Control of Postprandial Hyperglycemia in Type 1 Diabetes by 24-Hour Fixed-Dose Coadministration of Pramlintide and Regular Human Insulin: A Randomized, Two-Way Crossover Study

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OBJECTIVE

Healthy pancreatic β-cells secrete the hormones insulin and amylin in a fixed ratio. Both hormones are lacking in type 1 diabetes, and postprandial glucose control using insulin therapy alone is difficult. This study tested the pharmacodynamic effects of the amylin analog pramlintide and insulin delivered in a fixed ratio over a 24-h period.

RESEARCH DESIGN AND METHODS

Patients with type 1 diabetes were stabilized on insulin pump therapy with insulin lispro before a randomized, single-masked, two-way crossover, 24-h inpatient study in which regular human insulin was administered with pramlintide or placebo using separate infusion pumps in a fixed ratio (9 μg/unit). Meal content and timing and patient-specific insulin doses were the same with each treatment. The primary outcome measure was change in mean glucose by continuous glucose monitoring (CGM). Profiles of laboratory-measured glucose, insulin, glucagon, and triglycerides were also compared.

RESULTS

Mean 24-h glucose measured by CGM was lower with pramlintide versus placebo (8.5 vs. 9.7 mmol/L, respectively; P = 0.012) due to a marked reduction of postprandial increments. Glycemic variability was reduced, and postprandial glucagon and triglycerides were also lower with pramlintide versus placebo. Gastrointestinal side effects were more frequent during use of pramlintide; no major hypoglycemic events occurred with pramlintide or placebo.

CONCLUSIONS

Coadministration of fixed-ratio pramlintide and regular human insulin for 24 h improved postprandial hyperglycemia and glycemic variability in patients with type 1 diabetes. Longer studies including dose titration under daily conditions are needed to determine whether this regimen could provide long-term improvement of glycemic control.

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In healthy individuals, the hormones insulin and amylin are cosecreted by β-cells of the pancreatic islets in response to glucose and other nutrient stimuli (1,2). Together, these hormones contribute to the physiologic regulation of fasting and postprandial plasma glucose concentrations (2). In type 1 diabetes, both of these hormones are largely or entirely lacking, yet therapy traditionally relies on replacement of insulin by multiple daily injections (MDI) or continuous subcutaneous infusion (CSI) of insulin alone (3). These methods are insufficient to attain nearly normal glucose levels in most patients with type 1 diabetes, in large part because of an inability to prevent increases in blood glucose after meals (4,5).

Pramlintide is a stable, soluble, injectable, and equipotent analog of human amylin (5). It is approved in the U.S. for administration with mealtime insulin therapy in patients with type 1 or type 2 diabetes, and it is administered and titrated separately from the insulin component of treatment regimens (6). Despite some success in limiting postprandial hyperglycemia and body weight gain when pramlintide is added to MDI of insulin (7–10), this approach has not been widely used. Barriers to routine use of pramlintide include the need for additional injections, the occurrence of nausea, and increased risk of insulin-induced postprandial hypoglycemia, especially during initiation of therapy (8,10). Furthermore, because pramlintide has been given as a fixed dose in combination with varying amounts of insulin, the dose ratio is inconsistent. Mimicking the diurnal β-cell secretory pattern using basal and mealtime coverage with a fixed-ratio combination of pramlintide and regular human insulin may be more effective (11).

Preliminary studies have explored the feasibility of this approach, with the long-term objective of a coformulation of pramlintide and insulin in a single vial or cartridge (11,12). Based on these studies, a fixed-dose ratio of pramlintide 9 μg per unit of insulin was selected for further evaluation. The current study was designed to extend prior observations by examining the pharmacodynamic effects and safety of a fixed ratio of pramlintide and regular human insulin delivered over a 24-h period by separate CSI systems for patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Study Design
This randomized, single-blind, two-way crossover, placebo-controlled, phase 1 study was conducted at three centers in the U.S. (ClinicalTrials.gov identifier NCT02500979). The study protocol was approved by the institutional review boards, and all patients provided written informed consent before enrollment. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation Good Clinical Practice guidelines and applicable regulatory requirements. The study consisted of a 15- to 36-day ($\pm$ 3 days) screening, enrollment, and stabilization period; two 24-h inpatient treatment periods separated by a 7-day (+6/−5) washout interval; and a 21-day ($\pm$ 7) posttreatment safety observation period (Supplementary Fig. 1).

Patients
Adult patients (aged 18–70 years; BMI <30 kg/m^2) with a prior diagnosis of type 1 diabetes and no use of pramlintide in the previous 6 months were eligible for the study if they met the following criteria: immediate use of insulin after diagnosis of type 1 diabetes with no prior use (for >3 months) of oral glucose-lowering therapies; use of insulin therapy for ≥1 year before screening; no history of maturity-onset diabetes of the young, pancreatic surgery, or chronic pancreatitis; using MDI or CSI of insulin at a dose of ≤60 units/day for ≥3 months before screening; fasting C-peptide level <0.25 ng/mL; and inadequate glycemic control with a glycated hemoglobin (HbA$_{1c}$) of 7.2% to 9.0% (55 to 75 mmol/mol).

Candidates were excluded if they had recurrent severe hypoglycemia requiring assistance within 6 months before screening; had experienced diabetic ketoacidosis within the last 24 weeks; had a history of hypoglycemia unawareness; had a confirmed diagnosis of gastroparesis; were being treated or expecting to be treated with any oral or injectable glucose-lowering therapies other than insulin or with acetaminophen or drugs affecting gastrointestinal motility or slowing intestinal absorption; had undergone gastric surgery; had any other significant comorbid conditions (e.g., cardiovascular disease, malignancy, or psychiatric disorders) or clinically relevant abnormal laboratory findings; were pregnant or breastfeeding; had undergone major surgery or blood transfusion in the previous 2 months; were positive for hepatitis B or C or HIV; or had a history of alcohol or drug abuse.

Study Procedures
Eligible patients were instructed on the use of a continuous glucose monitoring (CGM) device (Dexcom G4 Platinum; Dexcom, Inc., San Diego, CA) and a CSI device (Paradigm Revel; Medtronic Mini-Med, Inc., Northridge, CA). Using this equipment, they were assisted by study personnel, via telephone or electronic communication, to maintain stable glycemic control with insulin lispro, administered at a single 24-h basal rate plus individualized mealtime and supplementary boluses. Patients continued to receive insulin lispro throughout the study, except during the two inpatient treatment periods when regular human insulin U-100 was administered. At the final ambulatory visit before the first inpatient treatment period, patients were randomized to receive either pramlintide or placebo, subsequently crossing over to the alternative treatment. Patients were unaware of the order of treatments, but study personnel knew the treatment sequence.

Study Treatments
During two 24-h inpatient study days, patients received either basal and bolus subcutaneous pramlintide or matching placebo at 9 μg per unit of infused regular human insulin. Treatments were administered simultaneously via separate CSI systems, beginning at 4:00 PM in the afternoon of admission to the clinical research facility and separate from concomitant administration of background regular human insulin. A basal insulin infusion was maintained for each 24-h dosing period, and bolus doses, which were judged appropriate for each patient based on experience during the stabilization period, were given 15 min before each of the three meals. Each patient's nutrient intake and insulin doses were identical during both inpatient studies. During the washout and follow-up periods, patients were maintained on CSI of insulin lispro, as during the stabilization period.

Outcome Measures

The primary outcome measure was 24-h mean weighted glucose (MWG), calculated as the area under the 24-h tissue glucose curve obtained with CGM divided by the time in hours. Secondary outcome measures included the incremental area under the concentration–time curve (AUC) for 3-h laboratory-measured plasma glucose following lunch (AUC$_{0-3h}$ lunch) and 2-h plasma glucose following dinner (AUC$_{0-2h}$ dinner) and breakfast (AUC$_{0-2h}$ breakfast), as well as fasting plasma glucose at 6:00 AM. Variability of 24-h CGM was assessed as the SD and coefficient of variation of all measurements, the mean amplitude of glycemic excursion (MAGE), total energy, 24-h rate of change, distance traveled, and excursion frequency, as well as by the percentage of time that glucose concentrations were in the target range (>3.9 to <10.0 mmol/L [>70 to <180 mg/dL]), hypoglycemic range (≤3.9 mmol/L [≤70 mg/dL]), and hyperglycemic range (≥10.0 mmol/L [≥180 mg/dL]). MAGE was defined as the mean of the absolute difference from nadir to peak for those differences that exceeded the SD of the tissue glucose assessments over 24 h (13). Total energy was calculated as the product of the sum of squared frequency and the amplitude of Fourier coefficients for the 24-h individual average tissue glucose curves (14). The 24-h rate of change was approximated as the average of the slopes of each consecutive tissue glucose measurement over the 24-h period. Distance traveled, defined as the arc length of the mean 24-h glucose curve (15), was calculated as the sum of the absolute difference in tissue glucose concentrations for 24 h of consecutive glucose measurement. Excursion frequency measured the number of tissue glucose excursions outside of the 3.9–10.0 mmol/L (70–180 mg/dL) range over the course of the 24-h period. Additional secondary outcome measures included 24-h profiles of plasma insulin, glucagon, and triglycerides, including measurement of incremental AUC of glucagon and triglycerides after meals.

Adverse events over the treatment period were recorded from the first administration of study medication through study termination. Vital signs and laboratory parameters were monitored on both inpatient study days and at the end-of-study visit. Major hypoglycemia was defined as a symptomatic event that required assistance because of severe impairment in consciousness or behavior, with a tissue or plasma glucose concentration ≤3.0 mmol/L (≤54 mg/dL). Minor hypoglycemia was defined as either a symptomatic event with a tissue or plasma glucose concentration <3.5 mmol/L (<63 mg/dL) but >3.0 mmol/L (>54 mg/dL) and no need for external assistance, or an asymptomatic tissue or plasma glucose concentration <3.5 mmol/L (<63 mg/dL).

Statistical Considerations

A sample size of 24 evaluable patients was estimated to provide ~84% power to detect a mean difference of 0.8 mmol/L (14 mg/dL) in 24-h MWG between the fixed-ratio pramlintide-to-insulin treatment arm and the placebo-to-insulin treatment arm, assuming a significance level of 0.05 (two-sided) and an SD of differences of 1.2 mmol/L (22 mg/dL). A patient who had at least 87% (or 21 h) of CGM data available at each of the two crossover treatment visits was considered evaluable for the main efficacy comparison. It was estimated that enrollment of 30 patients would allow 24 patients (12 per sequence) to be evaluable based on an assumed premature withdrawal and nonevaluable rate of approximately 25%. The efficacy analysis population included randomized patients who had at least one assessment of MWG available at each of the two crossover periods. The safety analysis population included all randomized patients who received any infused study treatment. Profiles of laboratory-measured glucose, insulin, glucagon, and triglycerides were analyzed among patients who received at least one dose of pramlintide and had evaluable data (pharmacokinetic/pharmacodynamic population).

Efficacy data for each treatment were combined from both treatment periods. A linear mixed-effects model was used to analyze 24-h MWG, with fixed factors for randomized treatment sequence, period, treatment, and baseline 24-h MWG as covariates in the efficacy analysis population. A random intercept for patient was included. Period was a repeated effect blocked by patient (within sequence). Using the final fit of the model, least-squares means (LSM) and corresponding two-sided 95% CIs were calculated for the 24-h MWG for each treatment. The LSM and corresponding two-sided 95% CI values were also calculated for the difference between treatments. Secondary outcome measures were analyzed using similar methods, excluding the baseline covariate. Natural logarithmic transformation was applied to plasma triglyceride measures. Adverse events occurring during the treatment period were summarized using frequency counts and percentages by treatment group. All statistical analyses were performed using SAS version 9.1.3 or higher (SAS Institute, Inc., Cary, NC).

RESULTS

Study Population

Of 34 randomized patients, 27 completed the study. Seven patients discontinued early (patient decision, $n = 2$; adverse event, $n = 1$; noncompliance with protocol, $n = 1$; loss of venous access to collect samples from, $n = 1$; other, $n = 2$ [one patient due to instability of baseline finger prick glucose level and one due to hyperglycemia]). Thirty-two patients received at least one dose of study medication; 28 received insulin and placebo, 32 received insulin and pramlintide, and 26 had complete CGM data for both treatment periods and were evaluable for the primary outcome measure. Demographics and baseline characteristics were similar among the efficacy and safety analysis populations (Table 1). The mean ± SD total daily insulin dose during inpatient studies was 35.2 ± 14.1 units during the pramlintide periods and 38.8 ± 13.9 units during the placebo periods. Corresponding mealtime insulin doses for the pramlintide and placebo periods, respectively, were 7.5 ± 3.5 and 7.2 ± 3.1 units for dinner, 5.9 ± 2.6 and 5.9 ± 2.4 units for breakfast the next morning, and 5.0 ± 2.0 and 5.7 ± 2.8 units for lunch.

CGM Profiles

Mean postprandial increments in blood glucose were almost entirely suppressed when pramlintide was coadministered with insulin (Fig. 1). The 24-h MWG (LSM ± SE) was significantly lower with pramlintide plus insulin compared with placebo plus insulin (8.5 ± 0.5 vs. 9.7 ± 0.5 mmol/L [152 ± 8 vs. 174 ± 8 mg/dL]; $P = 0.012$). Compared with placebo, patients receiving pramlintide spent less time in the hyperglycemic range (≥10.0 mmol/L [≥180 mg/dL])

Table 1—Patient demographics and clinical characteristics at baseline

	Efficacy analysis population (n = 26)	Safety analysis population (n = 32)
Age, years	41 ± 14	42 ± 14
Women, n (%)	21 (80.8)	25 (78.1)
Race, n (%)		
White	25 (96.2)	30 (93.8)
Black/African American	0 (0.0)	1 (3.1)
Asian	1 (3.8)	1 (3.1)
Hispanic ethnicity, n (%)	2 (7.7)	2 (6.3)
Duration of type 1 diabetes, years	24 ± 12	25 ± 12
HbA$_{1c}$		
%	8.1 ± 0.5	8.0 ± 0.5
mmol/mol	65 ± 6	64 ± 6
Fasting plasma glucose, mmol/L	8.4 ± 3.1	8.4 ± 2.9
Weight, kg	70.7 ± 8.8	70.4 ± 8.9
BMI, kg/m^2	25.3 ± 2.6	25.0 ± 2.6
Insulin dose, units/day	37.8 ± 10.2	37.4 ± 10.7

Data are mean ± SD unless otherwise stated.

and more time in the target glycemic range (>3.9 to <10.0 mmol/L [>70 to <180 mg/dL]) (Table 2). Other measures of glycemic variability all numerically favored pramlintide, with significantly lower variability found for SD ($P = 0.0050$), distance traveled ($P = 0.0009$), rate of change ($P = 0.0162$), and total energy ($P = 0.0003$) (Table 2).

Laboratory-Measured Profiles of Glucose, Insulin, Glucagon, and Triglycerides

Glucose profiles obtained from measurements of venous blood closely matched those obtained by CGM, with the mean profile during coadministration of pramlintide being nearly flat throughout 24 h (Fig. 2A). With pramlintide, laboratory-measured glucose (AUC$_{0-24h}$/24) was significantly lower than with placebo (LSM [95% CI]: 9.0 [8.0–10.0] vs. 10.2 [9.2–11.2] mmol/L [162 (144–180) vs. 184 (166–202) mg/dL], respectively; LSM difference: −1.2 [−2.2 to −0.2] mmol/L [−22 (−40 to −4) mg/dL]; $P = 0.026$). Mean glucose during the postprandial periods was also lower with pramlintide compared with placebo (Supplementary Table 1), whereas fasting plasma glucose levels at 6:00 AM did not differ between treatments (LSM [95% CI] for pramlintide vs. placebo: 8.5 [7.2–9.9] vs. 7.8 [6.6–9.2] mmol/L [153 (130–178) vs. 140 (119–166) mg/dL]; P = not significant).
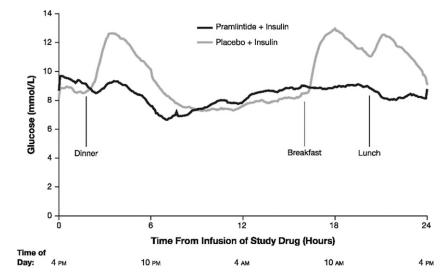
Plasma insulin profiles were similar during pramlintide and placebo treatment, with peak concentrations occurring approximately 2 h after dinner and breakfast (Fig. 2B). Mean 24-h glucagon profiles were similar with the two treatment regimens (Fig. 2C), but the small postprandial increments at breakfast and lunch seen with placebo resulted in lower mean values during these postprandial intervals with pramlintide than with placebo (Supplementary Table 1). Mean triglyceride profiles were generally flat with both regimens (Fig. 2D), although small but statistically significant mean reductions after dinner and breakfast were observed during treatment with pramlintide (Supplementary Table 1).

Adverse Events

Overall, including inpatient and ambulatory intervals, more patients treated with pramlintide (n = 22/32; 69%) compared with placebo (n = 9/28; 32%) experienced any adverse event. Most reported events occurred during the inpatient treatment studies. Gastrointestinal events were the most common, occurring in 15 of 32 patients (47%) while receiving pramlintide and 2 of 28 (7%) while receiving placebo (Supplementary Table 2). Pramlintide treatment was associated with headache in 8 patients (25%), while 1 patient (4%) reported headache while on placebo. There were no major hypoglycemic events with pramlintide or placebo during the study. Minor hypoglycemic events occurred during inpatient treatment in 7 of 32 patients (22%) during treatment with pramlintide and 8 of 28 patients (29%) during treatment with placebo.

CONCLUSIONS

Under controlled conditions in clinical research centers, this study tested the effects of continuous delivery of pramlintide in combination with individualized insulin dosing over a 24-h period, in a fixed ratio of 9 μg per unit of insulin. Compared with insulin alone, coadministration of pramlintide reduced 24-h mean glucose measured by CGM through a marked effect on postprandial increments of glucose. Coadministration of pramlintide, compared with insulin plus placebo, significantly reduced overall glycemic variability as well as increased time in the target glycemic range of >3.9 to <10.0 mmol/L (>70

Figure 1—Mean 24-h CGM profile in the efficacy analysis population by treatment, combining treatment period 1 and treatment period 2.

Table 2—Measures of glycemic variability assessed by CGM

	Pramlintide + insulin (n = 26)	Placebo + insulin (n = 26)	P value for difference
Time spent in glycemic range, mean ± SD, %			
≥10.0 mmol/L	31.1 ± 25.59	46.1 ± 22.49	0.0276
>3.9 to <10.0 mmol/L	61.5 ± 21.17	50.2 ± 20.13	0.0456
≤3.9 mmol/L	7.4 ± 8.73	3.7 ± 4.45	0.4719
SD of 24-h glucose, mmol/L	2.5 ± 0.2	3.3 ± 0.2	0.0050
CV of 24-h glucose	0.31 ± 0.02	0.35 ± 0.02	0.0672
MAGE, mmol/L	6.4 ± 0.45	7.5 ± 0.45	0.0820
Excursion frequency, excursions/24 h	2.88 ± 0.22	3.51 ± 0.22	0.0505
Distance traveled, mmol/L	38.2 ± 1.8	46.8 ± 1.8	0.0009
Rate of change, mmol/(L/h)	−0.057 ± 0.037	0.063 ± 0.037	0.0162
Total energy, geometric mean, (mmol/L)^2/h	105 ± 10.0	180 ± 17.2	0.0003

Data are mean ± SE unless otherwise noted. CV, coefficient of variation.

to <180 mg/dL). The findings of lower mean glucose and marked suppression of postprandial increments obtained with CGM were confirmed by laboratory-measured glucose profiles. As expected at the time of pramlintide initiation, the most common adverse events were gastrointestinal symptoms.

These observations significantly extend prior studies of this approach to the management of type 1 diabetes. Computer simulations based on data from 15 patients with type 1 diabetes previously suggested an optimal ratio for coadministration of pramlintide and insulin to be 9 μg of pramlintide per unit of insulin, with similar performance at ratios of 8 and 10 μg/unit (12). Consistent with prior clinical experience, the model predicted that an insulin dose reduction of around 21% might be required to avoid postprandial hypoglycemia during coadministration of pramlintide.
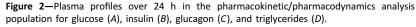
Subsequently, pramlintide was evaluated in a randomized, single-blind, single-dose study using regular human insulin injected simultaneously with placebo or with pramlintide at fixed-dose ratios of 6, 9, or 12 μg per unit of insulin (11). Regular human insulin was used in this study on the basis of prior studies showing less risk of hypoglycemia with regular insulin than with rapid-acting insulin analogs when given with pramlintide (9). For safety, the insulin dosage was reduced by 30% from the patients' usual estimates. All pramlintide-to-insulin dose ratios reduced postprandial glucose and glucagon increments by ≥50% (all P < 0.001 vs. placebo). The similarity of reductions between ratios suggests that the pramlintide doses delivered, which were generally in the 30- to 60-μg range,

were all close to maximally effective in slowing gastric emptying and suppressing glucagon secretion within the first 2 h following meals. Adverse events were infrequent and generally mild, and no symptomatic hypoglycemia occurred during 24 h of follow-up. Based on these previous studies, a fixed-dose ratio of pramlintide 9 μg per unit of insulin was selected for further evaluation in the current study.

The present findings, without adjustment of insulin doses during this 24-h study, provide further support for the potential of the continuous fixed-dose combination of pramlintide and insulin to improve glycemic control in patients with type 1 diabetes. Using the American Diabetes Association conversion table for estimating HbA$_{1c}$ levels from average glucose values (16), the observed reduction in mean glucose of 1.2 mmol/L (22 mg/dL) with pramlintide versus placebo (8.5 vs. 9.7 mmol/L [152 vs. 174 mg/dL], respectively) would be equivalent to a reduction in HbA$_{1c}$ of 0.8% (9 mmol/mol) from 7.7% (61 mmol/mol) to 6.9% (52 mmol/mol). Given that mean values shown in Fig. 1 do not reflect glycemic variability in individual patients, several specific measures of glycemic variability were also assessed. Significant reductions of the SD of measured glucose values and other measures of variability were observed during coadministration of pramlintide with insulin. Because glycemic variability was reduced, it seems likely that ongoing use of this treatment regimen, with appropriate dose titration, might attain yet lower mean glucose levels while limiting the risk of hypoglycemia.

Plasma profiles of insulin, glucagon, and triglycerides over 24 h provided

additional information. The lack of differences in mean insulin levels after dinner and breakfast confirmed that equivalent dosing was attained, as intended in the protocol. Increments of glucagon levels immediately after meals were seen with placebo, but these were reduced with pramlintide. However, continuous delivery of pramlintide overnight had no effect on basal glucagon levels. Finally, the statistically significant reductions in mean 24-h triglyceride levels with pramlintide could be a result of prolonged postprandial carbohydrate and fat absorption and may be relevant in the setting of cardiovascular risk.

The strengths of this study include standardization of meal timing and content, the timing of and continuous delivery of insulin and pramlintide/placebo dosing, and levels of physical activity, assuring that the observed changes reliably reflect the physiologic responses to treatment over a single day. In addition, the protocol tested the effect of continuous overnight delivery of pramlintide at the same dose ratio as with meals. Limitations of this study design include the short duration, which does not provide information about long-term exposure to the fixed-ratio regimen, during which patients would have greater variability of meals and physical activity and would have the opportunity to adjust and optimize dosing. As a result, it is not yet known whether longer-term use with individualized titration would result in reductions in HbA$_{1c}$ to levels that might not be achievable with CSI of insulin alone. This study was unable to determine whether the relatively high rate of gastrointestinal symptoms seen with short-term exposure to pramlintide at

Figure 2—Plasma profiles over 24 h in the pharmacokinetic/pharmacodynamics analysis population for glucose (A), insulin (B), glucagon (C), and triglycerides (D).

human insulin markedly reduced postprandial glucose and glycemic variability in patients with type 1 diabetes. Further studies are needed to determine whether this approach may safely allow attainment of lower HbA_{1c} values in addition to greater glycemic stability during ambulatory treatment.

the dosage used in the study would be reduced during longer exposure, as has been reported previously (5,8,10). Whether sustained attainment of within-range glycemic goals based on CGM, as proposed in a recent consensus statement (17), would be possible with fixed-ratio coadministration of pramlintide with insulin can also be determined only by longer-term ambulatory studies. To verify the safety of this approach, such studies could enroll a broader population of patients, including those with difficult-to-manage type 1 diabetes and high risk of hypoglycemia, and could assess both patient-reported and medical outcomes. Finally, for fixed-ratio coadministration of these two β-cell hormones to be convenient and affordable, a stable coformulation suited to delivery by a single infusion device may be needed.

In conclusion, this study showed that 24-h administration of fixed-dose ratio basal-bolus pramlintide with regular

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