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June 2026

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Received: 29 October 2025 | Revised: 13 November 2025 | Accepted: 14 November 2025

DOI: 10.1111/dom.70323

ORIGINAL ARTICLE

WILEY

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%

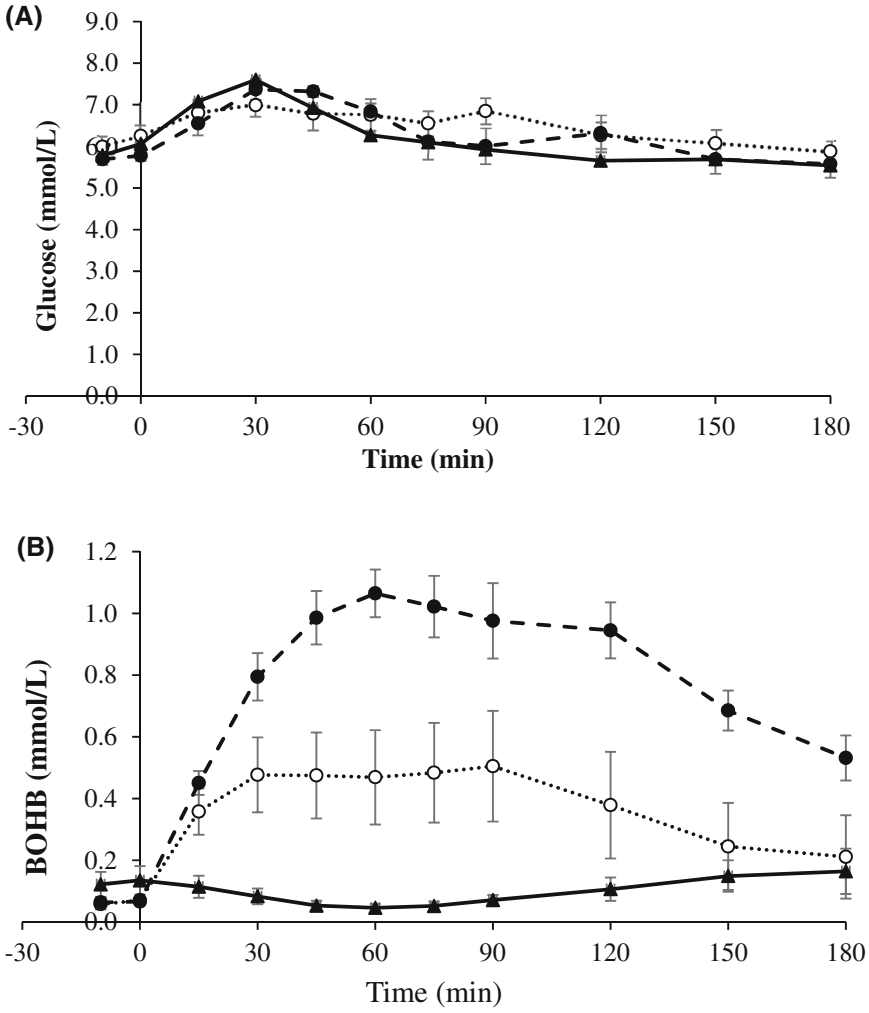

FIGURE 1 Plasma concentrations of (A) glucose and (B) BHB following the intake of FLO (open circle dotted line) or 2-FLO (closed circle dashed line) or SoC (closed triangle solid lines). Data are means ± SEM. There was no significant difference in glucose Cmax or AUC between treatments. AUC, area under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

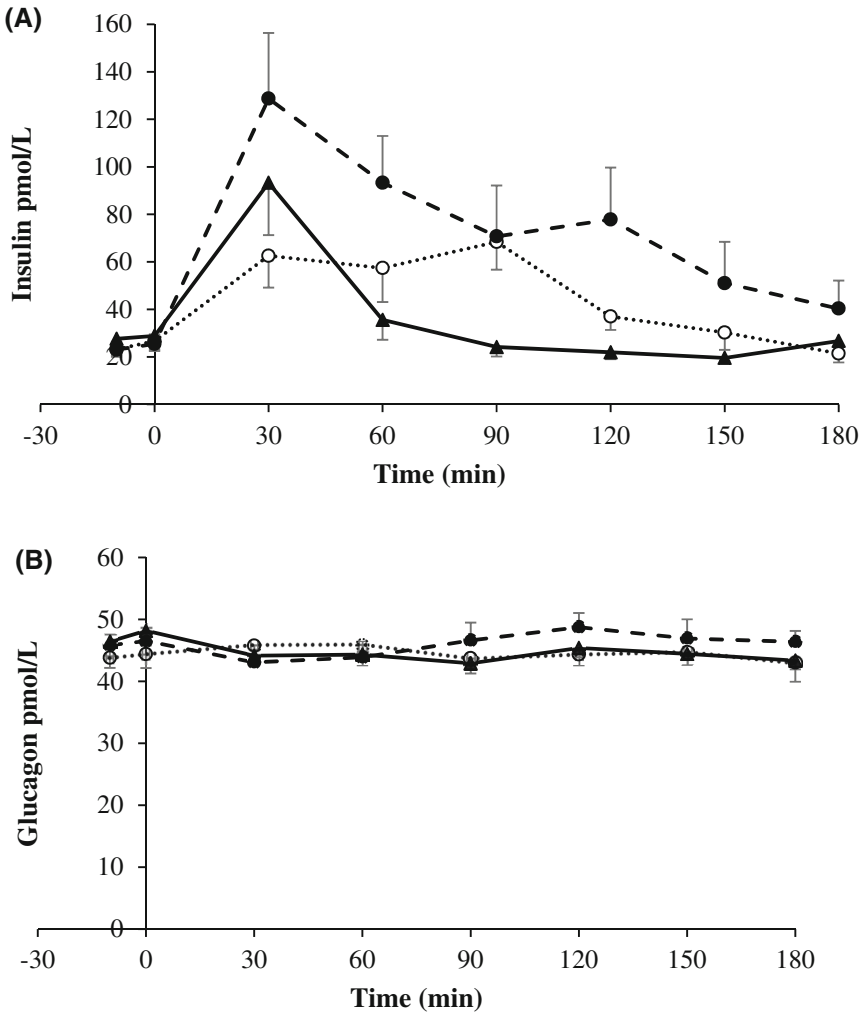

FIGURE 2 Plasma concentrations of (A) insulin and (B) glucagon following the intake of FLO (open circle dotted line) or 2-FLO (closed circle dashed line) or SoC (closed triangle solid lines). Data are means ± SEM.

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]

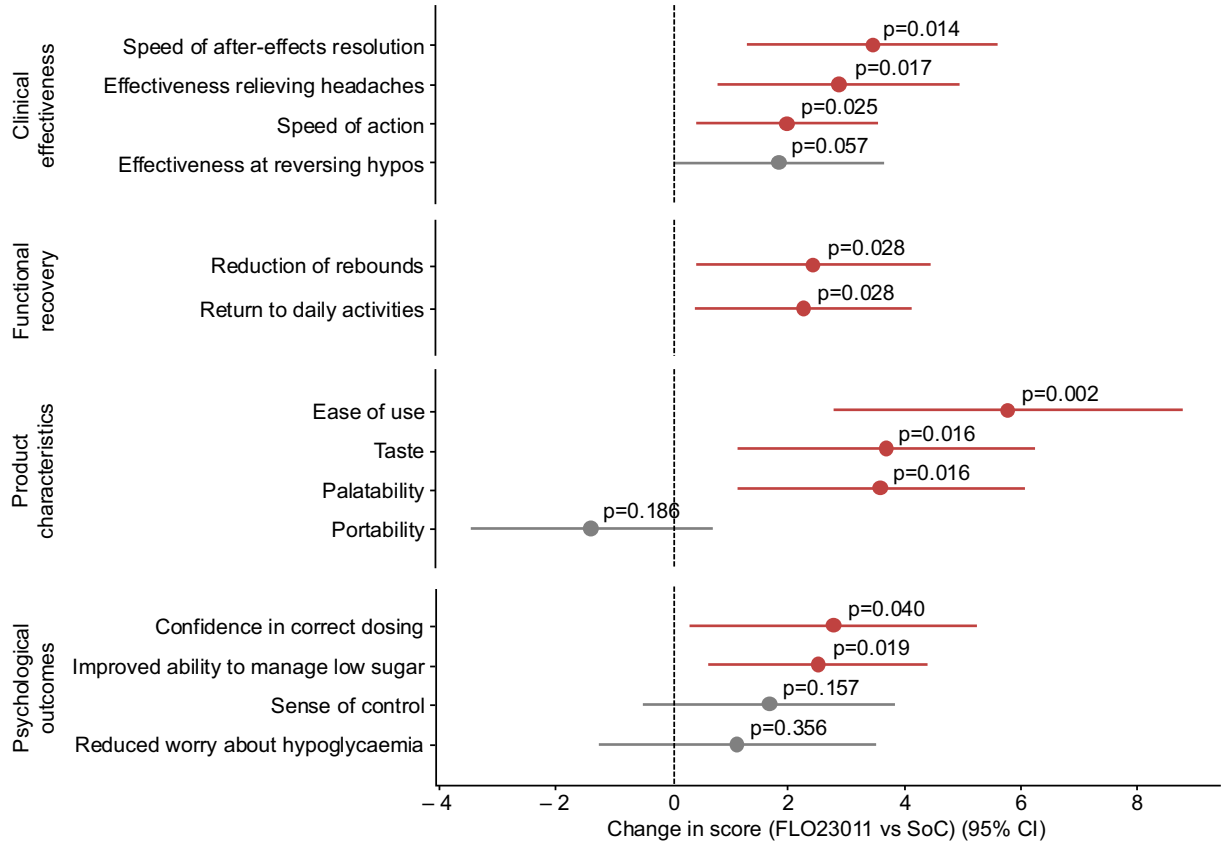

FIGURE 3 Estimated treatment effects for FLO versus standard of care across 14 assessed patient-reported outcome domains in 12 adults with type 1 diabetes. Points represent mean difference between treatments with 95% confidence intervals. Values to the right of zero indicate a preference for FLO. Red-shaded 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.

ACKNOWLEDGEMENTS

Terry Miller Charitable Foundation, Ms. A Burden, Dr. D Hall. ScienceMachine. (2025). Sam (AI Bioinformatician). Science Machine, Inc. https://www.sciencemachine.ai.

CONFLICT OF INTEREST STATEMENT

D Russell-Jones receives research funding or advisory board honoraria from Abbott Diabetes Care, Dexcom, Astra Zeneca, Eli Lilly, Medtronic, Novartis, Novo Nordisk A/S and Sanofi-Aventis. R Littlewood is a shareholder in Flow Health Science. G Myers is a shareholder and employee of Flow Health Science.

DATA AVAILABILITY STATEMENT

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

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How to cite this article: Russell-Jones D, Smout V, Roy S, Myers G, Littlewood R, Shojaee-Moradie F. A novel glucose beta-hydroxybutyrate combination improves hypoglycaemia recovery and patient-reported outcomes in type 1 diabetes. *Diabetes Obes Metab*. 2025;1-8. doi:10.1111/dom.70323

Diabetes, Obesity and Metabolism

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COMMENTARY OPEN ACCESS

Beyond Glucose: A Brain Energy Bottleneck Hypothesis for Multi-Energy Substrates in Hypoglycaemia Rescue

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Received: 7 January 2026 | **Revised:** 20 February 2026 | **Accepted:** 20 February 2026

Keywords: clinical physiology | diabetes complications | glycaemic control | hypoglycaemia | type 1 diabetes

This commentary proposes a brain energy bottleneck as a mechanistic hypothesis that could help explain observed benefits of combining glucose with alternative oxidative substrates in hypoglycaemia. Multi-energy substrates for hypoglycaemia (MESH) refer to formulations that combine glucose with alternative oxidative substrates such as beta-hydroxybutyrate (BHB) and lactate. In vitro data, preclinical studies in animals, and small clinical studies in humans suggest these combinations may improve cognitive recovery and resolution of neuroglycopenic symptoms after hypoglycaemia compared with glucose alone.

We propose that delayed cerebral energy recovery following hypoglycaemia may result from nicotinamide adenine dinucleotide (NAD^+) depletion during hypoglycaemia, inducing a transient glycolytic bottleneck that persists after plasma glucose restoration and constrains neuronal glucose utilisation. Accordingly, post-hypoglycaemia cerebral energy failure reflects more than a transient lack of glucose; convergent experimental evidence indicates that poly(ADP-ribose) polymerase (PARP-1) activation after glucose correction and associated NAD^+ consumption can transiently limit glycolytic capacity, thereby constraining neuronal glucose utilisation after plasma glucose correction (Figure 1) [1–4].

The brain has high energy demands but minimal energy storage, requiring continuous substrate supply to maintain neuronal activity and predominantly relies on glucose for this purpose. Alternative energy sources, such as ketone bodies (BHB, acetoacetate), lactate and pyruvate, play greater roles in cerebral metabolism during starvation and exercise [5]. This physiological capacity and the growing interest in using BHB as a sport performance supplement provide the foundation for hypothesising that exogenous provision of alternative energy sources may support recovery from hypoglycaemia-induced neurological impairment.

We propose that these energy sources may improve hypoglycaemia recovery: BHB and lactate enter oxidative metabolism downstream of the glycolytic bottleneck thereby helping sustain mitochondrial ATP production when glycolytic capacity is constrained [6]. In experimental models of hypoglycaemia and cerebral energy stress, provision of these energy substrates has been associated with preservation of neuronal energy status and reduced neuronal injury [1, 7–9], supporting the functional relevance of this metabolic bypass, although direct demonstration of this pathway in human hypoglycaemia is currently lacking.

Within this framework, glucose combined with alternative oxidative substrates represents a plausible approach for supporting cerebral energy recovery following hypoglycaemia, with potential importance for cognitive recovery. This concept is informed by experimental evidence and is illustrated by data from MESH formulations, including a glucose-BHB-lactate combination, FL023011 [10]. This may be the starting point for work to advance hypoglycaemia management from 'glucose alone' to 'glucose plus an oxidative substrate'.

2 | Clinical Problem and Unmet Need

Hypoglycaemia is a common problem in insulin-treated diabetes, with many experiencing 100–200 episodes/year, impacting quality of life [11]. Guidelines recommend 15–20 g rapidly absorbed carbohydrate to restore plasma glucose levels.

Plain Language Summary

- What is the context and purpose of this article?
  - Low blood sugar, known as hypoglycaemia, can leave people feeling "foggy" or slow to think, even after blood glucose levels return to normal. For many people with insulin-treated diabetes, these episodes occur frequently and can affect daily functioning, confidence and quality of life. Studies show that cognitive function (thinking, attention, and reaction time) often remains impaired for some time after blood glucose has been corrected. This suggests that restoring glucose in the bloodstream does not immediately restore energy inside brain cells.
  - This article proposes a new explanation for this delay, described as a "brain energy bottleneck." It examines whether multi-energy substrates for hypoglycaemia (MESH) treatments, which combine glucose with additional energy sources such as beta-hydroxybutyrate (BHB) and lactate, including the novel product FLO23011 (Klario), may help improve recovery after low blood sugar.
- What is the proposed mechanism?
  - The proposed mechanism centres on a molecule called NAD^+, which brain cells need in order to convert glucose into usable energy. During hypoglycaemia, stress within brain cells may activate an enzyme called PARP-1, which consumes NAD^+, reducing its availability. When NAD^+ levels fall, an important step in converting glucose into energy becomes less efficient. As a result, the brain may temporarily struggle to use glucose properly, even after blood glucose has been corrected.
  - Alternative energy sources such as BHB and lactate can enter the brain's energy-producing system through different pathways that do not rely on the blocked step in glucose breakdown. Providing these substrates alongside glucose may therefore help sustain energy production while normal glucose metabolism recovers.
- What evidence supports this idea?
  - Studies in brain cells show that glucose deprivation can trigger stress responses, including activation of PARP-1, which may reduce NAD^+ levels and temporarily impair the cell's ability to turn glucose into energy. Animal studies suggest that giving alternative energy sources with glucose after hypoglycaemia can help support the brain's energy supply, reduce brain cell injury, and preserve memory and learning.
  - Human studies have shown that raising levels of BHB or lactate alongside glucose during hypoglycaemia can lessen symptoms and speed up cognitive recovery. In the first clinical study in people self-managing hypoglycaemia, more than 1,000 episodes were analysed to evaluate a MESH product, FLO23011, combining glucose with BHB and lactate. Use of the formulation was linked to fewer repeat episodes and better patient-reported recovery compared with glucose alone. These findings do not directly confirm the mechanism in people, but they are consistent with this proposed explanation.
- Why is this important?
  - Drawing on evidence from experimental and clinical research, this article offers a new way of understanding why cognitive recovery can lag behind the return of normal blood sugar levels. The brain energy bottleneck hypothesis provides a biologically plausible explanation for the recovery benefits seen in recent studies of MESH treatments such as FLO23011 and may inform the evolution of hypoglycaemia self-care beyond glucose alone.

Hyperinsulinemia clamp studies in adults with Type 1 diabetes show cognitive performance on choice reasoning tasks can remain impaired for up to 40 min after euglycemia is restored [12]. Electrophysiological studies in insulin-dependent diabetes and clamp studies in healthy volunteers show cognitive recovery lags symptom resolution and normalisation of plasma glucose by 45–75 min [13, 14].

3 | Mechanistic Hypothesis: The Energy Bottleneck

We propose a mechanistic model whereby activation of PARP-1 can deplete cytosolic NAD^+, inhibit glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and thereby impair glycolytic flux.

Experimental studies in cultured rodent neurons demonstrate that even moderate glucose deprivation is sufficient to increase susceptibility to glutamate-mediated excitotoxicity [15]. Under conditions of energy deficit, glutamate excitotoxicity has been linked to zinc release, reactive oxygen species (ROS) generation and activation of PARP-1 which depletes NAD^+[1–3]. This cascade has been proposed to impair glycolytic flux, plausibly through inhibition of NAD^+-dependent steps such as GAPDH, limiting neuronal glucose utilisation even after systemic glucose levels are restored [4]. PARP-1-mediated NAD^+ depletion and the resulting GAPDH bottleneck are therefore framed as a plausible contributor to delayed cerebral energy recovery in humans.

Experimental models support a PARP-1–dependent impact on NAD^+ availability and glycolytic flux; however, the temporal dynamics and magnitude of PARP-1 activation, NAD^+ depletion and downstream GAPDH modulation during self-treated hypoglycaemia in humans remain undefined. This pathway is presented as a biologically plausible framework that may contribute to neuroglycopenic symptomatology, and as a suggested mechanism that might be shown to operate in the day-to-day hypoglycaemia experience of people with diabetes.

NAD^+ pools are compartmentalised within the cell and PARP-1-mediated depletion predominantly affects cytosolic NAD^+[16]. As a result, cytosolic glycolysis may be impaired, while mitochondrial oxidative pathways remain preserved. Glucose metabolism requires four $NAD^+ \rightarrow NADH$ conversions: two of which are cytosolic (GAPDH) and two are mitochondrial (pyruvate dehydrogenase); cytosolic NADH potential must be shuttled to mitochondria. In experimental glucose deprivation, depletion of cytosolic NAD^+ has been shown to inhibit GAPDH, creating a glycolytic bottleneck that reduces glycolytic flux and leads to

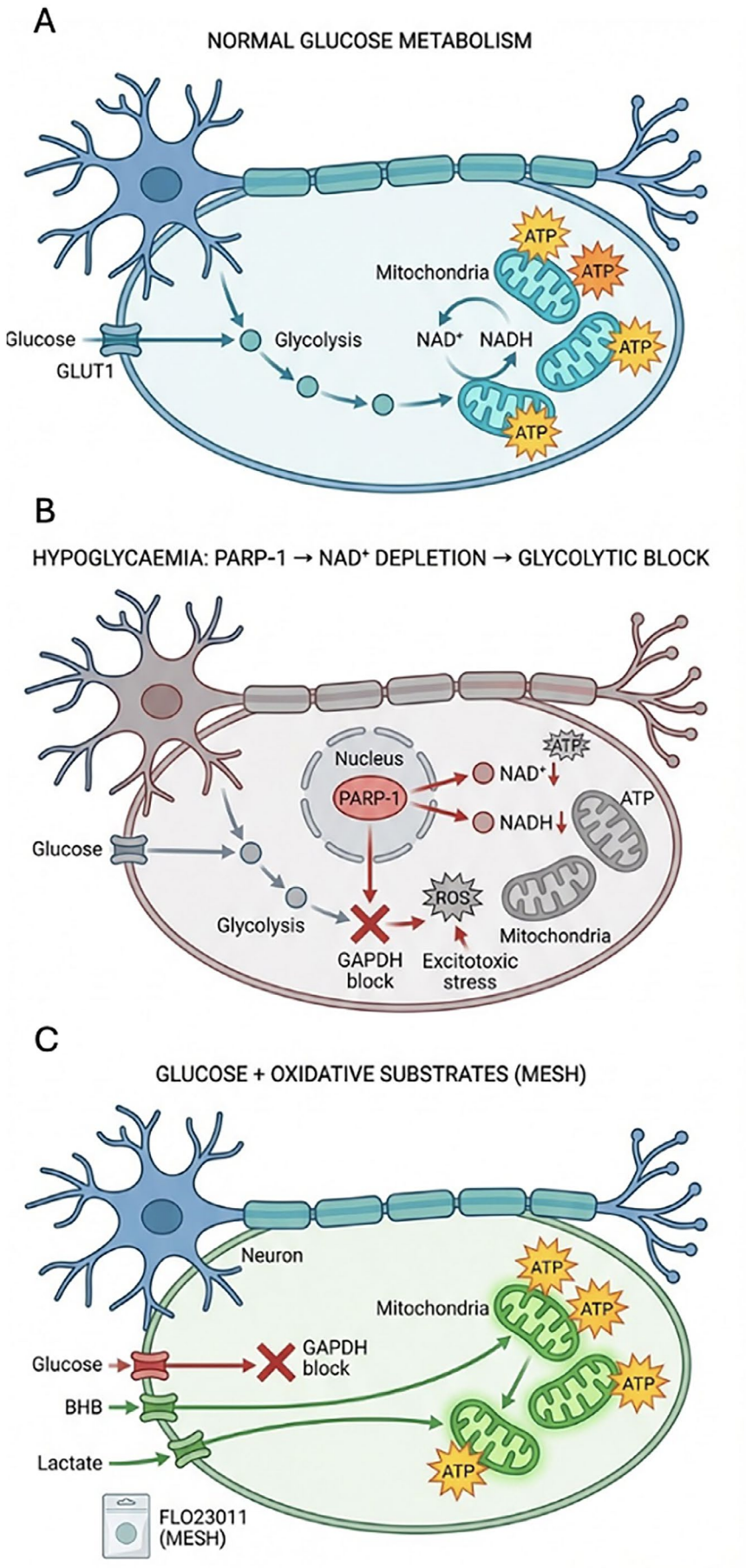

FIGURE 1 | Legend on next page.

FIGURE 1 | Mechanistic model of the proposed Poly [ADP-ribose] polymerase 1 (PARP-1)/Nicotinamide adenine dinucleotide (NAD^+) bottleneck hypothesis. (a) Normal energy metabolism. Glucose is the principal neuronal substrate, metabolised via glycolysis to pyruvate, which enters mitochondria for complete oxidation via the tricarboxylic acid (TCA) cycle, generating ATP. (b) Proposed energy bottleneck during hypoglycaemia. Experimental findings: In cellular and animal models of severe hypoglycaemia and energy stress, PARP-1 activation is associated with NAD^+ consumption. NAD^+ depletion under these conditions has been shown to impair NAD^+-dependent steps of glycolysis and reduce glycolytic flux. Hypothetical extension: We propose that this NAD^+ depletion creates a bottleneck at glyceraldehyde-3-phosphate dehydrogenase (GAPDH), impairing glycolytic flux and delaying ATP recovery even after plasma glucose normalisation. (c) Proposed therapeutic strategy (hypothesis-generating). Addition of alternative oxidative substrates (beta-hydroxybutyrate [BHB], lactate) which enter mitochondrial metabolism downstream of glycolysis, may help sustain ATP production during the recovery window if glycolytic capacity is transiently constrained. Translational and early clinical studies suggest that these substrates can attenuate neuroglycopenic symptoms and support cognitive recovery during hypoglycaemia. However, confirmation that this benefit operates via the proposed NAD^+-dependent bottleneck mechanism in humans remains to be established.

reduced ATP availability, an effect reversible by NAD^+ repletion or provision of downstream oxidative substrates [16].

In contrast, alternative energy sources, such as BHB and lactate, enter cerebral metabolism downstream of glycolysis. BHB is oxidised within mitochondria (BHB → acetoacetate → acetoacetyl-CoA → 2 acetyl-CoA). Lactate conversion to pyruvate involves NAD^+-dependent steps primarily in the cytosol, but pyruvate is removed to enter the TCA cycle, and these substrates, in experimental systems, support mitochondrial ATP under conditions of reduced glucose flux [6]. These metabolic pathway considerations provide a basis to explain why neuronal recovery may lag systemic glycaemic correction in practice.

Together, these findings reframe the potential effects of glucose reintroduction. Rather than uniformly marking recovery, glucose reperfusion is associated with secondary oxidative stress in both neuronal culture and in vivo models. In experimental systems, this can be injurious: restored glucose can support metabolic pathways that increase oxidative stress, including flux through the hexose monophosphate pathway, which increases NADPH and drives a secondary burst of superoxide via NADPH oxidase [17]. This oxidative surge has been shown to cause neuronal loss, particularly in vulnerable regions such as the hippocampal CA1 in animal models.

Identification of this glycolytic block provides a rationale for using alternative energy sources as oxidative substrates, such as BHB, to sustain mitochondrial ATP production during the recovery window and support neuronal function until glycolytic competence is restored. These observations derive from cell and animal models and may not fully extrapolate to human hypoglycaemia, where the magnitude and timing of PARP-1 activation and NAD^+ depletion are likely to vary between severe, non-severe and recurrent episodes. The 'brain energy bottleneck' is presented as a mechanistic hypothesis that may explain the dissociation between systemic glycaemic correction and delayed cognitive recovery.

Animal models provide evidence supporting the hypothesis of a brain energy bottleneck and the ability of alternative energy sources alongside glucose to improve post-hypoglycaemia recovery. In a rat model of insulin-induced severe hypoglycaemia, administering pyruvate with glucose after the insult was associated with ~70%–90% reductions in neuronal death in hippocampal and cortical regions, along with preservation of long-term cognitive performance [1]. These findings are consistent with the idea of NAD^+-independent entry of pyruvate into the tricarboxylic acid cycle (TCA), bypassing metabolic constraints arising from hypoglycaemia, including those linked to PARP-1 activation.

Related experimental work in non-severe and recurrent/moderate hypoglycaemia is potentially more representative of routine clinical experience: In rodent models, repeated post-hypoglycaemic administration of pyruvate with glucose was associated with the attenuation of cortical neuronal injury, zinc accumulation, oxidative injury, microglial activation, PARP-1 activation and glutathione loss [7]. Complementary studies show that lactate given with glucose can reduce hippocampal neuronal loss by ~80% in vivo [8]. Such studies demonstrate the potential of alternative energy sources to sustain oxidative metabolism during the period in which glucose utilisation may be compromised.

BHB extends this paradigm: In a rat model of non-coma hypoglycaemia, systemic BHB administration during and after hypoglycaemia preserved cortical ATP levels, reduced ROS, and prevented cortical neuronal death [9]. BHB may also modulate oxidative stress, inhibit NLRP3 inflammasome activity and HCA2-dependent signalling, supporting neuronal resilience beyond its role as an energy substrate [18]. Its protective effects may reflect both sustained energy provision and attenuation of oxidative stress. Although direct involvement of the PARP-1-NAD^+ pathway in humans has not been established, such effects support the hypothesis.

4 | Translational Implications

Human insulin clamp studies show that BHB and lactate can buffer the impact of hypoglycaemia: symptoms are attenuated, and cognitive recovery (attention, reaction time) occurs more rapidly when these substrates are elevated [19]. This supports the view that exogenous BHB, or lactate can sustain cortical function when glucose availability and/or glycolytic capacity are constrained, although these conditions may not fully reflect real-world diabetes care. Nonetheless, in adults with type 1 diabetes, oral medium-chain triglycerides that raise BHB levels protect cognition during hypoglycaemia, attenuating memory decline and improving processing speed [20].

Recently, a MESH formulation combining glucose, BHB and lactate (FLO23011) was evaluated in pragmatic clinical studies [10]. In a randomised, open-label, crossover trial in 12 adults with Type 1 diabetes, the formulation was compared with standard

oral glucose across more than 1000 real-world hypoglycaemic episodes. The MESH formulation was associated with higher Continuous Glucose Monitoring (CGM) time-in-range, 27% fewer recurrent hypoglycaemic episodes in the hours after treatment, and patient-reported improvements in the resolution of neuroglycopenic symptoms and fatigue. These small, open-label data are hypothesis-generating; they do not provide mechanistic validation but illustrate how the proposed brain energy bottleneck might have translational relevance. Although the episode-level dataset of > 1000 episodes is extensive, a study at this scale is optimised to detect within-participant differences in glycaemic trajectories and symptoms rather than to provide definitive estimates of rare safety or longer term outcomes. The open-label structure was chosen to reflect real-world self-treatment conditions and to ensure feasibility of repeated hypoglycaemia treatment over 12 weeks; nevertheless, this design can introduce expectancy and reporting biases for subjective symptom endpoints. CGM endpoints are influenced by behaviours such as insulin adjustment, carbohydrate intake and physical activity; accordingly, CGM-derived outcomes (time in range, recurrent hypoglycaemia) are interpreted in the context of the crossover design and consistent participant-level exposure to both treatments rather than as stand-alone population benchmarks.

5 | Conclusions

This hypothesis proposes the therapeutic principle of combining rapid glucose delivery with alternative oxidative substrates such as BHB and lactate in appropriate hypoglycaemia settings, to support cerebral energy recovery when glycolytic capacity may be transiently constrained by a brain energy bottleneck. Building on convergent in vitro, animal, and clinical data, this framework offers a rationale that may inform the evolution of hypoglycaemia management from 'glucose alone' towards 'glucose plus an oxidative substrate' where appropriate in day-to-day care and provides a focused agenda for mechanistic, translational and formulation research to refine its application.

Acknowledgements

Eliza Meehan.

Funding

The authors have nothing to report.

Conflicts of Interest

D. Russell-Jones will be named on a patent for FLO2311/Klario if this is granted. He has not received any payment for work on Klario by Flow Health Science Inc. He was the PI on the clinical studies of FLO23011; he did not receive payment for this work. He receives research funding or advisory board honoraria from Abbott Diabetes Care, Dexcom, Astra Zeneca, Eli Lilly, Medtronic, Novartis, Novo Nordisk A/S and Sanofi-Aventis. J. Mader is a member of advisory boards of Abbott Diabetes Care, Becton-Dickinson, Biomea Fusion, Dexcom, Eli Lilly, Embecta, Medtronic, myLife, Novo Nordisk A/S, Pharmasens, Roche Diabetes Care, Sanofi-Aventis, Tandem, Viatris and received speaker honoraria from A. Menarini Diagnostics, Abbott Diabetes Care, Dexcom, Eli Lilly, Medtrust, MSD, Novo Nordisk A/S, Roche Diabetes Care, Sanofi, Viatris and Ypsomed. She is a shareholder of decide Clinical Software GmbH and elyte Diagnostics and serves as CMO of elyte Diagnostics. J. Mader has not received any payment for work on FLO23011/Klario by Flow Health Science Inc. M. Laffan has not received any payment for work on FLO23011/Klario by Flow Health Science Inc.

Data Availability Statement

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

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.70632.

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Received: 21 December 2025 | Revised: 13 January 2026 | Accepted: 13 January 2026

DOI: 10.1111/dom.70512

COMMENTARY

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New paths to attenuate the burden of hypoglycaemia in type 1 diabetes

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KEYWORDS: hypoglycaemia recovery, impact of beta-hydroxybutyrate, type 1 diabetes

Russell-Jones and colleagues[1] raise the question of whether adding beta-hydroxybutyrate (BHB) to a standard oral glucose load of 15 g can improve recovery from iatrogenic hypoglycaemia compared with standard care in people with type 1 diabetes.

1 | PHYSIOLOGICAL AND BIOCHEMICAL RESPONSES TO HYPOGLYCAEMIA

To better comprehend the rationale of the present study, it seems mandatory to provide a brief overview of the pathophysiological impact of hypoglycaemia on the brain. Regulation of cerebral glucose uptake depends primarily on glucose transporters, mainly belonging to the GLUT-family.[2] Under normal conditions, these transporters—whose activity is independent of plasma insulin levels—maintain a stable concentration of glucose in the resting brain. D-glucose is the brain's primary energy substrate, supporting normal neuronal function through glycolysis and ATP production. However, cerebral glucose delivery must be tightly regulated, as excessive glucose concentration in the brain would otherwise result in neuronal damage.[2] This transport system is disrupted during hypoglycaemic episodes,[2,3] during which a biphasic response is typically observed. In the early phase of hypoglycaemia, glucose transporter activity is upregulated in an attempt to maintain cerebral glucose availability. However, when blood glucose concentrations fall to very low levels—such as those observed during levels 1 and 2 hypoglycaemia—this compensatory upregulation becomes insufficient, leading to a rapid decline in brain glucose levels. This reduction is accompanied by classical adrenergic and/or neuroglycopenic symptoms arising from the activation of counterregulatory mechanisms.[4]

In individuals with type 1 diabetes who experience recurrent and/or severe hypoglycaemia, this adaptative upregulation of glucose transporters may fail, thus resulting in impaired recovery, prolonged hypoglycaemia, and increased risk of recurrent hypoglycaemia with unawareness. This hypoglycaemia unawareness is further exacerbated when hypoglycaemic events occur in persons exhibiting defective sympathoadrenal and glucagon secretory responses, which normally begin to be activated when plasma glucose concentrations fall below 70 mg/dL (3.9 mmol/L). Such defects are more commonly observed in older people, those with long-standing diabetes, or in those with prior exposure to recurrent hypoglycaemia.[4,5]

To accelerate recovery from hypoglycaemic episodes, the authors propose the use of alternative energy substrates to glucose, such as ketone bodies. Ketone bodies are readily taken up by neuronal cells and rapidly metabolized to generate ATP, the metabolite directly available for energy supply.[6] This study was therefore conducted in patients with type 1 diabetes experiencing iatrogenic hypoglycaemic episodes to assess the impact and potential clinical benefits of combining oral glucose with beta-hydroxybutyrate (BHB), a substrate that efficiently crosses the blood–brain barrier and rapidly generates ATP via the tricarboxylic acid cycle, bypassing glycolysis.

2 | SPECIFIC COMMENTARY OF THE DATA REPORTED WITH BHB SUPPLEMENTATIONS

This proof-of-concept study[1] comprised two parts. The first part aimed to observe the pharmacokinetic profiles of a novel multi-substrate energy formulation FLO2311 (FLO), containing 15 g of glucose and 10 g of BHB. FLO was compared to standard glucose gel (SoC, 15 g) in six healthy, non-diabetic adults after a single oral dose over a 180-min period. The glucose responses were similar for both preparations with comparable peak glucose concentrations and glucose exposures as measured by areas under glucose profiles, thus indicating that the overall glucose absorption did not depend on the preparation used. After ingesting a single dose of FLO, BHB was

rapidly absorbed, reaching peak levels within 30 min. It then began to decline after 90 min but remained above baseline for the remaining duration of the study period.

The second part of the study yielded more intriguing results. Twelve subjects with type 1 diabetes were compared in a cross-over clinical effectiveness trial over two periods of 6 weeks during which the participants were randomly allocated to either FLO or SoC for managing hypoglycaemic episodes. While the overall glycaemic control was similar with both preparations, the time spent within the recommended glucose target range (TIR: 70–180 mg/dL; i.e., 3.9–10.0 mmol/L)[7] during the 2-h post-hypoglycaemic recovery period was slightly but significantly improved with FLO. There was little to no difference in glucose variability (as measured by CONGA analysis). Several other parameters were improved with the co-formulation compared to normal care. These improvements included clinical effectiveness (speed of recovery from hypoglycaemic effects), functional recovery (return of daily activities), product characteristics (ease of use and palatability), and psychological outcomes (improved ability to manage low blood sugar).

Despite the very encouraging information provided by the present study, one limitation is the absence of comprehensive data on the overall incidence rates of hypoglycaemia during the entire duration of this 6-week trial. A comparison between the two groups would have been useful to further support the significant reduction by 27% with FLO for the frequency in recurrent hypoglycaemia within 2 h. Nonetheless, the authors present promising findings suggesting that the addition of BHB to an oral glucose may enhance recovery from hypoglycaemia in both the short and potentially longer term. This preliminary phase warrants further investigation to assess the full glucocentric and even potential broader benefits of co-administering BHB and glucose.

3 | GENERAL COMMENTARY ON THE THERAPEUTIC MEASURES FOR ATTENUATING THE RISKS AND INCIDENCE RATES OF HYPOGLYCAEMIA

Currently, preventing hypoglycaemia—particularly in individuals with recurrent, severe episodes of hypoglycaemia and unawareness of such events—relies primarily on the most advanced technologies of insulin delivery that have been developed in recent years.[8,9] The common approach to both diminishing the frequency of hypoglycaemic episodes and preventing their onset involves minimizing glycaemic variability[10,11] and perhaps, at least temporarily, giving less priority to near normal glycaemic control, especially in patients with recurrent asymptomatic hypoglycaemia. In type 1 diabetes treated with either daily multi-injections of insulin or continuous subcutaneous insulin infusions, several studies[12–14] have demonstrated that real-time continuous glucose monitoring (rCGM) systems per se significantly reduce the percentage of time spent below the glycaemic thresholds (TBR) either 70 mg/dL, that is, 3.9 mmol/L (level 1 hypoglycaemia) or 54 mg/dL, that is, 3.0 mmol/L (level 2 hypoglycaemia). In one study,[14] the glycaemic variability (%CV glucose) decreased when persons with type 1 diabetes treated with daily multi-injections of insulin switched to wearing a rCGM.

Moreover, insulin delivery modalities play a critical role in reducing hypoglycaemia risk, and therefore, it would be interesting to see if there are differences in outcomes between patients using multiple daily injections versus those on insulin pump therapy. From a 'glucocentric' perspective, all therapeutic strategies for managing glycaemic disorders in type 1 diabetes should target all the components of the 'ominous quartet': chronic glucose exposure, postprandial glucose excursions, hypoglycaemic events, and glycaemic variability. Presently, it is well established that the two latter components are strongly intercorrelated. For instance, the analysis of data from 38 randomized controlled trials[15] examining the use of sensor augmented pumps (SAP) and automated insulin delivery (AID) therapies revealed an inverse relationship between glycaemic variability (% CV glucose) and times below range (TBR <70 mg/dL or 54 mg/dL, i.e., <3.9 mmol/L or 3.0 mmol/L). Specifically, each 2% reduction in % CV glucose was associated with approximately a 0.50% decrease in time spent with plasma glucose levels below 70 mg/dL (3.9 mmol/L).

From a practical standpoint, maintaining %CV glucose below 36% is crucial, as this threshold separates relatively stable from labile glycaemic control.[16] However, a value below 36% only guarantees that the incidence rate of hypoglycaemia should be less frequent and relatively acceptable for the patient. Our own studies suggest that total eradication of hypoglycaemic episodes (TBRs # 0) is only achieved when the % CV glucose falls below 27%, a value that corresponds to the upper limit of the normal distribution in healthy non-diabetic individuals.[15] Yet, such control has never been achieved, even with the implementation of a neuronal-net artificial pancreas (NAP) after encoding AID algorithms into a neuronal network.[17] Additionally, the risk of hypoglycaemia has long been known to be higher in individuals assigned to intensive insulin therapies compared to those on conventional insulin regimens, as demonstrated by the Diabetes Control and Complications Trial (DCCT).[18,19] Given that newer insulin delivery technologies allow for near-normal glucose homeostasis (in terms of HbA1c and mean glucose concentrations), the TBR thresholds in type 1 diabetes may need to be re-evaluated downward, at least in users of advanced systems of insulin delivery.[20] However, as a residual risk for hypoglycaemia will likely persist, even with these sophisticated treatment modalities, the present study published by Russell-Jones and colleagues offers valuable insights into improving the management and recovery from hypoglycaemic episodes, thereby establishing a potential new standard of care.

ACKNOWLEDGEMENTS

The authors have nothing to report.

FUNDING INFORMATION

The authors received no specific funding for this work.

CONFLICT OF INTEREST STATEMENT

Louis Monnier and David Owens declare they have no conflict of interest with this commentary.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.70512.

DATA AVAILABILITY STATEMENT

All data cited in this commentary article are listed in the reference section and can be consulted from such scientific databases as Medline, Google Scholar, for instance.

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How to cite this article: Monnier L, Owens D. New paths to attenuate the burden of hypoglycaemia in type 1 diabetes. *Diabetes Obes Metab*. 2026;1-3. doi:10.1111/dom.70512

American Diabetes Association

Multi Energy Substrate Hypoglycaemia (MESH) Rescue With FLO23011 Improves Patient-Reported Outcomes Versus Standard Glucose Treatment in Type 1 Diabetes

Russell-Jones et al. Abstract #1359-P, ADA Scientific Sessions 2026

Introduction & Objective: Hypoglycaemia management significantly impacts quality of life in Type 1 Diabetes. FLO23011 is a Multi Energy Substrate Hypoglycaemia (MESH) oral rescue treatment providing glucose, lactate, and beta-hydroxybutyrate, which targets multiple metabolic pathways. Superiority over standard of care glucose gel (SoC) has been previously shown in a randomized cross-over study. This is an evaluation of comparative patient-reported outcomes from the study.

Methods:
Twelve adults with Type 1 Diabetes (8 M/4 F; mean age 49) completed a randomized cross-over study using FLO23011 or SoC for hypoglycaemia self-care. Participants rated comparative preferences (0–10 Likert; 14 domains; scores >5 indicating FLO23011 preference) and completed structured interviews.

Results: FLO23011 showed preference in 13 of 14 domains (median scores 6–8). For effectiveness, 64–82% preferred FLO23011 for hypoglycaemia reversal, headache relief, and speed. After-effects were optimized: 70% reported less severe fatigue/weakness; 80% returned to activities faster. Rebound hypoglycaemia management favored FLO23011 (58%). Packaging: 75% preferred ease-of-use; 33% for portability. Psychological domains showed benefits: 82% felt increased control; 73% reported greater dosing confidence; 55% experienced reduced worry. Overall management preference: 64%. Interviews reinforced findings: 92% rated FLO23011 "Very/Extremely" effective versus 50% for SoC; 92% reported "Never/Rarely" experiencing ‘hangover’ symptoms versus 33%. Over half described rapid cognitive restoration, while 75% reported reduced glucose spikes, attributed to precise dosing and reduced over-treating.

Conclusion: FLO23011's superior patient-reported outcome profile demonstrates that MESH preparations may address unmet needs beyond glucose normalization in type 1 diabetes. FLO23011 represents a meaningful advance in hypoglycaemia self-care.

Diabetes UK Professional Conference

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

Russell-Jones et al. Abstract #P103, Diabet Med 43:e70288. doi:10.1111/dme.70288

Background: Hypoglycaemia is a common, potentially dangerous complication of glucose-lowering therapies. Current treatments raise blood glucose but have limitations: rapid glucose fluctuations, suboptimal cognitive recovery and fatigue; they may not address potential long-term harms. We investigated FLO23011, a novel combination product containing glucose and BHB.

Methods: Two studies compared FLO23011 with standard glucose treatment (SoC). Study A: a randomised crossover pharmacokinetic study in six healthy adults measuring responses over 180 minutes. Study B: a 12-week randomised, open-label, crossover trial in 12 adults with type 1 diabetes. Study B evaluated glycaemic control using continuous glucose monitoring (CGM) and patient-reported outcomes across 14 domains using structured questionnaires. This abstract reports the first full presentation of data from both studies.

Results: Study A demonstrated comparable glucose response between FLO23011 and SoC (Cmax 7.4 ±0.3 vs 7.9 ±0.2mmol/l, p=0.122) but with sustained BHB elevation (Cmax 0.6-1.2mmol/l).

Study B: participants used each treatment for six weeks in randomised order. FLO23011 achieved superior scores compared to SoC in 13/14 domains; 10 reached significance including Speed of action (+0.67, p=0.025, Cohen effect size d=0.720), After-effects improvement (+1.83, p=0.014, d=0.895), Overall low sugar management ability (+1.08, p=0.019, d=0.764), Taste preference (+2.33, p=0.016, d=0.816). Preliminary CGM analysis showed significantly improved post-hypoglycaemia time-in-range (p=0.019) and reduced recurrent episodes (p=0.031).

Conclusion: FLO23011 is the first novel hypoglycaemia treatment in 100 years, providing superior effectiveness, glycaemic stability, and user experience compared to glucose-only treatments. This novel product may represent an important advance in hypoglycaemia management, accelerating functional or complete recovery and enabling more confident diabetes self-management.

Patient assessment of problems in hypoglycaemia self-care and recommendations to improve treatment

Myers et al. Abstract #P221, Diabet Med 42:e15498.

Aims: Options for self-care (SC) of treatment-related hypoglycaemia (TRH) have limitations: this study assessed SC experience in TRH for people with type 1 diabetes to identify ways to improve treatment options.

Methods: A structured assessment instrument was developed with patients and expert clinicians to describe SC experience and recommendations. 40 adults (18 female, 22 male; mean age 38 years (range 18-71); diabetes history 21 years; TRH frequency 8/month) completed the assessment assisted by an expert trained facilitator familiar with the topic. Ethics committee approval was not sought in accordance with guidance from a Health Research Authority tool for project assessment.

Results: SC experience: majority (77%) reported problems with SC using conventional products (glucose containing gels or liquids): fatigue (43%), glucose spikes/'overshoot' (38%), weakness/sluggishness (28%), confusion/'brain fog' (20%), and nausea (15%). Other limitations noted: poor taste or texture of products, difficulty in achieving sufficient dose, hard to open packaging.

Patient recommendations for improvement:

(1) Effectiveness. 21 of 40, (53%): products to limit problems after successful SC (tiredness, confusion, getting back to normal quickly).

(2) Utility. 32 of 40, (80%): ensure products are easy to open, consume discreetly in public, convenient to store and transport.

(3) Overall wellness. 9 of 40 (23%): ensure products avoid potential problems of glucose spikes and crashes.

Conclusions: People expert in SC for TRH identify important limitations to current treatment with clear recommendations for improvement; relevant innovation should focus on improving treatment options with fewer problems such as tiredness, better taste, ease of use and a focus on overall wellness.

European Association for Study of Diabetes

A Breakthrough in Hypoglycaemia Management: Assessing the Efficacy and Acceptability of FLO23011, a novel ketone glucose combination product in Type 1 Diabetes

Russell-Jones et al. Abstract #876, 61st EASD Annual Meeting. Diabetologia 2025

Background & aims: Hypoglycaemia is a common, potentially dangerous complication of diabetes medication. Current treatments raise blood glucose but have limitations: rapid glucose fluctuations ("peak and crash"), suboptimal cognitive recovery, fatigue. The brain can use intermediary metabolites (ketones, lactate, pyruvate) in addition to glucose. This study evaluated effectiveness and acceptability of FLO23011, a novel combination product containing glucose and other brain energy sources, versus standard of care (SoC) glucose gel.

Materials & methods: 2 studies were performed: (A) pharmacokinetics study, healthy subjects, (B) clinical trial, subjects with type 1 diabetes (A): Six adults (3 M/3 F; mean age 46.5; BMI 24.7) received FLO23011 1-dose (1-FLO), 2-dose (2-FLO) or SoC after overnight fasts. 1-FLO and SoC were dose-matched for glucose. Blood samples were collected for 3 hours. (B): Twelve adults with type 1 diabetes used FLO23011 or SoC in random order over 12 weeks to treat hypoglycaemia at home. Effectiveness/ Recovery, User Experience, Emotional Impact, glucose control were assessed via structured questionnaires and CGM data. Ethics approval was obtained.

Results & Conclusion: (A): Glucose peak plasma concentrations were comparable between 1-FLO and SoC (1-FLO: 7.4 ± 0.3 mmol/L vs. SoC: 7.9 ± 0.2 mmol/L, p=0.122) as were total AUCs (1-FLO: 1292.3 ± 62.5 mmol/L*min vs. SoC 1194.5 ± 48.6 mmol/L*min, p=0.195). FLO23011 provided a more stable energy profile: glucose declined more slowly to baseline (1-FLO: 150 min vs. SoC: before 120 min), and levels of alternative energy substrates were elevated for 3 hours (Fig 1). Insulin increased in response to glucose load, with no difference between 1-FLO and SoC. Glucagon responses were similar.

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