained metabolic support provided by BHB appears to prevent the glucose fluctuations that predispose individuals to recurrent episodes. Although plasma glucose is rapidly corrected by replacement, cognitive dysfunction may take 1.5 days to recover[31]: the improved glycaemic stability observed with FLO, together with the BHB fuel supply, may attenuate these deleterious post-hypoglycaemic sequelae.

The consistent patient preference for FLO across multiple domains reflects meaningful improvements in treatment experience that extend beyond objective glycaemic metrics. Hypoglycaemia significantly impairs quality of life through its impact on daily activities, sleep quality, work productivity and social functioning.[32] The reported improvements in post-treatment effects and enhanced management confidence suggest FLO may address the psychological burden of hypoglycaemia that often leads to defensive behaviours and suboptimal diabetes management.

Current hypoglycaemia treatment guidelines recommend 15–20 g of rapidly absorbed carbohydrates, based on the requirement to restore plasma glucose levels. However, these recommendations do not address the persistence of neuroglycopenic symptoms that often accompany glucose correction. The superior patient-reported outcomes observed with FLO suggest that neurological recovery may be as important as glycaemic recovery for optimal treatment effectiveness. The equivalent overall glycaemic control observed between treatments demonstrates that FLO's benefits are specifically targeted to the post-hypoglycaemic recovery period rather than representing more general glycaemic effects.

The study population consisted of individuals with established type 1 diabetes who were well-controlled and thus experienced hypoglycaemia frequently. The crossover design allowed individuals to make a direct comparison in a real-world setting. Participants were permitted to consume as much product as they determined necessary, reflecting real-world self-management of hypoglycaemia.

Several study limitations warrant consideration. The 12-week crossover design, while appropriate for the desired study power, may not capture long-term effects on hypoglycaemia awareness or diabetes management behaviours. The relatively small sample size ($n = 12$) was offset by the crossover design which enabled each subject to experience both treatments, allowing for a direct comparison. Future work with larger numbers could evaluate FLO's impact on severe hypoglycaemia rates, healthcare utilisation, long-term glycaemic control and long-term cognitive function. It was not possible to blind participants due to the different taste and formulation of FLO compared to SoC and the open-label design may have influenced patient-reported outcomes. However, the objective CGM endpoints provide unbiased validation of clinical benefits.

These findings support the clinical development of FLO as an improved hypoglycaemia treatment with the potential to transform this area of diabetes care. The combination of improved glycaemic stability, reduced recurrence risk, and enhanced patient experience addresses multiple limitations of current glucose-only treatments. The therapeutic principles demonstrated with FLO may extend beyond hypoglycaemia treatment to other conditions characterised by metabolic brain injury and impaired glucose utilisation, including stroke, traumatic brain injury, and neurodegenerative diseases, where alternative energy substrates show neuroprotective potential.[33–35]

5 | CONCLUSION

FLO is the first novel treatment for hypoglycaemia in 100 years. It represents a potential paradigm shift in hypoglycaemia therapeutics, moving beyond simple glucose replacement towards comprehensive metabolic support that addresses both glycaemic correction and neurological recovery. These findings establish the foundation for a new standard of care in hypoglycaemia management with the potential to improve both clinical outcomes and quality of life of individuals with diabetes worldwide.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Authors agree to make data and materials supporting the results available upon reasonable request.

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