Reduced hypoglycaemia using liver-targeted insulin in individuals with type 1 diabetes

Ruth S. Weinstock MD | Bruce W. Bode MD | Satish K. Garg MD
David C. Klonoff MD | Caroline El Sanadi PhD | W. Blair Geho MD
Douglas B. Muchmore MD | Marc S. Penn MD

1SUNY Upstate Medical University, Syracuse, New York
2Atlanta Diabetes Associates, Atlanta, Georgia
3Barbara Davis Center for Childhood Diabetes, University of Colorado Denver, Aurora, Colorado
4Mills-Peninsula Medical Center, San Mateo, California
5Diasome Pharmaceuticals, Inc., Cleveland, Ohio
6Summa Health, Akron, Ohio

Abstract

Aim: To investigate whether an increased bolus: basal insulin ratio (BBR) with liver-targeted bolus insulin (BoI) would increase BoI use and decrease hypoglycaemic events (HEv).

Patient Population and Methods: We enrolled 52 persons (HbA1c 6.9% ± 0.12%, mean ± SEM) with type 1 diabetes using multiple daily injections. Hepatic-directed vesicle (HDV) was used to deliver 1% of peripheral injected BoI to the liver. A 90-day run-in period was used to introduce subjects to unblinded continuous glucose monitoring and optimize standard basal insulin (BaI) (degludec) and BoI (lispro) dosing. At 90 days, BoI was changed to HDV-insulin lispro and subjects were randomized to an immediate 10% or 40% decrease in BaI dose.

Results: At 90 days postrandomization, total insulin dosing was increased by ~7% in both cohorts. The 10% and 40% BaI cohorts were on 7.7% and 13% greater BoI with 6.9% and 30% (P = .02) increases in BBR, respectively. Compared with baseline at randomization, nocturnal level 2 HEv were reduced by 21% and 43%, with 54% and 59% reductions in patient-reported HEv in the 10% and 40% BaI cohorts, respectively.

Conclusions: Our study shows that liver-targeted BoI safely decreases HEv and symptoms without compromising glucose control. We further show that with initiation of liver-targeted BoI, the BBR can be safely increased by significantly lowering BaI dosing, leading to greater BoI usage.

Keywords
clinical trial, hypoglycaemia, insulin therapy, type 1 diabetes

1 | INTRODUCTION

In normal healthy people the liver is exposed to 100% of insulin released by the pancreas through the portal vein. A significant portion of insulin released in response to meal intake is taken up by the liver, facilitating carbohydrate uptake by the liver and enabling generation of glycogen. Physiological prevention of hypoglycaemia is the direct result of glucagon-activated hepatic glucose release after the conversion of hepatic glycogen to glucose through glycogenolysis. It is known that peripherally administered insulin does not reach the...
liver to a physiologically appropriate degree, resulting in impaired glycogen storage after eating and an inability to mobilize an adequate release of hepatic glucose to counteract hypoglycaemia. For these reasons, optimization of blood glucose levels requires restoration of prandial insulin action during therapy of type 1 diabetes (T1D), allowing insulin to act both on the liver and the peripheral tissues in a more physiologically appropriate manner to lower blood glucose levels and to protect from hypoglycaemia.

Studies with hepato-preferential pegylated insulin, peritoneal insulin delivery that results in insulin delivery to the portal vein, and hepatic vein islet cell transplantation have all shown that insulin delivery to the liver significantly lowers the risk of hypoglycaemia in individuals with T1D. While each of these approaches has shown clinical efficacy, they are challenged by side effects that have limited their clinical use or availability.

Hepatic-directed vesicle (HDV) insulin, a novel liver-targeted drug delivery system comprised of biotin phosphatidylethanolamine in a phospholipid matrix, has been shown to target subcutaneously injected insulin to the liver and provides more normal insulin biodistribution by mimicking portal vein insulin delivery. HDV was designed to efficiently deliver insulin to the liver through the embedded biotinylated phosphatidylethanolamine into the HDV complex. The insulin binds to the HDV complex through charge interaction at the surface of HDV. Because most biotin receptors in the body are contained in the liver, the HDV-insulin complex is targeted to the liver. The increased potency and flat dose-response of HDV for hepatic glucose balance, along with oral glucose tolerance results in preclinical studies, support low-dose, fixed combination (1% HDV-insulin, 99% unbound insulin) treatment.

In the randomized, double-blinded, 6-month phase 2b ISLE-1 study, we showed that in participants with an HbA1c of 8.5% or higher at baseline, the use of HDV-lispro decreased both time spent in level 2 hypoglycaemia by 53% (minutes per day when blood glucose was <54 mg/dl; measured by blinded continuous glucose monitoring [CGM]) and HbA1c by 0.5%. Lispro alone had the same decrease in HbA1c at the expense of increased risk of hypoglycaemia, with a 116% increase in time spent in level 2 hypoglycaemia. Unexpectedly, participants with baseline HbA1c less than 8.5% exhibited no effect on either HbA1c or level 2 hypoglycaemia with the use of HDV-insulin lispro.

We designed the OPTI-1 study to better ascertain the potential benefit of HDV-insulin in T1D in individuals with a baseline HbA1c of less than 8.5%, using unblinded CGM, and with a protocol-mandated increase in the bolus: basal insulin ratio, implemented by a forced reduction in basal insulin at the time of substituting HDV-insulin lispro for insulin lispro. This treatment paradigm was chosen based on our interpretation of the ISLE-1 study results, which suggest that subjects with lower baseline HbA1c (<8.5%) are unlikely to alter their bolus insulin-dosing regimens in the setting of blinded drug and blinded CGM. We hypothesized that lowering basal insulin dosage at the initiation of HDV-lispro treatment would encourage participants to more aggressively uptitrate bolus HDV-lispro dosing. We further hypothesized that if participants experienced fewer symptomatic or CGM hypoglycaemic events as basal insulin was titrated, they would continue to use a higher bolus: basal insulin ratio compared with baseline.

To test these hypotheses, the OPTI-1 study was designed to emulate an optimized clinical practice setting, in that participants were provided with unblinded insulin and unblinded CGM during a 12-week run-in period to optimize insulin dosing of current formulations of basal and bolus insulins, prior to transitioning to open-labelled HDV-insulin with lowering of the basal insulin dose.

2 | DESIGN AND METHODS

2.1 | Design and participants

The OPTI-1 study (clinicaltrials.gov: NCT03938740) was a 24-week, phase 2b, multicentre (eight US sites), randomized, open-label trial in participants with T1D treated with multiple daily injections of insulin. The protocol was approved by independent ethics boards and was compliant with the Declaration of Helsinki. The primary objective was to determine optimum basal insulin-dosing algorithms for T1D treated with HDV-insulin lispro. The primary endpoints were mean and median insulin doses (basal, bolus, total daily and basal/bolus ratio).

The main inclusion criteria were: age 18-65 years at time of informed consent, T1D for at least 12 months, HbA1c of 6.5% or higher and 8.5% or less, body mass index of 18.0 kg/m² or higher and 33.0 kg/m² or less, and treatment with rapid-acting insulin.
The notable exclusion criteria were: uncontrolled hypertension, use of an insulin pump delivery system within 2 months prior to screening, and nicotine use.

### Procedures

During the run-in period (the first 12 weeks of the study), participants were provided with insulin lispro (prandial) and insulin degludec (basal, morning injection), and an intensive insulin treatment plan was reviewed. The last 6 weeks of the run-in period were considered to represent ‘optimized standard of care’.

Following the run-in period, optimized bolus and basal doses were recorded, and participants were randomized 1:1 into two groups based on two stratification criteria: total daily insulin dose (<50 vs. ≥50 units/d) and the % of mean daily time for CGM-measured glucose below 70 mg/dl during the 2 weeks prior to randomization (<4.0% vs. ≥4.0%). Having optimized insulin dosing in the run-in

### Table 1

| Characteristic | Overall (N = 57) | Basal insulin intervention group | Reduced 10% (N = 29) | Reduced 40% (N = 28) |
|---------------|-----------------|---------------------------------|---------------------|---------------------|
| Sex           |                 |                                 |                     |                     |
| Male          | 34 (59.6%)      | 18 (62.1%)                      | 16 (57.1%)          |
| Female        | 23 (40.4%)      | 11 (37.9%)                      | 12 (42.9%)          |
| Race          |                 |                                 |                     |                     |
| White         | 53 (93.0%)      | 27 (93.1%)                      | 26 (92.9%)          |
| Black or African American | 3 (5.3%)      | 1 (3.4%)                        | 2 (7.1%)            |
| Multiple      | 1 (1.8%)        | 1 (3.4%)                        | 0                   |
| Ethnicity     |                 |                                 |                     |                     |
| Hispanic or Latino | 4 (7.0%)      | 2 (6.9%)                        | 2 (7.1%)            |
| Non-Hispanic or Latino | 53 (93.0%)  | 27 (93.1%)                      | 26 (92.9%)          |
| Age (y)       |                 |                                 |                     |                     |
| n             | 57              | 29                              | 28                  |
| Mean (SD)     | 42.8 (13.03%)   | 41.3 (12.00%)                   | 44.4 (14.05%)       |
| Median        | 43.0            | 42.0                            | 45.0                |
| Min, max      | 18.0, 65.0      | 20.0, 60.0                      | 18.0, 65.0          |
| Weight (kg)   |                 |                                 |                     |                     |
| n             | 57              | 29                              | 28                  |
| Mean (SD)     | 83.1 (14.30)    | 82.9 (14.58)                    | 83.4 (14.26)        |
| Median        | 82.9            | 82.1                            | 83.4                |
| Range         | 51.4, 108.6     | 59.8, 107.6                     | 51.4, 108.6         |
| Height (cm)   |                 |                                 |                     |                     |
| n             | 57              | 29                              | 28                  |
| Mean (SD)     | 173.9 (10.76)   | 173.3 (10.01)                   | 174.5 (11.63)       |
| Median        | 176.4           | 176.4                           | 176.6               |
| Min, max      | 155.0, 192.0    | 157.0, 191.0                    | 155.0, 192.0        |
| BMI (kg/m²)   |                 |                                 |                     |                     |
| n             | 57              | 29                              | 28                  |
| Mean (SD)     | 27.4 (3.46)     | 27.6 (3.95)                     | 27.3 (2.93)         |
| Median        | 26.7            | 26.7                            | 27.0                |
| Min, max      | 19.8, 35.3      | 20.8, 35.3                      | 19.8, 31.8          |
| Time since T1D diagnosis (y) |         |                                 |                     |                     |
| n             | 56              | 28*                            | 28                  |
| Mean (SD)     | 21.3 (12.00)    | 22.6 (10.67)                    | 20.0 (13.26)        |
| Median        | 18.3            | 20.1                            | 15.1                |
| Min, max      | 3.1, 50.7       | 6.2, 45.6                       | 3.1, 50.7           |

Abbreviations: BMI, body mass index; Max, maximum; Min, minimum; SD, standard deviation; T1D, type 1 diabetes.

*One participant did not have a reported start date for their T1D.
period, all participants were switched from insulin lispro to HDV-insulin lispro for all prandial dosing, and basal insulin dosing was reduced by either 10% or 40% from the last recorded dose from the run-in period prior to randomization. The first 6 weeks post-randomization were considered to be the ‘HDV-insulin dosing optimization period’, and the last 6 weeks of the period were considered to represent ‘optimized HDV-insulin treatment’.

HDV-lispro was formulated by mixing 0.8 ml of HDV solution into a 10-ml vial of commercial Humalog (Eli Lilly and Co.). Throughout the study, basal dosing was titrated on a weekly basis to achieve a target fasting blood glucose of 80-100 mg/dl. Participants wore unblinded CGM devices (Dexcom G6 CGM along with a smart phone-based application) for the entirety of the study period.

Vital signs, HbA1c, lipids, liver enzymes and C-peptide were measured at 12-week intervals (at screening, at randomization and at last visit). Hypoglycaemia was assessed using CGM data and participant-recorded (diary) events. Level 2 hypoglycaemic events were derived from CGM records, as previously described. Briefly, the beginning of a level 2 event was defined by three consecutive measures (15 minutes) of blood glucose less than 54 mg/dl. The end of an event was defined as three consecutive measures (15 minutes) of blood glucose more than 70 mg/dl. Participants presented every 3 weeks during the run-in period and every 2 weeks during the treatment period, and were assessed by site professionals via telephone between in-person visits to ensure that dosing titrations were implemented and manageable.

2.3 | Statistical analysis

The full analysis set (FAS) includes all safety set participants (defined as all enrolled participants who randomized, received any HDV-insulin lispro treatment, who did not violate any exclusion criterion, did not take a prohibited concomitant medication during the study, and had at least one non-missing treatment period assessment after visit 5). The FAS was used for all metrics reported except for the safety analysis, which used the safety set (all enrolled participants who were randomized and received any HDV-insulin lispro). Statistical analyses were performed using t-test and paired t-test where appropriate.

3 | RESULTS

Participants were randomly assigned to either treatment arm of the study (n = 29, 10% basal insulin reduction; n = 28, 40% basal insulin reduction; Figure 1). The baseline demographic data are listed in Table 1. There were no significant differences between the −10% basal and −40% basal cohorts for any of the baseline characteristics.

3.1 | Blood glucose control

Mean daily glucose (MDG) values (measured by CGM) during optimized standard of care (visits 4-5), HDV-insulin lispro dosing optimization (visits 6-8) and optimized HDV-lispro treatment (visits 9-11) for daytime and night-time are shown in Figure 2A. Comparing MDG during HDV-lispro dosing optimization to optimized standard of care revealed that decreasing basal insulin by 10% and 40% at randomization resulted in mean increases in MDG of 5.6% and 9.5% over the next 6 weeks, respectively. However, following titration of insulin doses (both basal and bolus) during the HDV-insulin dosing optimization period, no significant MDG differences (2.0% and 3.7% for the 10% and 40% basal insulin decrease groups, respectively) were found between the optimized HDV-insulin treatment period (visits 9-11) and the optimized standard of care period (visits 4-5).

HbA1c levels at baseline, randomization and at the end of the trial are shown in Figure 2b. These data show that, on average, the population studied achieved American Diabetes Association (ADA) goals of HbA1c less than 7.0% but HbA1c was not part of the stratification for randomization, and we observed a baseline imbalance for HbA1c. HbA1c levels for the −10% and −40% basal reduction cohorts were

![Figure 2A](image-url)  
**Figure 2A.** Mean daily glucose during the daytime (open circles) and night-time (grey filled circles) at randomization (visits 4-5, last 45 days of run-in), during titration of basal dose (visits 6-8, first 45 days of hepatic-directed vesicle [HDV] treatment) and during optimized HDV treatment (visits 9-11, last 45 days of HDV treatment) for subjects who decreased their basal insulin dose by 10% (dotted line) or 40% (solid line), and B, HbA1c at baseline (visit 1, baseline), randomization (visit 5, end of run-in) and study completion (visit 11, end of HDV treatment) for subjects who decreased their basal insulin dose by 10% (grey symbol) or 40% (black symbol) at randomization (visit 5). Data represent mean ± SEM.
7.2% and 6.6%, respectively (average baseline HbA1c 6.9%), and HbA1c levels did not change significantly from enrolment to randomization or at the end of the trial.

### 3.2 Insulin dosing

The data in Figure 3A-C show basal, bolus and total insulin dosing by visit for participants who were randomized to either a 10% or 40% decrease in basal dosing at visit 5. Also included in Figure 3D-F are the % changes from baseline at visit 5 in insulin dosing by visit. The baseline insulin values at visit 5 represent the optimized insulin dosages achieved using unblinded CGM during intensive standard of care insulin management with a basal dose titration goal of fasting blood glucose of 80-100 mg/dl prior to randomization.

During HDV-insulin optimization following randomization, basal dosing in the 40% decrease group was markedly decreased and bolus dosing was increased. Basal dosing in the 10% decrease basal group was increased above baseline within 2 weeks following randomization (visit 5 to visit 6), as was the bolus HDV-insulin lispro dosing in this group. Over the course of the 12-week period after randomization, basal dosing was titrated and ended the study at 0.37 and 0.34 units/kg/d in the 10% and 40% basal reduction cohorts, respectively, representing net 8.8% and 3.0% increases compared with the end of the standard of care optimization phase (Figure 3A,D). Bolus HDV-insulin lispro dosing was increased to a greater extent over baseline in the 40% decrease basal cohort early after randomization compared with the 10% decrease basal cohort (Figure 3B,E). Participants in both groups continued to titrate their bolus HDV-insulin lispro at a greater dosing level than baseline lispro at visit 5. HDV-lispro bolus dosing at the end of the study was 0.28 and 0.26 units/kg/d in the 10% and 40% basal reduction cohorts, respectively, representing 7.7% and 13% increases above insulin lispro doses at the end of optimized standard of care (Figure 3C,F).

The final total insulin dosing was 0.62 and 0.58 units/kg/d in the 10% and 40% basal reduction cohorts, respectively, representing 6.9% and 7.4% increases (Figure 3C,F) compared with the end of the

**FIGURE 3** A, Basal, B, Bolus, and C, Total insulin dose (units/kg/d) at visits 5 through 11 for subjects who decreased their basal insulin dose by 10% (grey symbol) or 40% (black symbol) at randomization (visit 5). Data represent mean ± SEM. Percentage change in D, Basal, E, Bolus, and F, Total insulin dose at visits 5 through 11 relative to dose at randomization (visit 5). Data are for subjects who decreased their basal insulin dose by 10% (grey symbol) or 40% (black symbol) at randomization (visit 5). Data represent mean % change per cohort at designated time point.
standard of care optimization phase (visit 5). Participants in the 40% basal reduction cohort had a 30% increase in bolus:basal ratio from visits 4-5 to visits 9-11 from 0.50 ± 0.76 to 0.65 ± 1.02 (P = .04), whereas the 10% basal reduction cohort had a 6.9% increase in bolus:basal ratio from 0.43 ± 0.62 to 0.46 ± 0.70.

At the end of the study compared with visit 5, there was a significant (P = .02) decrease in weight in participants in the 40% basal reduction (mean ± SD, −0.6 ± 2.4 kg) compared with the 10% basal reduction cohort (0.5 ± 2.8 kg).

### 3.3 Episodes of level 2 hypoglycaemia

The data in Figure 4 depict the rate of level 2 hypoglycaemic events per week for daytime (Figure 4A) and night-time (Figure 4B) measured by CGM as a function of phase of the trial and the % change relative to the rate of level 2 hypoglycaemia at the time of randomization (Figure 4C,D). It should be noted that the groups were treated as a single group prior to randomization. It is noteworthy that both groups had very similar levels of level 2 hypoglycaemia at randomization (Figure 4A,B).

Immediately following the decrease in basal dosing, there was a 50% decrease in level 2 hypoglycaemic events in the 40% basal insulin reduction cohort at both daytime and night-time (Figure 4C,D). While this decrease could be a result of the reduction in basal insulin, it is more probably attributable to the introduction of HDV-lispro, because subjects increased their bolus insulin such that at all times subjects were taking more total insulin compared with randomization (Figure 3C,F). Importantly, despite increasing basal, bolus and total insulin levels (Figure 3), in the presence of HDV-insulin lispro, the level 2 nocturnal hypoglycaemia rate was maintained as markedly lower at the end of the trial than it was at randomization (21% and 43% [P = .11] less for the 10% and 40% basal reduction cohorts, respectively). The effects of HDV-lispro on daytime reductions of level 2 hypoglycaemic events were 0% and 17% decreases for the 10% and 40% basal reduction cohorts, respectively.

Figure 5A depicts the % change in diary-recorded hypoglycaemic events based on symptoms relative to baseline at visit 5, just before randomization. The baseline number of events at randomization was 1.6 events per week across all participants. Hypoglycaemic symptoms rapidly decreased following decreasing basal insulin levels, but symptomatic hypoglycaemia continued to decrease throughout the trial despite titration of basal and bolus insulin that resulted in an increase in total insulin at the end of the trial (Figure 3).

The data in Figure 5B show that for all participants in the trial, 25 participants at randomization had no level 2 hypoglycaemic events and that this number increased by 24% to 31 participants at the end of the trial despite participants being on a greater amount of insulin (Figure 3) and with no increase in mean daily glucose or HbA1c (Figure 2). The number of participants with one to three events a week decreased by 41% from 22 to 13.

Safety monitoring during the trial disclosed no safety signals with specific reference to liver function testing, cholesterol and triglyceride levels (Table 2).

### 4 DISCUSSION

In the current study we show that the addition of HDV to mealtime insulin lispro at a concentration that binds 1% of the insulin in the vial resulted in a clinically meaningful decrease, especially at night-time, in both level 2 hypoglycaemic events measured by CGM and symptomatic hypoglycaemic events in individuals with T1D. This study follows.
the ISLE-1 study, in which we showed a significant reduction in level 2 hypoglycaemia with HDV-lispro compared with lispro in subjects with a baseline HbA1c of 8.5% or higher, but no significant change in hypoglycaemia in participants with a baseline HbA1c of less than 8.5%. The insulin usage data in ISLE-1 showed that well-controlled participants, without the use of unblinded CGM and specific directives to forcibly reduce their basal dosage, did not meaningfully change their insulin-dosing regimen in the setting of a blinded trial.

Using the OPTI-1 protocol, both randomized groups were using ~8% more total insulin at the end of the trial. This is a notable increase in insulin dosing in participants who started the study with a baseline HbA1c of 7.2% and 6.7% in the –10% and –40% basal cohorts, respectively. The –10% basal cohort increased total insulin because of balanced increases in basal (8.8%) and bolus (7.7%) insulins, while the –40% basal cohort achieved greater total insulin as a result of greater increases in bolus (13.0%) than basal (3%) insulin. These changes resulted in a 30.0% increase in the bolus: basal ratio in the –40% basal cohort and a 6.9% increase in the bolus: basal ratio in the –10% basal cohort. The insulin bolus/basal ratio changes and total insulin dose increases that were observed did not meaningfully alter HbA1c outcomes, but, as noted above, were associated with meaningful improvements in hypoglycaemia risks. Subjects who had the largest increase in bolus to basal insulin ratio (the –40% basal group) experienced the largest decrease in CGM-recorded level 2 hypoglycaemic events, despite having the lowest HbA1c.

It is noteworthy that there was a significant baseline HbA1c difference between the 10% and 40% basal reduction groups. Probably contributing to this imbalance was that the stratification of subjects into each group was based on risk of hypoglycaemia and total insulin dose, not baseline HbA1c. Despite this imbalance, both groups showed good HbA1c control at baseline and at the end of the trial, with the 40% basal reduction group achieving an HbA1c of 6.7%, substantially less than the ADA HbA1c goal of less than 7%. It is remarkable to note that a cohort of participants with an HbA1c of 6.7% was administered 8% more total insulin (13% more bolus insulin) and achieved a near 50% reduction in night-time level 2 hypoglycaemic events by better insulinization of the liver.

Our data show that by better insulinization of the liver, the risk of hypoglycaemia can be reduced, even in the setting of increasing doses of subcutaneous insulin. By liver-targeting a fraction of the bolus insulin dose, mealtime insulin can be safely increased, leading to a clinically meaningful increase in the bolus: basal ratio, with a resultant decrease in hypoglycaemic events and symptoms. This improvement occurred even though the basal insulin dosage at the end of the trial had returned to the level achieved after a prolonged run-in. We attribute this somewhat paradoxical finding to the benefit of HDV-insulin to enhance hepatic glucose uptake and storage following meals, providing a readily available store of releasable glucose to counteract the risk of hypoglycaemia. Whether the increased use of insulin over time will result in greater improvement in blood glucose control needs to be assessed in a study of longer duration.

A notable strength of the current study was the 12-week insulin-dose optimization run-in period, allowing for a sustained, stable baseline to be established. The postrandomization treatment period was

| Basal insulin intervention group | Reduced 10% (N = 29) | Reduced 40% (N = 28) |
|---------------------------------|----------------------|----------------------|
| Measure                         | Visit 5 | Visit 11 | Visit 5 | Visit 11 |
| Cholesterol (mg/dl)             | 169 ± 27 | 170 ± 31 | 175 ± 31 | 177 ± 36 |
| Triglycerides (mg/dl)           | 82 ± 30 | 76 ± 22 | 79 ± 36 | 76 ± 25 |
| Alanine amino transferase (ALT, U/L) | 21 ± 7 | 22 ± 6 | 28 ± 27 | 28 ± 25 |
| Aspartate amino transferase (AST, U/L) | 21 ± 5 | 22 ± 6 | 26 ± 12 | 25 ± 8 |

**TABLE 2** Liver-associated safety data
also of sufficient duration to allow for a stable postintervention period of data collection. The limitations of the current study include its comparatively small number of participants.

In summary, the OPTI-1 study results show that the addition of liver-targeted mealtime insulin can safely decrease hypoglycaemic events and symptoms without compromising overall glucose control in individuals with T1D using multiple daily injections.

AUTHOR CONTRIBUTIONS
Study design: MSP, WBG, DBM, RSW and BWB. Protocol development: MSP, DBM and CES. Trial execution: CES, RSW, BWB, DCK, WBG, MSP, DBM, SKG and WBG. Data analysis: MSP, WBG, DBM and CES. Manuscript preparation: MSP, WBG, DBM, CES, RSW, BWB, DCK, SKG and WBG. MSP, WBG, CES and DBM had full access to all of the data.

CONFLICT OF INTEREST
WBG and CES are consultants of Diasome Pharmaceuticals, Inc. and inventors of the HDV technology, and as such they receive a salary and are shareholders. MSP and DBM are consultants to Diasome Pharmaceuticals, Inc., and as such they receive consulting fees and stock options. There are no conflicts of interest to report for RSW, BWB, DCK, and SKG.

PEER REVIEW
The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14761.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID
David C. Klonoff  https://orcid.org/0000-0001-6394-6862
Marc S. Penn  https://orcid.org/0000-0002-2174-7467

REFERENCES
1. Edgerton DS, Kraft G, Smith M, et al. Insulin’s direct hepatic effect explains the inhibition of glucose production caused by insulin secretion. JCI Insight. 2017;2(6):e91863.
2. Matveyenko AV, Veldhuis JD, Butler PC. Measurement of pulsatile insulin secretion in the rat: direct sampling from the hepatic portal vein. Am J Physiol Endocrinol Metab. 2008;295(3):E569-E574.
3. Moore MC, Smith MS, Farmer B, et al. Morning hyperinsulinemia primes the liver for glucose uptake and glycogen storage later in the day. Diabetes. 2018;67(7):1237-1245.
4. Pagliassotti MJ, Holste LC, Moore MC, Neal DW, Cherrington AD. Comparison of the time courses of insulin and the portal signal on hepatic glucose and glycogen metabolism in the conscious dog. J Clin Invest. 1996;97(1):81-91.
5. Edgerton DS, Moore MC, Winnick JJ, et al. Changes in glucose and fat metabolism in response to the administration of a hepatopreferential insulin analog. Diabetes. 2014;63(11):3946-3954.
6. Gregory JM, Kraft G, Scott MF, et al. Peripherally delivered hepatopreferential insulin analog insulin-406 mimics the hypoglycaemia-sparing effect of portal vein human insulin infusion in dogs. Diabetes Obes Metab. 2019;21(10):2294-2304.
7. Bergenstal RM, Lunt H, Franek E, et al. Randomized, double-blind clinical trial comparing basal insulin peglispro and insulin glargine, in combination with prandial insulin lispro, in patients with type 1 diabetes: IMAGINE 3. Diabetes Obes Metab. 2016;18(11):1081-1088.
8. Buse JB, Rodbard HW, Tescoletti Serrano C, et al. Randomized clinical trial comparing basal insulin Peglispro and insulin glargine in patients with type 2 diabetes previously treated with basal insulin: IMAGINE 5. Diabetes Care. 2016;39(1):92-100.
9. Selam JL, Micossi P, Dunn FL, Nathan DM. Clinical trial of programable implantable insulin pump for type 1 diabetes. Diabetes Care. 1992;15(7):877-885.
10. Holmes-Walker DJ, Gunton JE, Hawthorne W, et al. Islet transplantation provides superior glycemic control with less hypoglycemia compared with continuous subcutaneous insulin infusion or multiple daily insulin injections. Transplantation. 2017;101(6):1268-1275.
11. Harris C, Forst T, Heise T, et al. Hypoglycemia risk related to double dose is markedly reduced with basal insulin Peglispro versus insulin glargine in patients with type 2 diabetes mellitus in a randomized trial: IMAGINE 8. Diabetes Technol Ther. 2017;19(8):463-470.
12. Mudalal S, Henry RR, Ciaraldi TP, et al. Reduced peripheral activity leading to hepatopreferential action of basal insulin peglispro compared with insulin glargine in patients with type 1 diabetes. Diabetes Obes Metab. 2016;18(Suppl 2):17-24.
13. Gin H, Resard E, Mekl V, et al. Combined improvements in implantable pump technology and insulin stability allow safe and effective long term intraperitoneal insulin delivery in type 1 diabetic patients: the EVADIAC experience. Diabetes Metab. 2003;29(6):602-607.
14. Davis SN, Geho B, Tate D, et al. The effects of HDV-insulin on carbohydrate metabolism in type 1 diabetic patients. J Diabetes Complications. 2001;15(5):227-233.
15. Geho WB, Geho HC, Lau JR, Gana TJ. Hepatic-directed vesicle insulini: a review of formulation development and preclinical evaluation. J Diabetes Sci Technol. 2009;3(6):1451-1459.
16. Klonoff D, Bode B, Cohen N, Penn M, Geho WB, Muchmore DB. Divergent hypoglycemic effects of hepatic-directed prandial insulin: a 6-month phase 2b study in type 1 diabetes. Diabetes Care. 2019;42(11):2154-2157.
17. Forlenza GP, Li Z, Buckingham BA, et al. Predictive low-glucose suspend reduces hypoglycemia in adults, adolescents, and children with type 1 diabetes in an at-home randomized crossover study: results of the PROLOG trial. Diabetes Care. 2018;41(10):2155-2161.
18. Holt RIG, DeVries JH, Hess-Fischl A, et al. The Management of Type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of diabetes (EASD). Diabetes Care. 2021;44(11):2589-2625.

How to cite this article: Weinstock RS, Bode BW, Garg SK, et al. Reduced hypoglycaemia using liver-targeted insulin in individuals with type 1 diabetes. Diabetes Obes Metab. 2022;24(9):1762-1769. doi:10.1111/dom.14761