CLINICAL STUDY PROTOCOL

A Phase 2, Single-Dose, Randomized, Open-Label, Active-Controlled, Crossover, Pharmacodynamic, and Pharmacokinetic Comparative Study of a Novel Pramlintide-Insulin Co-Formulation in Adults with Type 1 Diabetes Mellitus

Protocol Number:	DPI-201
Phase:	2
IND Number:	142004
Study Drug:	Pramlintide-insulin injection (PRAM9)
Sponsor:	Xeris Pharmaceuticals, Inc. 180 North LaSalle Street Suite 1600 Chicago, IL 60601
Medical Monitor:	Khaled Junaidi, MD
Date of Protocol:	Version 1.0, 6/14/2019 Version 2.0, 8/14/2019 Version 3.0, 9/6/2019 Version 4.0, 12/13/2019
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Xeris (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

PROTOCOL SIGNATURE PAGE

Please see esignatures on the last page	
Joy Geallis Senior Manager, Clinical Operations Xeris Pharmaceuticals, Inc.	Date
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SUMMARY OF REVISIONS

Summary of Changes From Version 1.0 to Version 2.0

Affected Section(s)	Summary of Revisions Made	Rationale
Synopsis, 6.1, 8.5	Changed definition of hypoglycemia to blood glucose <70 mg/dL and instructions on rescue with IV dextrose concentration and administration.	FDA Requested
Synopsis, 7.3	Exclusionary Criteria for Hematocrit changed to <35.5% (female) and <38.3% (males) Exclusionary Criteria for Hemoglobin changed to <11.5 g/dL (females) and <12.5 mg/dL (males).	FDA Requested
Reference	Added reference of American Diabetes Association Guideline for Treatment of Hypoglycemia by IV glucose.	Clarification
Reference	Joslin Diabetes Center and Beth Israel Deaconess Medical Center, Guideline for management of uncontrolled glucose in hospitalized adult.	Clarification

Summary of Changes From Version 2.0 to Version 3.0

Affected Section(s)	Summary of Revisions Made	Rationale
Title Page	Publishing Reference Error	Administrative

Summary of Changes From Version 3.0 to Version 4.0

Affected Section(s)	Summary of Revisions Made	Rationale
Synopsis	No. of study centers increased to 4.	Enrollment
10.1	Screening criteria allows for a single rescreening for laboratory and vital sign failures	Clarification

INVESTIGATOR'S AGREEMENT

I have received and read the protocol for Study DPI-201 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name, Title, & Address	Email Address & Telephone Number
Sponsor's Study Leader & Primary Contact	Joy Geallis Senior Manager, Clinical Operations Xeris Pharmaceuticals, Inc. 180 North LaSalle Street Suite 1600 Chicago, IL 60601	JGeallis@xerispharma.com (312) 736-1234 (direct) (815)-546-9130(cell)
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Reporting of Study Drug Concerns	Xeris Medical Affairs	safetyDPI201@xerispharma.com (630) 915-5885 (815) 593-2218

1. SYNOPSIS

Name of sponsor/company: Xeris Pharmaceuticals, Inc.	
Name of investigational product: Pramlintide-insulin injection (PRAM9)	
Name of active ingredient: Pramlintide acetate and recombinant human insulin	
Study title	A Phase 2, Single-Dose, Randomized, Open-Label, Active-Controlled, Crossover, Pharmacodynamic, and Pharmacokinetic Comparative Study of a Novel Pramlintide-Insulin Co-Formulation in Adults with Type 1 Diabetes Mellitus
Protocol number	DPI-201
No. of study centers	Up to 4 sites in the United States (US)
Clinical phase	Phase 2
Study background	Most people with diabetes are still unable to achieve glycemic targets with sole insulin therapy alone, particularly after mealtime. Physiologic restoration of the hormonal responses during meals, via pramlintide and insulin, has been demonstrated to reduce postprandial hyperglycemia and to improve blood glucose time in range. The synergy between insulin and pramlintide provides improved glucose control while reducing meal-time insulin requirements. Reduced insulin utilization may also reduce the effects associated with long-term insulin use such as weight gain and higher risks of hypoglycemia. A pramlintide-insulin co-formulation may help reduce the burden associated with co-administration (eg, reduce the number of injections per day). Additionally, co-formulations of pramlintide and insulin may also improve treatment compliance and persistency.
Study rationale	People with diabetes may have a significant loss of pancreatic beta cell function. This leads to a deficiency of 2 hormones: insulin and amylin. The combined effect of insulin and amylin is to regulate and normalize blood sugar levels. Pramlintide is an injectable drug that closely resembles amylin. Many clinical studies that add pramlintide to insulin have demonstrated improved control of blood sugar. However, the benefits of these products used together also are associated with increased risk of pramlintide-associated nausea and vomiting; increased number of required injections; and tailoring of insulin and pramlintide doses. Xeris Pharmaceuticals has developed a novel, liquid-stable, co-formulation of pramlintide plus regular insulin (PRAM9) that can be delivered as a single, subcutaneous (SC) injection. The fixed dose combination product is expected to allow better management of patient glycemic conditions through improved compliance.
Study objectives	**Primary objective** • Evaluate the pharmacodynamic (PD) properties of a single dose of PRAM9 compared to single doses of regular insulin and regular insulin plus pramlintide (co-administered as separate injections) in adults with type 1 diabetes mellitus (T1D)

	Secondary objectives • Evaluate the safety and pharmacokinetic (PK) profiles of a single dose of PRAM9 compared to single doses of regular insulin and regular insulin plus pramlintide (co-administered as separate injections) in adults with T1D
Study endpoints	**Primary** The PD effects upon plasma glucose levels will be compared between the treatments as defined by the following primary endpoint: • Area under the curve area from administration to 180 minutes (AUC_{0-180}) (mg/dL × minutes) for plasma glucose > 180 mg/dL **Secondary** **Safety:** • Incidence of adverse events (AEs), serious adverse events (SAEs) • Change from baseline in clinical safety laboratory evaluations (hematology and serum chemistry) • Change in vital sign measurements (temperature, respiration, heart rate [HR], and blood pressure [BP]) • Change from baseline in body weight • Local tolerability assessments (modified Draize Scale and injection site discomfort questionnaires) **PK/PD:** Key secondary endpoints include the following. The full list of secondary endpoints is provided in Section 13.3.2. • Mean proportional time with plasma glucose > 180 mg/dL for 0-180 minutes after study drug administration • PK plasma levels ($AUC_{0-90\ min}$, $AUC_{0-180\ min}$, $AUC_{0-360\ min}$, C_{max}, and T_{max}) for both insulin and pramlintide
Study design	This is a randomized, open-label, active-controlled, single-dose, 3-treatment, 3-period, 3-way crossover, comparative PD, and PK inpatient study in adults with T1D.
Methodology	The study comprises 5 visits: Screening (Visit 1), Treatment Periods (Visits 2 − 4), and Follow-Up (Visit 5). To determine eligibility, subjects will complete the Screening procedures (Visit 1) up to 28 days before the first treatment visit (Visit 2). Subjects will be instructed to eat normally and take their usual medications, but to refrain from alcohol for 24 hours prior to checking in for treatment visits. **Treatment periods** For Treatment Period Visits 2 through 4, eligible subjects will be instructed to arrive for an overnight stay at the clinical research facility on the day prior to each treatment visit. At the clinic, subjects will be given a standardized dinner meal, and instructed to take their prescribed evening mealtime insulin regimen and basal insulin dose. The subjects will fast after midnight but will be allowed to drink

water ad libitum (ie, tap water, bottled water, distilled water, etc. [water without carbohydrates]) and take any prescribed medications.

During each Treatment Period Visit (Visits 2, 3, and 4), eligible subjects will receive a single SC dose of PRAM9, regular insulin, or co-administered regular insulin plus pramlintide. On the morning of each treatment visit and prior to dosing, a fasting blood sample will be tested using a blood glucose meter (BGM) to confirm that blood glucose is in the range of 80 to 150 mg/dL.

- If the blood glucose is > 150 mg/dL after repeat test, then the investigator may treat with an intravenous (IV) bolus dose of regular insulin, per discretion, to bring the subject into the required blood glucose range. Before initiating study treatment, at least 40 minutes should have passed from the last dose of administered insulin and the subject's glucose level should be within the range of 80 to 150 mg/dL.
- If the blood glucose is < 80 mg/dL after repeat test, then the investigator may treat with oral glucose tabs/solution or IV glucose, per discretion, to bring the subject into the required blood glucose range. Before initiating study treatment, at least 30 minutes should have passed from the last dose of administered glucose and the subject's glucose level should be within the range of 80 to 150 mg/dL.
- If the subject's blood glucose cannot be optimized to 80 to 150 mg/dL within 2 hours, then the visit should be rescheduled after a minimum 24-hour wait, per investigator's discretion.

At Visit 2, once blood glucose is confirmed to be within the range of 80 to 150 mg/dL, subjects will be randomized to their study drug treatment sequence.

Sequence of Study Drug Administration

Cohort	Period 1	Period 2	Period 3
1	PRAM9	Regular insulin	Regular insulin + pramlintide
2	Regular insulin	Regular insulin + pramlintide	PRAM9
3	Regular insulin + pramlintide	PRAM9	Regular insulin
4	PRAM9	Regular insulin + pramlintide	Regular insulin
5	Regular insulin	PRAM9	Regular insulin + pramlintide
6	Regular insulin + pramlintide	Regular insulin	PRAM9

Insulin-to-carbohydrate calculations will be used to identify subject doses. All subjects will get flexible doses of insulin, pramlintide, and PRAM9. See Section 9.1 for complete information on study drug dosing. The dose of regular insulin will be calculated to correspond to a ratio of 9 µg of pramlintide for every 1 unit of insulin. Additionally, the dose of regular insulin will be calculated from the subject's insulin-to-carbohydrate (I:C) ratio to match a 75-gram carbohydrate challenge. Rule 450 will be used for carbohydrate counting and insulin dose calculation in this study (see Appendix 3).

	Prior to study drug administration, a peripheral catheter for blood sampling will be placed into a vein ideally located within the antecubital fossa. The hand of the arm used for blood sampling will be kept warm by use of a heated hand box to increase blood flow and achieve "arterialized" samples. The subject will remain supine and kept warm and be allowed to drink only water (ad libitum). Once the catheter and hand box are in place, study drug(s) will be administered SC over 1 to 3 seconds to the abdomen (around the umbilicus). Co-administered regular insulin plus pramlintide injections should be administered to opposite sides of the abdomen (ie, left and right peri-umbilicus, opposite quadrants). Injection sites should be rotated to avoid injecting at a previously used site. To monitor for hypoglycemia, BGM will be performed in real time at each subject's bedside at 10, 20, 30, 40, 50, 60, 90, 120, and 180 minutes post dosing at Visit 2 through 4. To evaluate drug PD (plasma glucose response) and PK (plasma insulin/pramlintide concentrations), blood samples are to be drawn at the time points described in the Schedule of Assessments (Table 2). Within 2 minutes after the 30 minutes post-dose blood draw, a standardized 75-gram oral glucose challenge should be ingested (within 5 to 10 minutes) by the subject. After the last blood collection (at 360 minutes post-study drug administration), subjects are to be provided a regular meal and insulin (per investigators' discretion). Injection sites will be evaluated by the investigator using the modified Draize scale (Appendix 1) and subjects will complete injection site discomfort questionnaires (Appendix 2). A subject may be discharged from the clinic, per investigator's criteria, when the following has occurred: • Subject has consumed their meal • Subject has returned to their usual medication regimen, including insulin • Subject's capillary glucose concentration is confirmed to be > 100 mg/dL • Subject is considered medically stable Any time during the visit if hypoglycemia occurs (ie, blood glucose < 70 mg/dL), the subject will be rescued with IV dextrose using the following formula to calculate the dose of dextrose: **D50% mL = (100 minus BG) × 0.4** **Where D50% = the dose of IV dextrose, mL = the volume of dextrose, BG = the subject's hypoglycemic blood glucose value** **The dose of dextrose should be administered slowly, over 2 to 5 minutes.** If D50% is administered, then blood glucose will be remeasured by blood glucose meter at 10, 20, and 30 minutes following the end of administration of IV dextrose. Successful plasma glucose recovery should be confirmed (ie, glucose returns to ≥ 70 mg/dL) and the subject medically stabilized. When the subject is medically stable, they can be discharged from the clinic (per criteria above). After a first washout period of 7 to 11 days, subjects will return to the clinic for Treatment Period 2 (Visit 3) and the treatment visit procedures will be repeated

	with each subject crossed over to the next randomized study drug treatment sequence. Upon check-in and completion of morning activities, the subject will receive their second administration of study drug(s). After a second washout period of 7 to 11 days, subjects will return to the clinic for Treatment Period 3 (Visit 4) and the treatment visit procedures will be repeated with each subject crossed over to the last randomized study drug treatment sequence. Upon check-in and completion of morning activities, the subject will receive their third administration of study drug(s). During the Treatment Periods, subjects will undergo symptom-directed PEs, vital sign measurements, AE assessments, concomitant medication assessments, and pregnancy testing for females of childbearing potential. **Follow-Up** A Follow-up Visit (Visit 5) will be conducted 7 to 11 days after the subject's last dose of study drug(s). Subjects will return to the clinic and undergo complete PE, vital sign measurements, weight measurements, sample collection for hematology and chemistry, AE assessments, concomitant medication assessments, and pregnancy testing for females of childbearing potential.
Number of subjects	Approximately 48 subjects may need to be screened in order to obtain 18 randomized subjects (3 subjects per treatment sequence).
Diagnosis and main entry criteria	**Inclusion criteria:** Subjects must meet the following criteria to be included: 1. Understands the study procedures, alternative treatment available, and risks involved with the study, and voluntarily agrees to participate by giving written informed consent 2. Male or non-pregnant, non-lactating female diagnosed with T1D for at least 24 months prior to Screening. 3. Aged 18 to 64 years of age, inclusive 4. On a stable insulin regimen for 21 days prior to Screening (no greater than ± 20% variability in total daily dose) 5. Have a plasma C-peptide level < 0.6 ng/mL at Screening 6. Have an HbA1c < 10% at Screening 7. Body mass index (BMI) in the range of ≥ 18 to ≤ 35 kg/m^2 at Screening 8. For women of childbearing potential, there is a requirement for a negative urine pregnancy test at Screening and for agreement to use contraception throughout the study and for 7 days after the last dose of study drug. Acceptable contraception includes birth control pill/patch/vaginal ring, Depo-Provera® (medroxyprogesterone acetate), Norplant® System (levonorgestrel), an intra-uterine device (IUD), the double barrier method (the woman uses a diaphragm and spermicide and the man uses a condom), or abstinence. 9. Fasting Serum Triglycerides concentration <200 mg/dL
	Exclusion criteria: Subjects meeting any of the following criteria are to be excluded. Laboratory criteria will be based on testing performed at the Screening Visit. 1. Currently being treated with pramlintide or has discontinued pramlintide within 21 days of Screening 2. Currently using an insulin pump

	3. Has renal insufficiency (serum creatinine > 3.0 mg/dL) or end-stage renal disease requiring renal replacement therapy 4. Has hepatic disease, including serum ALT or AST ≥ 3 times the upper limit of normal (ULN) 5. Has hepatic synthetic insufficiency (serum albumin < 3.0 g/dL) 6. Has a hematocrit value that is exclusionary, as shown below: a. Female <35.5% b. Male <38.3% 7. Has a hemoglobin value that is exclusionary, as shown below: a. Female <11.5 g/dL b. Male <12.5 g/dL 8. Has out-of-range systolic or diastolic BP readings at Screening (systolic BP < 90 or > 150 mm Hg or diastolic BP < 50 or > 100 mm Hg) 9. Has clinically significant ECG abnormalities at Screening 10. Has congestive heart failure, NYHA Class III or IV 11. Has history of myocardial infarction, unstable angina, or revascularization within 6 months prior to Screening 12. Has history of a cerebrovascular accident in 6 months prior to Screening with major neurological deficits 13. Has active malignancy within 5 years prior to Screening (exception: basal cell or squamous cell skin cancers) 14. Has had major surgical operation within 60 days prior to Screening or planned surgical operation during the study 15. Has a seizure disorder (other than with suspected or documented hypoglycemia) 16. Has a current bleeding disorder, treatment with anticoagulants, or platelet count < 50 $\times 10^9$/L 17. Has a history of allergies or significant hypersensitivity to pramlintide or any pramlintide-related products or to any of the excipients in the investigational formulation 18. Has a history of positive test result for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) 19. Has a concurrent illness not controlled by a stable therapeutic regimen 20. Tests positive for drugs of abuse at Screening. Subjects testing positive for tetrahydrocannabinol (THC) at Screening or reporting active marijuana use will be allowed to participate in the study at the discretion of the investigator. 21. Has active substance or alcohol abuse (> 21 drinks/week for males or > 14 drinks/week for females). 22. Has participated in other studies involving administration of an investigational drug within 30 days or 5 half-lives prior to Screening (whichever is longer) or during participation in the current study. 23. There is any reason the investigator deems exclusionary 24. Has donated blood within 8 weeks prior to Screening.

Study drug, dosage, and administration	**PRAM9**, a pramlintide-regular insulin co-formulation Dose: See Sections 9.1.3and 9.1.4 for a full description of pramlintide dose adjustment. Route of administration: SC (in the abdomen, peri-umbilicus)
Active Controls, dose, and route of administration	**Regular insulin**: **Humulin® R (U-100) (regular insulin human injection)** Dose: See Section 9.1.2. Route of administration: SC (in the abdomen, peri-umbilicus)
	Regular Insulin plus pramlintide (co-administered as separate injections) Dose: See Sections 9.1.3 and 9.1.4 for a full description and pramlintide dose adjustment. Route of administration: SC (in the abdomen, peri-umbilicus). The separate, co-administered regular insulin and pramlintide injections should be given to opposites sides of the abdomen (ie, left and right peri-umbilicus, opposite quadrants).
Duration of subject participation and duration of study	Screening Phase of up to 4 weeks; Treatment Periods of up to 3 weeks; and 7 to 11 days of follow-up. The estimated duration of subject participation is 8 weeks.

Concomitant medications	All medications taken within 28 days before the first study treatment visit (Day 1), including insulin, will be documented in the electronic case report form (eCRF). Any changes to a subject's concomitant medication regimen after the first treatment on Day 1 will also be documented in the eCRF.
	Ideally, subjects should be on a stable regimen of all concomitant medications except insulin for at least 28 days prior to Screening, and they will be encouraged to avoid making changes (excepting insulin) to their concomitant medication regimen during participation in the study. In addition, investigators are encouraged to avoid adding to or changing a participant's medications during study participation unless deemed medically necessary.
	Diabetes Medication
	Subject diabetes medication will be recorded on the day of Screening:
	• Total daily meal-time insulin
	  ○ Type of insulin (regular insulin, lispro, or aspart)
	• Basal insulin
	  ○ Type of insulin (glargine, detemir, or degludac)
	• Total daily dose of insulin
	• Glucagon-like peptide-1 (GLP-1) analogue

Safety assessments	Safety assessments include reporting of AEs and SAEs, vital sign measurements, clinical safety laboratory evaluations, and reasons for treatment discontinuations due to toxicity. In addition, the investigator will use a modified Draize scale to evaluate the injection sites after each administration for signs of erythema and edema (Appendix 1) and subjects will complete questionnaires to assess injection site discomfort (Appendix 2).

	To monitor for hypoglycemia, BGM will be performed in real time at each subject's bedside at 10, 20, 30, 40, 50, 60, 90, 120, and 180 minutes post dosing at Visit 2 through 4. Safety assessments will be performed at specified time points. Vital sign measurements, including BP, HR, respiratory rate, and temperature will be taken after ≥ 5 minutes of seated rest. The AE reporting period for a subject enrolled in the study begins when the subject provides informed consent and is continued through the Follow-Up Visit. All AEs that occur in subjects during the AE reporting period must be recorded, regardless of the relationship of the AE to study drug. All AEs are to be followed until resolution or the subject is medically stable.
Pharmacodynamics	At Visits 2, 3, and 4, samples will be drawn to measure plasma glucose levels. Venous blood samples will be drawn 10 ± 2 minutes before and immediately prior to dosing (-2 to 0 minutes), and then 10, 20, 30, 40, 50, 60, 90, 120, 150, 180, 240, 300, and 360 minutes post-dosing (window allowance of ± 2 minutes). Plasma glucose levels will be used to calculate the following PD parameters: C_{max}, T_{max}, area over the curve (AOC), and AUC (see Section 13.3.2).
Pharmacokinetics	At Visits 2, 3, and 4, samples will be drawn to measure plasma insulin and pramlintide levels. Venous blood samples will be drawn 10 ± 2 minutes before and immediately prior to dosing (-2 to 0 minutes), and then 10, 20, 30, 40, 50, 60, 90, 120, 150, 180, 240, 300, and 360 minutes post-dosing (window allowance of ± 2 minutes). Insulin and pramlintide concentrations will be used to calculate the following PK parameters: C_{max}, T_{max}, AUC_{0-90}, AUC_{0-180}, and AUC_{0-360}
Statistical methods	Complete details for the statistical analyses are included in a separate Statistical Analysis Plan (SAP).

Table 2: Schedule of Assessments

Study Phase	Screening	Treatment Period			Follow-Up
Study Visit	V1	Period 1 V2	Period 2 V3	Period 3 V4	V5
Study Day	-28 to -1	1	(V2+7-11 days)[14]	(V3+7-11 days)[14]	(V4+7-11 days)[14]
Informed consent	X				
Medical history & demographics	X				
Inclusion/exclusion review	X				
Urine drug screen[1]	X				
Physical exam & body weight[2]	X	X	X	X	X
Height	X				
12-lead ECG	X				
Vital sign measurements[3]	X	X	X	X	X
Hematology	X				X
Clinical chemistry	X				X
C-peptide & HbA1c	X				
Urine pregnancy test	X	X	X	X	X
IV catheter placement		X	X	X	
Clinic admission/discharge[4]		X	X	X	
Overnight fast from midnight		X	X	X	
Blood glucose measurement (BGM)[5]		X	X	X	
Randomization[6]		X			
Study drug(s) injection(s)[7]		X	X	X	
PK collection[8]		X	X	X	
PD collection[9]		X	X	X	
Draize scales[10]		X	X	X	
Injection site discomfort[11]		X	X	X	
Oral glucose administration[12]		X	X	X	
Meal[13]		X	X	X	
Review AEs		X	X	X	X
Concomitant medications	X	X	X	X	X

AE = adverse event; ECG = electrocardiogram; PD = pharmacodynamics; PK = pharmacokinetics; V = visit

1) **Urine Drug Screen:** To include cocaine, THC, opiates, amphetamines, methamphetamine, and phencyclidine.
2) **PE:** Full PE (excluding breast, pelvic, rectal, and genitourinary systems) to be performed at Screening and Follow-Up Visits; includes height at Screening. Symptom-directed PEs to be performed at Visits 2, 3, and 4.

3) **Vital signs:** Temperature, respiration, HR and BP (after 5 minutes seated rest) to be performed at all visits. During injection visits, HR and BP measurements to be repeated 30 ± 5 minutes, 180 ± 5, and 360 ± 5 minutes post-dose.
4) **Admission and discharge:** Arrival for an overnight stay at the clinical research facility on the day prior to treatment visits. Subject to be discharged the next day after study procedures have been performed and after the following have occurred: 1) subject has consumed their meal; 2) subject has returned to their usual medication regimen [including insulin]; 3) capillary glucose concentration is confirmed to be > 100 mg/dL; and 4) subject is considered medically stable.
5) **Blood glucose measurement (BGM):** BGM will be performed in real time at each subject's bedside at 10, 20, 30, 40, 50, 60, 90, 120, and 180 minutes post dosing at Visit 2 through 4. Prior to dosing, a capillary blood sample will be tested to confirm that blood glucose is in the range of 80 to 150 mg/dL. If result is > 150 mg/dL after repeat test, the visit should be rescheduled after a minimum 24-hour wait. If the blood glucose is > 150 mg/dL after repeat test, then the investigator may treat with a bolus dose of IV regular insulin, per discretion, to bring the subject into the required blood glucose range. Before initiating study treatment, at least 40 minutes should have passed from the last dose of administered insulin, and the subject's blood glucose level should be within the range of 80 to 150 mg/dL If the blood glucose is < 80 mg/dL after repeat test, then the investigator may treat with oral glucose tabs/solution or IV glucose, per discretion, to bring the subject into the required blood glucose range. Before initiating study treatment, at least 30 minutes should have passed from the last dose of administered glucose, and the subject's blood glucose level should be within the range of 80 to 150 mg/dL. If hypoglycemia occurs (ie, blood glucose <70 mg/dL), the subject will be rescued with IV dextrose, according to the formula shown in Section 8.5, Occurrence of Hypoglycemia.
6) **Drug sequence randomization:** To be performed just prior to first study drug injection at Period 1 (Visit 2).
7) **Study drug administration:** Glucose must be 80 to 150 mg/dL prior to administration of study drug(s). Injection sites should be rotated to avoid injecting at a previously used site.
8) **PK:** Venous blood samples will be drawn 10 ± 2 minutes before and immediately prior to dosing (-2 to 0 minutes), and then 10, 20, 30, 40, 50, 60, 90, 120, 150, 180, 240, 300, and 360 minutes post-dosing (window allowance of ± 2 minutes).
9) **PD:** Venous blood samples will be drawn 10 ± 2 minutes before and immediately prior to dosing (-2 to 0 minutes), and then 10, 20, 30, 40, 50, 60, 90, 120, 150, 180, 240, 300, and 360 minutes post-dosing (window allowance of ± 2 minutes).
10) **Draize scales:** To be performed by the investigator using the modified Draize scale at 30, 90, and 360 minutes (± 2 minutes) post-study drug injection (Appendix 1).
11) **Injection site discomfort evaluation:** To be performed by the subject at 10 and 30 minutes (± 2 minutes) post-study drug injection. Subjects should complete injection site discomfort questions at 10 mins and then Question Q1c is to be answered at 360 mins post-study drug injection (Appendix 2).
12) **Oral glucose Within 2 minutes of** the blood draw at 30 minutes post-dose, a standardized 75-gram oral glucose challenge (eg, 75 grams of glucose syrup and water) should be given to the subject. Subject should consume the solution within 5 to 10 minutes.
13) **Meal:** After the last blood collection (at 360 minutes post-study drug administration), subjects will be provided a regular meal and insulin (per investigator's discretion) as per the site's usual practice
14) .Previous visit +7 to 11 days.

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LIST OF TABLES

3. LIST OF ABBREVIATIONS

The following abbreviations are used in this study protocol.

Table 3: Abbreviations and Specialist Terms

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANOVA	analysis of variance
AOC	area over the curve
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-90}	area under the concentration-time curve from 0 to 90 minutes post-dosing
AUC_{0-180}	area under the concentration-time curve from 0 to 180 minutes post-dosing
AUC_{0-360}	area under the concentration-time curve from 0 to 360 minutes post-dosing
BGM	blood glucose measurement
BMI	body mass index
BP	blood pressure
CLIA	Clinical Laboratory Improvement Act
C_{max}	maximum plasma concentration
CRF	case report form
CRO	contract research organization
eCRF	electronic case report form
ECG	electrocardiogram
EDC	electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GLP-1	Glucagon-like peptide-1
HbA1c	glycated hemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
I:C	insulin-to-carbohydrate
ICF	informed consent form
IEC	Independent Ethics Committee
ICH	International Conference on Harmonisation
IME	important medical event
IND	Investigational New Drug

Abbreviation	Definition
IRB	institutional review board
IUD	intra-uterine device
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numeric Rating Scale
PD	pharmacodynamics
PE	physical examination
PK	pharmacokinetic
PT	Preferred Term
PRAM9	Co-formulation of a fixed-ratio combination of 9 µg pramlintide per unit of regular insulin
RBC	red blood cells
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SOC	System Organ Class
T1D	Type 1 diabetes mellitus
TEAE	treatment-emergent adverse event
Tmax	time to maximum plasma concentration
ULN	upper limit of normal
WHO	World Health Organization

4. INTRODUCTION

4.1. Medical Need

The response of insulin and amylin to food intake is absent in patients with type 1 diabetes (T1D) due to autoimmune β-cell destruction [Ludvik 1991, Koda 1992, Herrmann 2016]. Insulin therapy is the primary treatment option for patients with T1D.

Despite considerable advances in insulin chemistry, delivery, and pharmacology, only a small percentage of diabetic patients achieve near normal glycemic levels with insulin replacement alone [Klein 1996, Whitehouse 2002]. The increased risk of severe hypoglycemia and undesired weight gain that usually accompany glycemic improvements with insulin therapy represent major obstacles toward achieving satisfactory glycemic control [DCCT 1997, DCCT 1988, Purnell 1998].

Pramlintide [AstraZeneca Pharmaceuticals, LP, 2016], a soluble, nonaggregating, equipotent synthetic analog of amylin, is approved by the FDA and used to treat T1D and T2D patients who are unable to obtain near-normoglycemia with insulin therapy. In a study conducted in subjects with T1D with a mean HbA1c of 8.1 (mean age=41 years, mean duration of diabetes=20 years, mean body mass index (BMI)=28 kg/m^2), pramlintide (SYMLIN®) or placebo was administered at major meals as an add on to insulin therapy at a dose of 15 µg and titrated upward at weekly intervals of 15 µg to maintenance doses of 30 µg or 60 µg. The insulin dose was reduced by 30% to 50% in order to minimize the risk of developing hypoglycemia. Those who received pramlintide had a mean percent reduction of 7.1% in the mealtime insulin dose at 6 months post study drug administration initiation compared with 2.4% reduction in the placebo group [AstraZeneca Pharmaceuticals, LP, 2016].

Many clinical studies that add pramlintide to insulin have demonstrated improved control of blood sugar, lower hemoglobin A1c, and better patient satisfaction and well-being. However, the benefits of these products used together also are associated with increased risk of pramlintide-associated nausea and vomiting ; increased number of required injections; and tailoring of insulin and pramlintide doses [AstraZeneca Pharmaceuticals, LP, 2016].

Although pramlintide does not cause hypoglycemia, when combined with insulin, the risk of severe hypoglycemia is increased. In subjects with T1D, in 6-month controlled trials without insulin reduction at initiation, the incidence of severe hypoglycemia was 16.8% (0 to 3 months, n=716) in subjects receiving pramlintide and insulin, as compared with 10.8% (0 to 3 months, n=538) in subjects receiving placebo and insulin [AstraZeneca Pharmaceuticals, LP, 2016].

In addition to the risk of hypoglycemia, separated administrations of insulin and amylin at distinct times before meals, varying doses, and multiple injection sites are impediments to patient compliance that counter the known therapeutic benefits of pramlintide. A fixed-ratio, single-injection of a co-formulated insulin-pramlintide preparation would be desirable in mimicking physiological patterns [Riddle 2015, da Silva 2018].

4.2. Xeris' Pramlintide-Insulin Injection

Xeris Pharmaceuticals has developed a liquid-stable, co-formulation of a fixed-ratio combination of 9 µg pramlintide per unit of regular insulin (PRAM9) that can be delivered as a single SC

injection. The fixed-dose combination is designed to reduce the treatment burden associated with concomitant insulin and pramlintide therapy, ie, reduce the number of daily aggregate injections because the pramlintide would not require separate mealtime injections.

In nonclinical studies, the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of pramlintide and Humulin® (or regular insulin) or Humalog® (lispro insulin) were studied in normal and streptozotocin-induced diabetic rats (STZ; mimicking T1D). Treatments were given as separate injections of commercial products or as Xeris' pramlintide-insulin combined dose single injection. Consistent with pramlintide's known pharmacological action, there was no glucose lowering with pramlintide alone for either the commercial or Xeris formulation. Additionally, glycemic profiles for pramlintide were similar to saline or Xeris vehicle administered by SC injection in rats. Xeris' pramlintide-insulin formulation showed a longer duration of glucose lowering compared to separate injections of commercial pramlintide (Symlin®) and insulin (Humulin®).

This clinical study has been designed to compare the PD, PK, and safety of PRAM9 with regular insulin and regular insulin plus pramlintide (co-administered as separate injections) when injected subcutaneously (SC) in the abdomen of fasted adults with T1D. A detailed description of, and rationale for the dosing regimen for this study is located in Section 9.1.

5. STUDY OBJECTIVES AND PURPOSE

5.1. Primary Objective

The primary objective of this study is to evaluate the PD properties of a single dose of PRAM9 compared to single doses of regular insulin and regular insulin plus pramlintide (co-administered as separate injections) in adults with T1D.

5.2. Secondary Objectives

The secondary objectives of this study are to evaluate the safety and PK profiles of a single dose of PRAM9 compared to single doses of regular insulin and regular insulin plus pramlintide (co-administered as separate injections) in adults with T1D.

5.3. Study Endpoints

Primary

The PD effects upon plasma glucose levels will be compared between the treatments as defined by the following primary endpoint:

- Area under the curve area from administration to 180 min ($AUC_{0\text{-}180}$) (mg/dL × minutes) for plasma glucose > 180 mg/dL

Secondary

See Section 13.3 for a complete listing of secondary endpoints to be analyzed in this study. Additionally, full description of secondary endpoints will be included in a separate Statistical Analysis Plan (SAP).

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a randomized, open-label, active-controlled, single-dose, 3-treatment, 3-period, 3-way crossover, comparative PD and PK inpatient study in adults with T1D. The study comprises 5 visits: Screening (Visit 1), Treatment Periods (Visits 2 − 4), and Follow-Up (Visit 5).

To determine eligibility, subjects will complete the Screening procedures (Visit 1) up to 28 days before the first treatment visit (Visit 2). Subjects will be instructed to eat normally and take their usual medications, but to refrain from alcohol for 24 hours prior to checking in for treatment visits.

Treatment Periods

For Treatment Period Visits 2 through 4, eligible subjects will be instructed to arrive for an overnight stay at the clinical research facility on the day prior to each treatment visit. At the clinic, subjects will be given a standardized dinner meal, and instructed to take their prescribed evening mealtime insulin regimen and basal insulin dose. The subjects will fast after midnight but will be allowed to drink water ad libitum (ie, tap water, bottled water, distilled water, etc. [water without carbohydrates]) and take any prescribed medications.

During each Treatment Period Visit, subjects will receive a single SC dose of PRAM9, regular insulin, or co-administered regular insulin plus pramlintide. On the morning of each treatment visit and prior to dosing, a fasting blood sample will be tested using a blood glucose meter (BGM) to confirm that blood glucose is in the range of 80 to 150 mg/dL.

- If the blood glucose is > 150 mg/dL after repeat test, then the investigator may treat with an intravenous (IV) bolus dose of regular insulin, per discretion, to bring the subject into the required blood glucose range. Before initiating study treatment, at least 40 minutes should have passed from the last dose of administered insulin and the subject's glucose level should be within the range of 80 to 150 mg/dL.
- If the blood glucose is < 80 mg/dL after repeat test, then the investigator may treat with oral glucose tabs/solution or IV glucose, per discretion, to bring the subject into the required blood glucose range. Before initiating study treatment, at least 30 minutes should have passed from the last dose of administered glucose and the subject's glucose level should be within the range of 80 to 150 mg/dL.
- If the subject's blood glucose cannot be optimized to 80 to 150 mg/dL within 2 hours, then the visit should be rescheduled after a minimum 24-hour wait, per investigator's discretion.

At Visit 2, once blood glucose is confirmed to be within the range of 80 to 150 mg/dL, subjects will be randomized to their study drug treatment sequence.

Table 4: Sequence of Study Drug Administration

Cohort	Period 1	Period 2	Period 3
1	PRAM9	Regular insulin	Regular insulin + pramlintide
2	Regular insulin	Regular insulin + pramlintide	PRAM9
3	Regular insulin + pramlintide	PRAM9	Regular insulin
4	PRAM9	Regular insulin + pramlintide	Regular insulin
5	Regular insulin	PRAM9	Regular insulin + pramlintide
6	Regular insulin + pramlintide	Regular insulin	PRAM9

Insulin-to-carbohydrate calculations will be used to identify subject doses. All subjects will get flexible doses of insulin, pramlintide, and PRAM9. See Section 9.1 for complete information on study drug dosing. The dose of regular insulin is calculated to correspond to a ratio of 9 µg of pramlintide for every 1 unit of insulin. Additionally, the dose of regular insulin is calculated from the subject's insulin-to-carbohydrate (I:C) ratio to match a 75-gram carbohydrate challenge. Rule 450 will be used for carbohydrate counting and insulin dose calculation in this study (see Appendix 3).

Prior to dose administration, a peripheral catheter for blood sampling will be placed into a vein ideally located within the antecubital fossa. The hand of the arm used for blood sampling will be kept warm by use of a heated hand box to increase blood flow and achieve "arterialized" samples. The subject will remain supine and kept warm and be allowed to drink only water (ad libitum).

Once the catheter and hand box are in place, study drug(s) will be administered SC over 1 to 3 seconds to the abdomen (around the umbilicus). Co-administered regular insulin plus pramlintide injections should be administered to opposite sides of the abdomen (ie, left and right peri-umbilicus, opposite quadrants). Injection sites should be rotated to avoid injecting at a previously used site.

To monitor for hypoglycemia, BGM will be performed in real time at each subject's bedside at 10, 20, 30, 40, 50, 60, 90, 120, and 180 minutes post dosing at Visit 2 through 4. BGM measurements from the cool hand are allowed.

To evaluate drug PD (plasma glucose response), blood samples are to be drawn at 10 ± 2 minutes before and immediately (-2 to 0 minutes) prior to study drug injection. After study drug injection, blood samples also will be collected at 10, 20, 30, 40, 50, 60, 90, 120, 150, 180, 240, 300, and 360 minutes post-dosing (window allowance of ± 2 minutes). After the 60-minute postdose time point, the subject's hand must be reinserted into the heated box for at least 10 minutes prior to the next blood collection.

To evaluate drug PK (plasma insulin/pramlintide concentrations), blood samples are to be drawn at 10 ± 2 minutes before and immediately (-2 to 0 minutes) prior to study drug injection. After study drug injection, blood samples also will be collected at 10, 20, 30, 40, 50, 60, 90, 120, 150, 180, 240, 300, and 360 minutes post-dosing (window allowance of ± 2 minutes).

Within 2 minutes after the 30 minutes post-dose blood draw, a standardized 75-gram oral glucose challenge should be ingested (within 5 to 10 minutes) by the subject.

After the last blood collection (at 360 minutes post-study drug administration), subjects are to be provided a regular meal and insulin (per investigators' discretion).

At 30, 90, and 360 minutes (± 2 minutes) post-dose, injection sites will be evaluated by the investigator using the modified Draize scale (Appendix 1). Additionally, subjects will complete an injection site discomfort questionnaire at 10 and 30 minutes (± 2 minutes) post-dose (Appendix 2).

A subject may be discharged from the clinic, per investigator's criteria, when the following has occurred:

- Subject has consumed their meal
- Subject has returned to their usual medication regimen, including insulin
- Subject's capillary glucose concentration is confirmed to be > 100 mg/dL
- Subject is considered medically stable

Any time during the visit if hypoglycemia occurs (ie, blood glucose < 70 mg/dL), the subject will be rescued with IV dextrose using the following formula to calculate the dose of dextrose:

D50% mL = (100 minus BG) × 0.4

Where D50% = the dose of IV dextrose, mL = the volume of dextrose, BG = the subject's hypoglycemic blood glucose value (ADA, 2008; Joslin Center, 2013)

The dose of dextrose should be administered slowly, over 2 to 5 minutes.

If D50% is administered, then blood glucose will be remeasured by blood glucose meter at 10, 20, and 30 minutes following the end of administration of IV dextrose.

Successful plasma glucose recovery should be confirmed (ie, glucose returns to ≥ 70 mg/dL) and the subject medically stabilized. When the subject is medically stable, they can be discharged from the clinic (per criteria above).

After a first washout period of 7 to 11 days, subjects will return to the clinic for Treatment Period 2 (Visit 3) and the treatment visit procedures will be repeated with each subject crossed over to the next randomized study drug treatment sequence. Upon check-in and completion of morning activities, the subject will receive their second administration of study drug(s).

After a second washout period of 7 to 11 days, subjects will return to the clinic for Treatment Period 3 (Visit 4) and the treatment visit procedures will be repeated with each subject crossed over to the last randomized study drug treatment sequence. Upon check-in and completion of morning activities, the subject will receive their third administration of study drug(s).

During the Treatment Periods, subjects will undergo vital sign measurements; AE assessments; concomitant medication assessments; and pregnancy testing for females of childbearing potential as outlined in the Schedule of Assessments (Table 2).

Follow-Up

A Follow-Up Visit will be conducted 7 to 11 days after the subject's last dose of study drugs(s). Subjects will return to the clinic and undergo a full PE, vital sign measurements, weight, AE assessments, concomitant medication assessments, sample collection for hematology, chemistry, C-peptide, and pregnancy testing for females of childbearing potential.

6.2. Treatment Assignment

Eligible subjects will receive single SC doses of PRAM9, regular insulin, and co-administered regular insulin plus pramlintide. At Visit 2, subjects will be randomized to 1 of 6 study drug treatment sequences (3 subjects per treatment sequence). See Table 4 for study drug administration sequences.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Number of Subjects

Approximately 48 subjects may be needed to screen in order to obtain 18 randomized subjects (3 subjects per treatment sequence).

7.2. Subject Inclusion Criteria

Subjects must meet the following criteria to be included:

1. Understands the study procedures, alternative treatment available, and risks involved with the study, and voluntarily agrees to participate by giving written informed consent
2. Male or non-pregnant, non-lactating female diagnosed with T1D for at least 24 months prior to Screening.
3. Aged 18 to 64 years of age, inclusive
4. On a stable insulin regimen for 21 days prior to Screening (no greater than ± 20% variability in total daily dose)
5. Have a plasma C-peptide level < 0.6 ng/mL at Screening
6. Have an HbA1c < 10% at Screening
7. Body mass index (BMI) in the range of ≥ 18 to ≤ 35 kg/m^2 at Screening
8. For women of childbearing potential, there is a requirement for a negative urine pregnancy test at Screening and for agreement to use contraception throughout the study and for 7 days after the last dose of study drug. Acceptable contraception includes birth control pill/patch/vaginal ring, Depo-Provera® (medroxyprogesterone acetate), Norplant® System (levonorgestrel), an intra-uterine device (IUD), the double barrier method (the woman uses a diaphragm and spermicide and the man uses a condom), or abstinence.
9. Fasting Serum triglyceride concentration < 200 mg/dL

7.3. Subject Exclusion Criteria

Subjects meeting any of the following criteria are to be excluded. Laboratory criteria will be based on testing performed at the Screening Visit.

1. Currently being treated with pramlintide or has discontinued pramlintide within 21 days of Screening
2. Currently using an insulin pump
3. Has renal insufficiency (serum creatinine > 3.0 mg/dL) or end-stage renal disease requiring renal replacement therapy
4. Has hepatic disease, including serum ALT or AST ≥ 3 times the upper limit of normal (ULN)
5. Has hepatic synthetic insufficiency (serum albumin < 3.0 g/dL)

6. Has a hematocrit value that is exclusionary, as shown below:
   a. Female <35.5%
   b. Male <38.3%
7. Has a hemoglobin value that is exclusionary, as shown below:
   a. Female <11.5 g/dL
   b. Male <12.5 g/dL
8. Has out-of-range systolic or diastolic BP readings at Screening (systolic BP < 90 or > 150 mm Hg or diastolic BP < 50 or > 100 mm Hg)
9. Has clinically significant ECG abnormalities at Screening
10. Has congestive heart failure, NYHA Class III or IV
11. Has history of myocardial infarction, unstable angina, or revascularization within 6 months prior to Screening
12. Has history of a cerebrovascular accident in 6 months prior to Screening with major neurological deficits
13. Has active malignancy within 5 years prior to Screening (exception: basal cell or squamous cell skin cancers)
14. Has had major surgical operation within 60 days prior to Screening or planned surgical operation during the study
15. Has a seizure disorder (other than with suspected or documented hypoglycemia)
16. Has a current bleeding disorder, treatment with anticoagulants, or platelet count $< 50 \times 10^9$/L
17. Has a history of allergies or significant hypersensitivity to pramlintide or any pramlintide-related products or to any of the excipients in the investigational formulation
18. Has a history of positive test result for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV)
19. Has a concurrent illness not controlled by a stable therapeutic regimen
20. Tests positive for drugs of abuse at Screening. Subjects testing positive for tetrahydrocannabinol (THC) at Screening or reporting active marijuana use will be allowed to participate in the study at the discretion of the investigator.
21. Has active substance or alcohol abuse (> 21 drinks/week for males or > 14 drinks/week for females)
22. Has participated in other studies involving administration of an investigational drug within 30 days or 5 half-lives prior to Screening (whichever is longer) or during participation in the current study
23. There is any reason the investigator deems exclusionary
24. Has donated blood within 8 weeks prior to Screening.

7.4. Subject Withdrawal Criteria

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject to determine the reason(s) why the subject failed to return for the scheduled visit, and to reschedule the missed visit. This includes contacting subjects via email and telephone, including family members or emergency contacts. If such efforts fail, a certified letter should be sent to the subject's last known address requesting they contact study staff.

In all circumstances, every effort should be made to document subject outcome, per the follow-up. Information regarding the reason for not completing the study will be recorded in the electronic case report form (eCRF). The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, and follow-up with the subject regarding any unresolved AEs. It will be documented whether each subject completed the study.

If a decision by the investigator or sponsor is made to withdraw a subject, a final visit should be scheduled soon after the decision to withdraw is made. The subject will be asked to return to site for the assessments listed in Section 10.3 (Follow-Up Visit).

If the subject withdraws from the study and withdraws consent, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.5. Criteria for Study Termination

The study may be prematurely terminated at any time because of a regulatory authority decision, change in opinion of the IRB or Xeris.

Circumstances that may warrant premature study termination include, but are not limited, to the following:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Failure to enter subjects at an acceptable rate
- Insufficient adherence to the requirements of the protocol
- Insufficient provision of complete and evaluable data
- Plans to modify, suspend, or discontinue development of the study drug

If the study is prematurely terminated or discontinued, Xeris will promptly notify the investigators and document the reason for study termination. Specific procedures for termination will be arranged by the sponsor in coordination with the investigators. After notification, the investigators must contact all participating subjects within 7 days. All study materials must be collected and all eCRFs completed to the greatest extent possible, and all study materials must be returned to Xeris or its designee within 28 days of receiving notice of study termination from the sponsor.

8. TREATMENT OF SUBJECTS

8.1. Concomitant Medications

All subjects will be questioned about concomitant medications at each visit. Medications taken within 28 days before Day 1, including insulin, will be documented in the eCRF. Any changes to a subject's concomitant medication regimen after the first treatment on Day 1 will also be documented in the eCRF.

Ideally, subjects should be on a stable regimen of all concomitant medications except insulin for at least 28 days prior to Screening, and they will be encouraged to avoid making changes (excepting insulin) to their concomitant medication regimen during participation in the study. In addition, investigators are encouraged to avoid adding to or changing a participant's medications during study participation unless deemed medically necessary.

Diabetes Medication

Subject diabetes medication will be recorded on the day of screening:

- Total daily meal-time insulin
  - Type of insulin (regular insulin, lispro, or aspart)
- Basal insulin
  - Type of insulin (glargine, detemir, or degludac)
- Total daily dose of insulin
- Glucagon-like peptide-1 (GLP-1) analogue

8.2. Randomization

On the morning of Visit 2, subjects will be randomized into the appropriate treatment sequence order to receive each of the 3 study treatments (PRAM9, regular insulin, and co-administered regular insulin plus pramlintide). The study statistician will create the randomization sequence using random permuted block methodology. See Table 4 for study drug administration randomization sequence.

8.3. Treatment Compliance

Not applicable as study drug will be administered in an inpatient setting.

8.4. Subject Replacements

Subjects who are randomized but do not receive the first study drug will be replaced. Up to 3 subjects may be replaced.

8.5. Occurrence of Hypoglycemia

If hypoglycemia occurs (ie, blood glucose <70 mg/dL), the subject will be rescued with IV dextrose using the following formula to calculate the dose of dextrose:

D50% mL = (100 minus BG) × 0.4

Where D50% = the dose of IV dextrose, mL = the volume of dextrose, BG = the subject's hypoglycemic blood glucose value (ADA, 2008; Joslin Center, 2013**)**

The dose of dextrose should be administered slowly, over 2 to 5 minutes.

If D50% is administered, then blood glucose will be remeasured by blood glucose meter at 10, 20, and 30 minutes following the end of administration of IV dextrose.

Successful plasma glucose recovery should be confirmed (ie, glucose returns to ≥ 70 mg/dL) and the subject medically stabilized. When the subject is medically stable, they can be discharged from the clinic. A subject may be discharged from the clinic, per investigator's criteria, when the following has occurred:

- Subject has consumed their meal
- Subject has returned to their usual medication regimen, including insulin
- Subject's capillary glucose concentration is confirmed to be > 100 mg/dL
- Subject is considered medically stable

Any occurrence of hypoglycemia must be recorded in the Adverse Event (AE) eCRF.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drugs and Doses

PRAM9, insulin, and pramlintide will be supplied by the sponsor.

9.1.1. PRAM9

PRAM9 is a stable, liquid, and ready-to-use co-formulation of pramlintide and regular insulin for SC injection.

The pramlintide and insulin injection drug product is prepared as a sterile liquid for injection that is packaged as a 0.9 mg/mL pramlintide + 3.5 mg/mL insulin solution for injection in a 3-mL glass vial (2.5 mL fill volume).

The dose of PRAM9 is to be based upon the subject's historical mealtime insulin dose (based upon the subject's historical carbohydrate: insulin ratio). The historical insulin dose will be reduced by 50% to derive the new insulin dose. The associated pramlintide dose will be related to the dosage of insulin (eg, 9 µg pramlintide per 1 U of insulin).

PRAM9 is to be administered SC (in the abdomen, peri-umbilicus).

9.1.2. Regular Insulin: Humulin® R (U-100) (regular insulin human injection)

The dose of regular insulin is to be based upon the subject's historical mealtime insulin dose (based upon the subject's historical carbohydrate: insulin ratio). Insulin is to be administered SC (in the abdomen, peri-umbilicus).

Note: The calculated insulin dose should be rounded to the closest whole unit. For rounding, if the digit to the right of the decimal is ≤ 4, round down (example 4.3 units = 4 units). If the digit to the right of the decimal is ≥ 5, round up (example 4.5 units = 5 units).

9.1.3. Regular Insulin Plus Pramlintide

Regular insulin plus pramlintide is to be co-administered as separate injections.

The new insulin dose is to be based upon the subject's historical mealtime insulin dose (based upon the subject's historical carbohydrate: insulin ratio). This historical dose will be reduced by 50% to be the new insulin dose. The associated pramlintide dose will be calculated from the new dosage of insulin (eg, 9 µg pramlintide per 1 U of insulin). The dosage of pramlintide will then be adjusted to the nearest increment on the Symlin® pen (eg, nearest 15 µg increment).

Regular insulin plus pramlintide is to be administered SC (in the abdomen, peri-umbilicus). The separate, co-administered regular insulin and pramlintide injections should be given to opposite sides of the abdomen (ie, left and right peri-umbilicus, opposite quadrants).

9.1.4. Study Drug Doses

All subjects will get flexible doses of insulin, pramlintide, and PRAM9. The dose of regular insulin is calculated to correspond to a ratio of 9 µg of pramlintide for every 1 unit of insulin. Additionally, the dose of regular insulin is calculated from the subject's insulin-to-carbohydrate

(I:C) ratio to match a 75-gram carbohydrate challenge. Rule 450 will be used for carbohydrate counting and insulin dose calculation in this study (see Appendix 3). Table 5 presents study drug doses for each study cohort.

Table 5: Study Drugs Dosing

Calculated Insulin Dose (U)[a] Based on Subject I:C Ratio	Regular Insulin Arm	Pramlintide + Regular Insulin Co-Administration Arm (Two Separate Injections)		PRAM9 Co-Formulation Acm (Single Injection)[c]
	Insulin Dose (U)	Insulin Dose (U)	Pramlintide Dose (µg) Modified for Symlin® Pen[b]	Insulin/Pramlintide Dose (U)
2	2	1	15	1
4	4	2	15	2
6	6	3	30	3
8	8	4	30	4
10	10	5	45	5
12	12	6	60	6
14	14	7	60	7

a: The calculated insulin dose, if necessary, will be rounded to the closest whole unit (example 4.5 units = 5 units).
b: The dosage of pramlintide should be adjusted to the nearest increment on the Symlin® pen (eg, nearest 15-µg increment).
c: Each unit of PRAM9 contains 1 unit of insulin and 9 µg of pramlintide.

9.2. Study Drug Packaging and Labeling

PRAM9 will be labeled according to 21 CFR 312.6 investigational drug labeling regulatory requirements. Study drug labels will include the protocol number, lot number, description of the study drug, dosing and storage instructions, name of Sponsor and manufacturer, and a statement that it is for clinical trial use only.

9.3. Administration of Study Drugs

Prior to administration, the intended injection sites should be cleansed with an alcohol swab and examined to ensure they have a normal appearance and are free from signs of inflammation or injury. At Visits 3 and 4, injection sites should be rotated to avoid injecting at a previously used site.

Study drug(s) will be administered SC to the abdomen (around the umbilicus). When applicable, the regular insulin and pramlintide injections should be given to opposite sides of the abdomen (ie, left and right peri-umbilicus, opposite quadrants).

Study drug(s) should be injected over 1 to 3 seconds. Following injection, light pressure should be applied to the injection site, as the needle is withdrawn.

9.4. Study Drug Storage and Accountability

PRAM9 must be stored in a freezer (-20°C) and thawed only once on the day of use (avoid repeated freeze-thaw cycles). On the morning of a dosing visit, the vial of PRAM9 should be placed at room temperature for 1 hour to thaw. Prior to use, the vial should be inverted 25 times to mix. If thawed and not used, then PRAM9 must be stored at a controlled temperature of 20°C to 25°C (68°F to 77°F) and discarded if not used within 30 days.

The investigator or an approved study staff will ensure that the study drug is stored in a secure area under recommended storage conditions and in accordance with applicable regulatory requirements.

The site will maintain appropriate documentation of continuous storage conditions and these records will be monitored on an ongoing basis by the monitor. Any deviations in the storage conditions must be documented (including minimum and maximum temperature excursion as well as estimate of total duration of storage outside the recommended storage conditions). Such deviations must be communicated to the sponsor as soon as identified by the site with appropriate course of action taken regarding the future use of the study drugs upon consultation with Xeris Pharmaceuticals.

The investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational drug products and supplies.

9.5. Study Drug Handling and Disposal

Unused PRAM9 will be returned to Xeris at the end of the study.

Unused regular insulin and pramlintide will be destroyed per site standard operating procedures (SOP).

10. STUDY PROCEDURES

A schedule of procedures for this study is provided in the Schedule of Assessments (Table 2).

10.1. Visit 1 – Screening

Prior to completing any Screening activities, the investigator or study team member will obtain informed consent from each subject in accordance with the procedures described in Section 16.3.

Subjects will complete a Screening Visit at least 1 day (to allow for receipt of blood test results), and no more than 28 days prior to the anticipated date of the first treatment visit (Treatment Period 1, Study Day 1). The following evaluations will be completed during the Screening Visit:

- Collection of medical history and demographic data
- Assessment of inclusion/exclusion criteria by a study investigator
- Urine drug screen. Note: At the investigator's discretion, subjects with a positive result for drugs other than THC (which is allowed at the investigator's discretion) will be allowed to participate if the subject reports use of a concomitant medication that explains the result (eg, positive urine test for opiates in a subject reporting use of cough syrup containing dextromethorphan).
- Full PE (excluding breast, pelvic, rectal, and genitourinary exams); to include measurement of height and weight (no shoes, lightly clothed)
- 12-lead ECG (after the subject has completed a 5-minute supine or seated rest; ECG to be obtained before assessment of BP and HR, and prior to blood collections)
- Assessment of vital signs, including temperature, respiration rate, HR, and BP, after a 5-minute seated rest
- Collection of venous blood for hematology, serum chemistry, and measurement of C-peptide and HbA1c (see Section 11.3.4 for complete listing of laboratory parameters)
- Urine pregnancy test for women of childbearing potential and discussion about study requirements regarding contraception
- Assessment of baseline concomitant medications, including diabetes medication:
    - Total daily meal-time insulin
        - Type of insulin (regular insulin, lispro, or aspart)
    - Basal insulin
        - Type of insulin (glargine, detemir, or degludac)
    - Total daily dose of insulin
    - GLP analogue

Once laboratory results are obtained and a final determination of eligibility is made, subjects should be contacted to schedule the first treatment visit. While immediate re-testing of laboratory results is not allowed, subjects failing to meet laboratory-based eligibility criteria may

be re-screened after a 30-day wait. A single re-screening is permitted, and this re-screening is only permissible if the reason for the prior screen failure was for laboratory measurements or vital signs. Blood for clinical laboratory tests can be redrawn after a 30-day wait; however, other Screening procedures do NOT need to be repeated. Vital signs can be remeasured after a 24-hour wait and other screening procedures do not need to be repeated if within the 28-day window. If the new clinical laboratory test results or vital signs meet eligibility, the subject may be dosed. Otherwise, the subject is not eligible for dosing or further re-screening.

10.2. Visits 2, 3, and 4

10.2.1. Clinic Arrival (Evening Before Dosing)

Subjects will be instructed to eat normal meals during the day but to refrain from alcohol (for 24 hours prior to the visit), and to follow their usual insulin regimen prior to their evening clinic arrival. Subjects will be instructed to arrive at the clinic on the day prior to the visit.

At the clinic, subjects will be given a standardized dinner meal (per investigator's discretion) and instructed to take their prescribed evening mealtime insulin regimen and basal insulin dose. The subjects will fast after midnight but will be allowed to drink water ad libitum (ie, tap water, bottled water, distilled water, etc. [water without carbohydrates]) and take any prescribed non-diabetic medications. Blood glucose concentrations will be kept in the range of 80 to 150 mg/dL per investigator discretion, via IV glucose and/or IV insulin infusion.

10.2.2. Day of Study Drug Administration

The following procedures will be carried out on the day of dosing.

- Symptom-directed PE
- Assessment of vital signs. Note: HR and BP measurements are to be repeated 30 ± 5 minutes, 180 ± 5, and 360 ± 5 minutes after study drug administration
- Women of childbearing potential will undergo a urine pregnancy test, which must be negative before further participation is allowed
- Prior to dosing, a capillary blood glucose measurement (BGM) will be tested to confirm that blood glucose is in the range of 80 to 150 mg/dL
    - If the blood glucose is > 150 mg/dL after repeat test, then the investigator may treat with a bolus dose of IV regular insulin, per discretion, to bring the subject into the required blood glucose range. Before initiating study treatment, at least 40 minutes should have passed from the last dose of administered insulin and the subject's glucose level should be within the range of 80 to 150 mg/dL.
    - If the blood glucose is < 80 mg/dL after repeat test, then the investigator may treat with oral glucose tabs/solution or IV glucose, per discretion, to bring the subject into the required blood glucose range. Before initiating study treatment, at least 30 minutes should have passed from the last dose of administered glucose and the subject's glucose level should be within the range of 80 to 150 mg/dL.

- If the subject's blood glucose cannot be optimized to 80 to 150 mg/dL within 2 hours, then the visit should be rescheduled after a minimum 24-hour wait, per investigator's discretion.

- Randomization (at Visit 2 only)
- Placement of peripheral catheter and hand placed in heated hand box
- Study drug(s) administration (to be injected over 1 to 3 seconds)
- PK sample collection at 10 ± 2 minutes before and immediately prior to dosing (-2 to 0 minutes), and then 10, 20, 30, 40, 50, 60, 90, 120, 150, 180, 240, 300, and 360 minutes post-dosing (window allowance of ± 2 minutes)
- PD sample collection at 10 ± 2 minutes before and immediately prior to dosing (-2 to 0 minutes), and then 10, 20, 30, 40, 50, 60, 90, 120, 150, 180, 240, 300, and 360 minutes post-dosing (window allowance of ± 2 minutes)
- Injection site assessment at 30, 90, and 360 minutes (± 2 minutes) post-dose using the modified Draize scale (Appendix 1)
- Subject injection site discomfort questionnaire at 10 and 30 minutes (± 2 minutes) post-dose (Appendix 2). Question Q1c is to be answered at 360 mins post-study drug injection.
- Within 2 minutes of the 30-minute post-dose blood draw, a standardized 75-gram oral glucose challenge (eg, 75 grams of glucose syrup and water) should be given to the subject and consumed within 5 to 10 minutes
- After the last blood collection (at 360 minutes post-study drug administration), subjects are to be provided a regular meal and insulin (per investigators' discretion)
- AE assessment
- Concomitant medications assessment

A subject may be discharged from the clinic, per the investigator's criteria, after the following has occurred:

- Subject has consumed their meal
- Subject has returned to their usual medication regimen, including insulin
- Subject's capillary glucose concentration is confirmed to be > 100 mg/dL
- Subject is considered medically stable

After a washout period of 7 to 11 days, subjects will return to the clinic for the next Treatment Period Visit and the treatment visit procedures will be repeated with each subject crossed over to the next randomized study drug treatment.

10.3. Visit 5 – Follow-Up

A Follow-Up Visit will be conducted 7 to 11 days following Visit 4 or if a subject is discontinued prematurely. This visit will include the following assessments:

- Full PE (excluding breast, pelvic, rectal, and genitourinary exams); to include measurement of weight (no shoes, lightly clothed)
- Assessment of vital signs after a 5-minute seated rest
- Collection of venous blood for hematology and serum chemistry (see Section 11.3.4 for complete listing of laboratory parameters)
- Urine pregnancy test for women of childbearing potential
- AE assessment
- Concomitant medications assessment

11. ASSESSMENTS

11.1. Pharmacodynamics

At Visits 2, 3, and 4 (Treatment Periods), samples will be drawn to measure plasma glucose levels. Venous blood samples will be drawn 10 ± 2 minutes before and immediately prior to dosing (-2 to 0 minutes), and then at 10, 20, 30, 40, 50, 60, 90, 120, 150, 180, 240, 300, and 360 minutes post-dosing (window allowance of ± 2 minutes).

Over the course of the study, approximately 15 blood samples (approximately 3 mL each) will be collected for each subject, for an approximate total volume of 45 mL per subject.

Plasma glucose levels will be used to calculate the following PD parameters: C_{max}, T_{max}, area over the curves (AOCs), and AUCs.

Detailed instructions for sample collection and preparation will be provided in a separate laboratory manual.

11.2. Pharmacokinetics

At Visits 2, 3, and 4 (Treatment Periods), samples will be collected for determination of plasma insulin and pramlintide concentrations. Venous blood samples will be drawn 10 ± 2 minutes before and immediately prior to dosing (-2 to 0 minutes), and then at 10, 20, 30, 40, 50, 60, 90, 120, 150, 180, 240, 300, and 360 minutes post-dosing (window allowance of ± 2 minutes).

Over the course of the study, approximately 15 blood samples (approximately 4 mL each) will be collected for each subject, for an approximate total volume of 60 mL per subject.

Insulin and pramlintide concentrations will be used to calculate the following PK parameters: C_{max}, T_{max}, and $AUC_{0\text{-}90}$, $AUC_{0\text{-}180}$, $AUC_{0\text{-}360}$.

Detailed instructions for sample collection and preparation will be provided in a separate laboratory manual.

11.3. Safety Parameters

11.3.1. Vital Sign Measurements

Vital signs, including measurements of temperature (ºC), respiration (breathes per minute), HR (beats per minute), and BP (mmHg) will be measured (after 5 minutes seated rest) at the times specified in the Schedule of Assessments. Additional or changes to collection times, or collection using automated devices is permitted, as necessary, to ensure appropriate subject's safety.

Vital signs will be measured according to standard of practice of the site and recorded in the eCRF.

11.3.2. Physical Examination

Full PEs will be performed at Screening and Follow-Up Visits. The PE will include a review of all body systems (excluding breast, pelvic, rectal, and genitourinary) and include measurements

of weight (in kg) and height (in cm; height to be measured only at Screening Visit). Symptom-directed PEs are to be performed at Visits 2, 3, and 4.

Findings at Screening are to be recorded as medical history. Any abnormal or clinically significant findings from the PE must be recorded in the AE eCRF.

11.3.3. Electrocardiogram (12-Lead ECG)

Single, supine 12-lead ECGs should be obtained at Screening per the site's standard practice and before assessment of BP and HR, and prior to blood collections.

11.3.4. Laboratory Assessments

The tests outlined in Table 6 will be performed at the specified time points described in the Schedule of Assessments.

Table 6: Clinical and Safety Related Laboratory Tests

Hematology	Chemistry	Urine	Laboratory
Hematocrit	Albumin	β-hCG	C-peptide
Hemoglobin	Alkaline phosphatase	Drug screen	HbA1c
Platelet count	ALT		Pramlintide
RBC count	AST		Insulin
WBC count	Calcium		
	Creatinine		
	Glucose		
	Potassium		
	Sodium		
	Triglycerides		

The site's laboratory will be used for safety lab analysis. A procedures manual will be provided to each site by the central laboratory. This manual will cover procedures for the collection, processing, and shipping of blood samples, along with the Clinical Laboratory Improvement Act (CLIA) certification and normal ranges for the central laboratory.

The laboratory will provide sites with all supplies needed for collection, processing, and shipping of all blood samples, as well as point-of-care urine pregnancy tests.

11.3.4.1. Drug Screen

A urine drug screening is to be performed at Screening and include cocaine, THC, opiates, amphetamines, methamphetamine, and phencyclidine. Investigator will exercise discretion in allowing of excluding a subject from study participation based on a positive test for one of these additional analytes.

At the investigator's discretion, subjects with a positive result for drugs other than THC (which is allowed at the investigator's discretion) will be allowed to participate if the subject reports use

of a concomitant medication that explains the result (eg, positive urine test for opiates in a subject reporting use of cough syrup containing dextromethorphan).

11.3.4.2. Pregnancy Screen

Female participants of childbearing potential require a negative urine pregnancy test at Screening and Visits 2 through 5.

11.3.5. Local Tolerability

Local tolerability will be assessed at Visits 2, 3, and 4 as follows:

- The investigator will use the modified Draize scale (Appendix 1) to assess erythema and edema formation at the injection site at 30, 90, and 360 minutes (± 2 minutes) after injection of study drug(s). If any scores remain > 1 at the 360-minute evaluation, the subject may leave the clinic but will be instructed to contact a study staff member if the condition fails to resolve. Every effort should be made to ensure that the same investigator will assess the injection sites on the subject at each visit.
- Subjects will complete a 11-point Numeric Rating Scale (NRS) questionnaire regarding injection site discomfort 10 and 30 minutes (± 2 minutes) after injection of study drug (Appendix 2). Question Q1c is to be answered at 360 mins post-study drug injection.

12. SAFETY AND ADVERSE EVENT (AE) REPORTING

12.1. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which is not necessarily required to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether considered related to the medicinal product. Examples of AEs include:

- Abnormal test findings
- Clinically significant symptoms and signs
- Changes in PE findings which are untoward and deemed clinically significant by the investigator
- Allergy/hypersensitivity

The criteria for determining whether an abnormal objective test finding may be reported as an AE are as follows:

- Test result is associated with accompanying symptoms
- Test result requires additional diagnostic testing or medical/surgical intervention
- Test result leads to a change in study dosing or discontinuation from the study significant additional concomitant drug treatment or other treatment
- Test result is considered to be an AE by the investigator or sponsor

Repeat of a test based on an abnormal result in the absence of the above conditions does not constitute an AE. Any abnormal test result determined to be an error does not require reporting as an AE.

A treatment-emergent AE (TEAE) is an AE that either commenced following initiation of study treatment or was present prior to study treatment but increased in frequency or severity following initiation of study treatment.

Standard medical terminology should be used in describing AEs. Informal descriptions should be avoided.

12.1.1. Adverse Events of Special Interest

An adverse event of special interest (AESI) (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an event might require further investigation in order to characterize and understand it (ICH E2F, 2008). AESIs for PRAM9 are as follows: hypoglycemia, nausea, and vomiting.

12.2. Reporting Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the study treatment will be reported with 2 exceptions. Injection site reactions will not be considered an AE unless a skin reaction or pain requires medical intervention.

For all AEs, the investigator must pursue and attempt to obtain information adequate to determine the outcome of the AE and to assess whether it meets the FDA criteria for classification as an SAE, requiring immediate notification to Xeris Pharmaceuticals.

For all AEs, follow-up by the investigator is required until the event resolves or stabilizes at a level acceptable to the investigator to consider it resolved. For unresolved AEs to be considered stable, the Xeris Medical Monitor must concur with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined to be serious (according to the FDA definitions of an SAE) will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

12.3. Reporting Period

For all AEs, the reporting period to Xeris Pharmaceuticals begins from the subject providing informed consent, through the Follow-Up Visit. All AEs will be followed until resolution or the subject is medically stable.

12.4. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose which:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (IME)

Medical and scientific judgment should be exercised in determining whether expedited reporting is appropriate in other situations, such an IME that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm or blood dyscrasias or convulsions which do not result in hospitalization.

12.5. Severity Assessment

On the AE eCRF, the investigator will use the adjectives "mild," "moderate," or "severe" to describe the maximum intensity of the AE. These intensity grades are defined as follows in Table 7, which follows.

Table 7: Adverse Event Severity Assessment

Mild	Does not interfere with subject's usual function
Moderate	Interferes to some extent (< 50%) with subject's usual function
Severe	Interferes significantly (≥ 50%) with subject's usual function

The terms "serious" and "severe" are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event. The event itself, however, may be of relatively minor medical significance. This is not the same as "serious," which is based on subject/event outcome or action criteria. Accordingly, a severe event is not necessarily a serious event.

12.6. Causality Assessment

The investigator will use the following question when assessing causality of an AE to the study drug, where an affirmative answer designates the event as a suspected adverse reaction: "Is there a reasonable possibility that the drug caused the event?" A ''reasonable possibility'' means that there is evidence to suggest a causal relationship between the drug and the AE. The investigator's assessment of causality must be provided for all AEs (related or unrelated). The investigator must record the causal relationship in the eCRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable (Section 12.9). All investigator assessments of AEs must be documented in the source documentation.

12.7. Withdrawal Due to Adverse Events

Withdrawal due to AE should be distinguished from withdrawal due to insufficient response and recorded on the appropriate eCRF. When a subject withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements (see Section 12.9).

12.8. Eliciting Adverse Event Information and Reporting

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. Each study subject will be questioned about AEs. Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow the provisions of Section 12.9.

12.9. Serious Adverse Event Reporting Requirements

If an SAE occurs, Xeris Pharmaceuticals is to be notified within 24 hours of awareness of the event by the investigator. If the SAE is fatal or life-threatening, notification to Xeris

Pharmaceuticals must be made immediately, irrespective of the extent of available AE information. This time frame also applies to follow-up on previously forwarded SAE reports.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, a study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of the event and document the time of first awareness of the AE.

A death occurring during the study, during the study follow-up period, or within 14 days after stopping treatment with test drug must be reported to Xeris Pharmaceuticals or its designee(s) immediately, whether it is considered treatment-related. Initial SAE reports must be followed by detailed descriptions. These should include copies of hospital case records and other documents when requested. Telephone and email reports must be confirmed promptly either by facsimile or by overnight courier or mail.

Under 21 CFR 312.32(c), Xeris Pharmaceuticals or its designee(s) is required to notify FDA and all participating investigators in an IND safety report (ie, 7- or 15-day expedited report) of potentially serious risks from clinical trials or any other source as soon as possible, but no later than 15 calendar days after the safety information is received and a determination is made that the information qualifies for reporting.

12.10. Nonserious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the eCRF. AEs should be reported using concise medical terminology on the eCRFs as well as on the form for collection of the SAE information.

12.11. AE Reporting Requirements to Regulatory Authorities

AE reporting by the sponsor, including suspected serious unexpected adverse reactions, will be carried out in accordance with applicable regulations.

The investigator must notify the IRB/Independent Ethics Committee (IEC) of the occurrence of any SAE, in writing, as soon as is practicable and in accordance with local regulations. A copy of this notification must be provided to Xeris Pharmaceuticals or its designee.

In the event of an SAE that meets the criteria for expedited reporting, an SAE report will be prepared for submission to the FDA and any other applicable authorities by Xeris Pharmaceuticals or its designee.

12.12. Pregnancy

The active pharmaceutical products in Xeris Pharmaceuticals' PRAM9 pramlintide-insulin are in Pregnancy Category B. Female subjects of childbearing potential will be tested (urine) for pregnancy at the Screening Visit. A woman is considered to be of childbearing potential if she is post menarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Any subject found to be pregnant at the Screening Visit (Visit 1) will not be randomized to a treatment sequence. Any subject who is found to be pregnant at one of the treatment visits will be withdrawn from the study immediately and no further study treatments will be given.

Pregnancy at the Follow-Up Visit will be noted, but the visit will be completed. Any pregnancy in a subject who received at least one dose of study drug will be followed until resolution (ie, birth or voluntary or spontaneous termination of the pregnancy). Any pregnancy outcome that meets the criteria for an SAE will be reported as an SAE.

12.13. Subject Monitoring

Subjects will be monitored for AEs throughout the study by the study unit staff. The principal investigator or designated sub-investigator will be on site for drug administration and until 6 hours after administration of study drug to the last subject. The principal investigator or designated sub-investigator will also be available (eg, "on call") for the remainder of the treatment visit. If necessary, a physician, either at the study site or in a nearby hospital, will administer treatment for any AEs.

Safety parameters, including laboratory results, will be assessed by the principal investigator or his delegate using the site's criteria for clinical laboratory acceptance ranges as suggested guidelines in making the medical assessment.

Scheduled safety measurements will be repeated according to appropriate SOPs or upon request from a physician. Any abnormal repeated measurement will be evaluated by a physician and repeated if judged necessary. Further action may be taken on the physician's request.

Subjects will be advised to notify their health care professionals (eg, physician, dentist, and/or pharmacist) that they are participating in a clinical research study of a drug called PRAM9 before taking any medicines or undergoing any medical procedure.

13. DATA ANALYSIS AND STATISTICAL METHODS

13.1. General Approach

Detailed methodology for PK, PD, descriptive and inferential statistical analyses of the data collected in this study will be documented in the SAP.

Descriptive statistics will be used to summarize the clinical and laboratory data. Continuous data will be represented by number of subjects, mean, median, standard deviation (SD), and range, while categorical variables will be presented by number and percentage of subjects. Baseline values are determined by the last evaluable measurement before study drug injection in each treatment period. Point estimates may be derived with 2-sided 95% confidence intervals. An analysis of variance (ANOVA) will be performed to evaluate effect of study treatment and period. There is no reason to think that sequence will have an effect on the outcome.

13.1.1. Sample Size Calculation

Up to 21 subjects will be qualified for the study and will complete the overnight stay as part of Visit 2 to ensure that 18 total subjects are randomized to a study treatment sequence. The target of 18 randomized subjects is considered sufficient to allow an initial evaluation of PK/PD response and safety of these novel pramlintide-insulin formulations. Formal sample sizes were not conducted.

13.2. Primary Endpoint Analysis

All PK/PD analyses will be performed using the PK/PD analysis population.

The following variable will be compared among the treatments for PD purposes:

- $AUC_{0\text{-}180}$ (mg/dL × minutes) for plasma glucose > 180 mg/dL

13.3. Secondary Endpoint Analysis

13.3.1. Safety Endpoints

All safety analyses will be performed using the safety population.

The following variables will be compared between the treatments for safety purposes:

- Incidence of AEs and SAEs
- Change from baseline in laboratory safety variables
- Change from baseline in vital sign measurements
- Change from baseline in body weight
- Local tolerability assessments, including:
    - Incidence of erythema and or edema formation at site of injection assessed using the Draize scale (Appendix 1).
    - Subjective injection site discomfort as reported by subjects using a 11-point NRS (Appendix 2).

13.3.2. Pharmacodynamic and Pharmacokinetic Endpoints

All PK/PD analyses will be performed using the PK/PD analysis population.

The following variables will be compared between the treatments for PD and PK purposes:

- Mean proportional time with plasma glucose > 180 mg/dL for 0-180 minutes
- Mean proportional time after glucose challenge for plasma glucose levels between 126 to 180 mg/dL
- Mean proportional time* for plasma glucose < 70 mg/dL
- Mean proportional time* for plasma glucose < 54 mg/dL
- Mean proportional time* for plasma glucose > 180 mg/dL
- Mean proportional time* for plasma glucose > 250 mg/dL
- $AUC_{0\text{-}360}$ (mg/dL × minutes) for plasma glucose > 180 mg/dL
- $AUC_{0\text{-}360}$ (mg/dL × minutes) for plasma glucose > 250 mg/dL
- $AOC_{0\text{-}360}$ (mg/dL × minutes) for plasma glucose < 70 mg/dL
- $AOC_{0\text{-}360}$ (mg/dL × minutes) for plasma glucose < 54 mg/dL
- Plasma glucose C_{max} and T_{max}
- Plasma levels ($AUC_{0\text{-}90\ min}$, $AUC_{0\text{-}180\ min}$, $AUC_{0\text{-}360\ min}$, C_{max}, and T_{max}) for both insulin and pramlintide

* *Mean proportional time during 0 to 360 minutes post-injection of study drug.*

13.4. Adverse Events

All safety analyses will be performed using the safety analysis population. TEAEs will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA®) system organ class (SOC) and preferred term (PT), classified from verbatim terms. Listings of all AEs (including non-TEAEs), treatment-emergent SAEs, and TEAEs leading to study drug discontinuation will be provided by treatment group, subject, verbatim term, MedDRA SOC and PT, start and end dates, seriousness, severity, relationship to study drug, action taken with study treatment, frequency, and outcome.

AEs will be summarized overall by the number and percentage of subjects who experienced at least one AE of the following categories in each treatment group: any AE, any TEAE, any drug-related TEAE, any severe or life-threatening TEAE, any serious TEAEs, any drug-related SAE, any SAE leading to death, any TEAE leading to premature discontinuation of study drug, and any SAE leading to premature study drug discontinuation.

The number and percentage of subjects reporting a TEAE in each treatment group will be tabulated by SOC and PT; by SOC, PT, and severity (mild, moderate, and severe/life-threatening/death); and by SOC, PT, and relationship (unrelated or related to study drug).

The numbers and percentages of subjects reporting an SAE or reporting a TEAE leading to premature discontinuation of study drug in each treatment group will be summarized by SOC and PT.

13.5. Laboratory Safety Assessments

Laboratory values will be flagged if outside the normal range. A listing of clinically significant abnormal values will be presented. The individual values will be listed indicating values outside normal range. Laboratory assessments will be summarized at Screening and at the end of the study. Significant deviations/changes from the Screening Visit to the Follow-Up Visit will be documented as AEs if the investigator judges these as being clinically significant.

13.6. Physical Examination

Subjects with any findings in the PE evaluation at Screening will be listed on the Medical History CRF. Changes to PE from Screening to end of trial will be recorded as AEs if they meet the definition of an AE or if the investigator judges these changes as being clinically significant.

13.7. Vital Signs and Body Weight

Vital signs will be summarized by descriptive statistics. Changes from pre- to post-dosing at each of the Treatment Period Visits will be conducted. If there are changes that meet the definition of an AE or if the investigator judges these as being clinically significant, they will be recorded on the eCRF as an AE.

Observed values as well as change from baseline data will be summarized descriptively in tabular format. The pre-study drug collections of vital signs at each Treatment Period will be considered as baseline.

13.8. Electrocardiogram

Any clinically significant ECG results will be recorded and followed as appropriate. The investigator's evaluations will be summarized in a data listing.

13.9. Local Tolerability

The incidence of any injection site discomfort (score > 0 on the ordinal rating scale) will be analyzed descriptively. The incidences of erythema and edema will be analyzed in a similar manner. Descriptive statistics will be provided for time of onset and duration (of discomfort) and discomfort description (ie, pain, irritation, itching, etc.).

Mean NRS scores will be compared between the treatments.

13.10. Prior and Concomitant Medications

Prior and concomitant medications will be mapped to a World Health Organization (WHO) drug classification. The number and percent of subjects taking concomitant medications will be summarized.

13.11. Subgroup Analysis

No subgroup analyses are planned.

13.12. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all subjects overall and by Treatment Period. Summary statistics (eg, number of subjects, mean, median, SD and range) will be generated for continuous variables (eg, age and weight) and the number and percentage of subjects within each category will be presented for categorical variables (eg, sex, ethnicity, and race).

13.13. Subject Disposition

A detailed description of subject disposition will be provided and will include the following:

- A summary of overall subject enrollment status (consented, screened, screen failures, randomized, replaced)
- A summary of subjects who discontinued the study
- An account of identified protocol deviations

All subjects who are consented for the study will be accounted for in the summation. The number of subjects who do not qualify for certain analysis populations and who did not complete all 3 treatment periods will also be summarized.

14. DATA HANDLING, RECORD KEEPING, MONITORING AND AUDITS

14.1. Case Report Forms/Electronic Data Record

Data collection is the responsibility of the clinical study staff under the supervision of the investigator. During the study, the investigator will maintain complete and accurate documentation for the study.

As defined in the ICH Guidelines for Good Clinical Practice (E6(R2)), Section 1.52, source documents may include: original documents, data, and records (eg, hospital records, clinical and office charts, laboratory notes, memoranda, participant's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies, or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study).

As used in this protocol, the term CRF is understood to refer to an electronic data record, ie, an eCRF. An eCRF is required and should be completed for each individual subject. The completed original eCRFs are the property of Xeris Pharmaceuticals and should not be made available in any form to third parties, except for authorized representatives of Xeris Pharmaceuticals or appropriate regulatory authorities, without written permission from Xeris Pharmaceuticals.

Queries generated by Data Management and within the EDC will be sent to the study site for resolution. The investigator is responsible for the review and approval of all responses to eCRF queries.

14.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Xeris Pharmaceuticals, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, eCRFs and hospital records), all original signed informed consent documents, copies of all eCRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to the ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The investigator must obtain Xeris Pharmaceuticals' written permission before disposing of any records, even if retention requirements have been met.

14.3. Monitoring

Monitoring and auditing procedures developed by Xeris Pharmaceuticals and/or its designee will be implemented to ensure compliance with FDA and ICH GCP and Good Laboratory Practices (GLP) guidelines.

The Xeris Pharmaceuticals' designated representative (the monitor or auditor) will contact the investigator and conduct regular visits to the clinical site. The monitor will be expected and

allowed to verify the investigator's qualifications, to inspect clinical site facilities, and to inspect study records, including proof of IRB/IEC review, with the stipulation that subject confidentiality will be maintained in accordance with local and federal regulations, including Health Insurance Portability and Accountability Act HIPAA) requirements. The monitor will also be responsible for confirming adherence to the study protocol, inspecting eCRFs and source documents, and ensuring the integrity of the data. eCRFs will be checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents, including laboratory test reports and other subject records. Instances of missing or uninterpretable data will be resolved in coordination with the investigator.

The monitor/auditor will also investigate any questions concerning adherence to regulatory requirements. Any administrative concerns will be clarified and followed. The monitor will maintain contact with the site through frequent direct communications with the study site by email, telephone, facsimile, and mail. The investigator and all other site personnel agree to cooperate fully with the monitor and will work in good faith with the monitor to resolve all questions raised, and difficulties detected by the monitor.

14.4. Audits and Inspections

The investigator understands that regulatory authorities, the IRB/IEC, and/or Xeris Pharmaceuticals or their designees have the right to access all eCRFs, source documents, and other study documentation for on-site audit or inspection and will retain this right from the start of the study to at least 2 years after the last approval of a marketing application or for at least 2 years after clinical development of the study drug for the indication being studied has been discontinued. The investigator is required to guarantee access to these documents and to cooperate with and support such audits and inspections.

15. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Xeris Pharmaceuticals or its agent will conduct periodic visits to ensure that the protocol and Good Clinical Practices are being followed. The monitor may review source documents to confirm that the data recorded on eCRFs is accurate. The investigator and institution will allow Xeris Pharmaceuticals' monitor or its designee, and appropriate regulatory authorities, direct access to source documents to perform this verification.

The study site may be subjected to review by the Institutional Review Board and/or to quality assurance audits performed by Xeris Pharmaceuticals or its designee, and/or to inspection by appropriate regulatory authorities. It is important that the investigator and study staff are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

16. ETHICAL CONSIDERATIONS

16.1. Conduct

The investigator will ensure that the study described in this protocol is conducted in full conformance with those principles, the protocol, current FDA regulations, ICH Good Clinical Practices (GCP) guidelines, GLP guidelines, local ethical and regulatory requirements, including the Federal Food, Drug and Cosmetic Act, US applicable Code of Federal Regulations (Title 21), any IRB/IEC requirements relative to clinical studies.

Should a conflict arise, the investigator will follow whichever law or guideline affords the greater protection to the individual subject. The investigator will also ensure thorough familiarity with the appropriate administration and potential risks of administration of the study drug, as described in this protocol and the Investigator's Brochure, prior to the initiation of the study.

16.2. Institutional Review Board and Ethics Committee

The IRB/IEC must be a properly constituted board or committee operating in accordance with 21 CFR Part 56, "Institutional Review Boards." This protocol, any protocol amendments, the associated informed consent forms, and the informed consent procedures must be submitted to the IRB for review and approved before the enrollment of any subject into the trial. Study drug may not be shipped to the investigator until Xeris Pharmaceuticals has received a copy of the letter or certificate of approval from the IRB/IEC for the protocol and any protocol amendments.

All types of subject recruitment or advertising information must be submitted to Xeris Pharmaceuticals or its designee and to the IRB/IEC for review and approval prior to implementation. IRB approval of any protocol amendments must be received before any of the changes outlined in the amendments are put into effect, except when the amendment has been enacted to eliminate a potential hazard to study subjects. In such cases, the chair of the IRB/IEC should be notified immediately, and the amendment forwarded to the IRB/IEC for review and approval.

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the investigator file. Copies of IRB/IEC approvals should be forwarded to Xeris Pharmaceuticals.

16.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures. Subject names, address, date of birth and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Xeris Pharmaceuticals to de-identify the study subject. In the case of data transfer, Xeris Pharmaceuticals will maintain confidentiality and protection of subject personal data.

The informed consent document used in this study, and any changes made during the study, must be prospectively approved by both the IRB/IEC and Xeris Pharmaceuticals before use. The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a study staff designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document. Receipt of written informed consent will be documented in each subject's or potential subject's eCRF. The signed informed consent document must remain on file at the study site and be available for verification by the study monitors at all times.

16.4. Subject Recruitment

All types of subject recruitment or advertising information must be submitted to Xeris Pharmaceuticals or its designee and to the IRB/IEC for review and approval prior to implementation. Advertisements approved by the IRB/IEC may be used as recruitment procedures.

16.5. Reporting of Safety Issues and Serious Breaches of the Protocol

In the event of any prohibition or restriction imposed (ie, clinical hold), or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Xeris Pharmaceuticals should be notified immediately. In addition, the investigator will inform Xeris Pharmaceuticals immediately of any urgent safety measures taken by the investigator to protect study subjects against any immediate hazard, and of any serious breaches of this protocol.

During study conduct, Xeris Pharmaceuticals or its agent will conduct periodic visits to ensure that the protocol and GCPs are being followed. The monitor may review source documents to confirm that the data recorded on eCRFs is accurate. The investigator and institution will allow Xeris Pharmaceuticals' monitor or its designee, and appropriate regulatory authorities, direct access to source documents to perform this verification.

The study site may be subjected to review by the Institutional Review Board and/or to quality assurance audits performed by Xeris Pharmaceuticals or its designee, and/or to inspection by appropriate regulatory authorities. It is important that the investigator and study staff are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

17. PROCEDURES FOR MODIFYING THE PROTOCOL OR TERMINATING THE STUDY

17.1. Protocol Modifications and Deviations

The principal investigator must sign this protocol and its amendments (if any) before initiating the study at a particular site. The investigator will make all reasonable efforts to comply with the written protocol. Protocol modifications to ongoing studies that affect the safety of subjects or that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosing, study assessments, the number of subjects exposed to test drug, or subject selection criteria must be made only after consultation between Xeris and the investigator. All protocol modifications must be reviewed and approved by the IRB/IEC before the revised protocol can be implemented. Emergency revisions that eliminate an apparent hazard to subjects do not require preapproval by the IRB/IEC. However, the IRB/IEC must be notified in writing as soon as possible after the modification has been made. A copy of this communication must be forwarded to Xeris. All departures from the protocol must be fully documented in the source documents and the eCRFs of the subjects involved. Protocol deviations will be tracked in an electronic system implemented by the sponsor or designated representative.

17.2. Study Termination

The study may be prematurely terminated at any time because of a regulatory authority decision, change in opinion of the IRB/Ethics Committee, safety problems resulting in subject deaths, or at the discretion of Xeris Pharmaceuticals or the principal Investigator.

Circumstances that may warrant premature study termination include, but are not limited, to the following:

- Determination of unexpected, significant, or unacceptable risk to subjects,
- Failure to enter subjects at an acceptable rate,
- Insufficient adherence to the requirements of the protocol,
- Insufficient provision of complete and evaluable data, or
- Plans to modify, suspend, or discontinue development of the study drug.

If the study is prematurely terminated or discontinued, Xeris Pharmaceuticals will promptly notify the Investigators and document the reason for study termination. Specific procedures for termination will be arranged by the Sponsor in coordination with the Investigators. After notification, the Investigators must contact all participating subjects within 7 days. All study materials must be collected and all CRFs completed to the greatest extent possible, and all study materials must be returned to Xeris Pharmaceuticals or its designee within an additional 28 days.

18. LIST OF REFERENCES

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19. APPENDICES

Appendix 1. DRAIZE SCALE

Study Personnel Instructions: The modified Draize Scale as shown in the table below will be used for physical examination/rating of abnormalities at the injection site.

The injection site should be examined for formation of both erythema and edema and results recorded in the eCRF. Evaluations of the injection site should be performed at 30, 90, and 360 minutes (± 2 minutes) post-treatment.

If any scores remain > 1 at the 360-minute evaluation, the subject may leave the clinic but will be instructed to contact study staff if the condition fails to resolve.

Erythema Formation		**Edema Formation**	
Description	**Score**	**Description**	**Score**
No erythema	0	**No edema**	0
Very slight erythema Barely perceptible	1	**Very slight edema** Barely perceptible	1
Well defined erythema	2	**Slight edema** (edges of area well defined by definite raising)	2
Moderate erythema	3	**Moderate edema** Raised approx. 1 mm	3
Severe erythema Beet redness to slight eschar formation	4	**Severe edema** Raised more than 1 mm and beyond exposure area	4

Sources:

Guidance for Industry, Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). December 1999. Appendix A.

Draize JH, Woodard G, Calvery HO. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *Journal of Pharmacology and Experimental Therapeutics.* November 1944;82(3):377-390.

Appendix 2. INJECTION SITE DISCOMFORT ASSESSMENT

Numeric Rating Scale (NRS) for Injection Site Discomfort

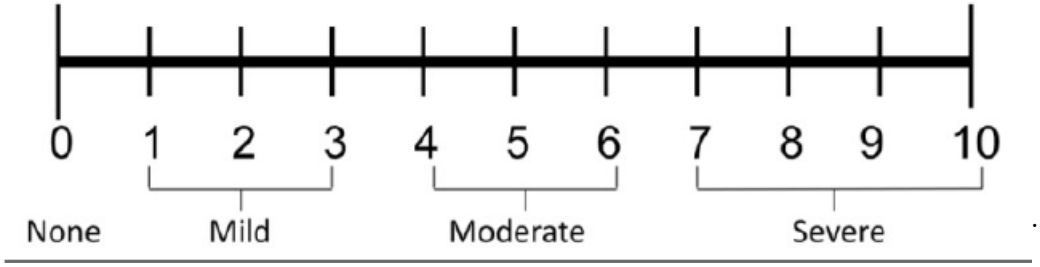
Investigative Site Instructions: The subject should complete the 11-point NRS for Injection Site Discomfort at 10 and 30 minutes (± 2 minutes) after injection of study drug. The subject will complete the NRS by drawing a circle around the number corresponding to the perceived intensity (severity) of discomfort according to the instructions below. The goal is for the subject to report the amount of discomfort, if any, remaining at each time point, as opposed to reporting the transient pain associated with needle insertion.

Note: If a subject is unable to physically complete the questionnaire, the subject will indicate the number on the NRS corresponding to their level of discomfort, and study staff will circle it. Documentation will be provided on each completed questionnaire as to who completed the form.

Subject Instructions: Ignoring any pain from insertion of the needle, please draw a circle around the number on the scale below that corresponds to the intensity (severity) of any discomfort you are feeling **right now** at the study drug injection site.

For example, if you are currently feeling no discomfort, you should circle the number "0" on the left end of scale. If you are currently feeling the worst discomfort possible, you should circle number "10" on the right end of the scale.

NRS



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Injection Site Discomfort Description and Duration Questionnaire

Study Personnel Instructions: Question 1a should be completed by the subject at **10 ± 2** minutes after injection of study drug. If response is anything other than "None," the subject should also answer Question 1b. All subjects should also answer Question 1c at 30 ± 2 minutes post-injection.

The goal is for the subject to report the qualitative nature and duration of discomfort, if any, associated with injection of study drug, ignoring any transient pain associated with needle insertion.

Note: If a subject is unable to physically complete the questionnaire, the subject will provide verbal responses, which will be recorded on the questionnaire by study staff. Documentation will be provided on each completed questionnaire as to who completed the form.

Subject Instructions: Please answer question 1a and 1c, and, if applicable to you, question 1b. In answering these questions, you should ignore any pain from insertion of the needle.

*1a. How would you describe any discomfort you felt from the study drug? (Check **all** that apply):*

_____None (**Please ignore question 1b.**)

_____Pain (eg, throbbing, soreness, muscle ache)

_____Itching

_____Tingling, twitching, or numbness

_____Irritation (eg, burning, stinging)

Other or additional comments:_____

1b. About how long did the discomfort last after the injection? (Check one):

_____Less than 1 minute

_____1-2 minutes

_____3-5 minutes

_____6-9 minutes

_____at least 10 minutes (**Please complete question 1c before leaving the clinic.**)

1c. In total, how long did the discomfort last after the injection? (Please enter a number below):

_____ Minutes

Reference:

McCaffery M, Beebe A, et al. Pain: Clinical Manual for Nursing Practice. 1989. Mosby:St Louis.

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APPENDIX 3. INSULIN TO CARBOHYDRATE RATIO

Insulin-to-Carb Ratio

This ratio tells you how many grams of carb are covered by one unit of bolus insulin.

Use your insulin-to-carb ratio every time you eat a meal. You may use it with snacks if advised by your provider.

The starting insulin to carb ratio is calculated by using the **450 Rule**. Here's how it works:

- Determine your total daily dose (TDD) of insulin.
    - This includes both your meal time and basal insulin used within a day.
    - TDD = _____
- Divide 450 by the TDD to get your ratio.
    - Insulin Carbohydrate Ratio = 450/TDD = _____
- To use the ratio, add up the grams of carb that you plan to eat at your meal, and divide this number by your ratio to obtain your regular insulin dose.

Example 1:
Someone's TDD = 45 units (e.g., the total amount of say Humalog and Lente insulins they used per day). 450 divided by 45 = 10. Therefore, 10 grams of carbohydrate are covered by each unit of regular insulin.

The insulin to carbohydrate has a ratio of 1:10, meaning that 1 unit of regular insulin "covers" 10 grams of carbohydrate.

If you will be eating 70 grams of carbohydrate, then divide 70 by 10, which equals 7. This means that you would take 7 units of insulin to cover the 70 grams of carb.

Example 2:
Someone's TDD = 50 units (e.g., the total amount of say Humalog and Lente insulins they used per day). 450 divided by 50 equals 9. Therefore, 9 grams of carbohydrate are covered by each unit of regular insulin.

The insulin to carbohydrate the starting insulin to carb ratio is 1:9, meaning that 1 unit of regular insulin "covers" 9 grams of carbohydrate.

If you will be eating 72 grams of carbohydrate, then divide 72 by 9, which equals 8. This means that you would take 8 units of insulin to cover the 72 grams of carb.

Based upon your ratio, the accompanying tables may be helpful to estimate the regular insulin mealtime dose:

Insulin to Carbohydrate Ratio: ½:10 ½ unit of insulin for every 10 grams of carbohydrate	
Grams of Carbohydrates	Units of Insulin
6-15	0.5
16-25	1
26-35	1.5
36-45	2
46-55	2.5
56-65	3
66-75	3.5
76-85	4
86-95	4.5
96-105	5
106-115	5.5

Insulin to Carbohydrate Ratio: ½:12 ½ unit of insulin for every 12 grams of carbohydrate	
Grams of Carbohydrates	Units of Insulin
10-18	0.5
19-31	1
32-42	1.5
43-56	2
57-68	2.5
69-81	3
82-93	3.5
94-106	4
107-118	4.5
119-130	5
131-148	5.5

Insulin to Carbohydrate Ratio: ½:15 ½ unit of insulin for every 15 grams of carbohydrate	
Grams of Carbohydrates	Units of Insulin
7-22	0.5
23-37	1
38-52	1.5
53-67	2
68-82	2.5
83-97	3
98-112	3.5
113-127	4
128-142	4.5
143-157	5
158-172	5.5

Insulin to Carbohydrate Ratio: ½:20 ½ unit of insulin for every 20 grams of carbohydrate	
Grams of Carbohydrates	Units of Insulin
11-30	0.5
31-50	1
51-70	1.5
71-90	2
91-110	2.5
111-130	3
131-150	3.5
151-170	4
171-190	4.5
191-210	5

Insulin to Carbohydrate Ratio: ½:25 ½ unit of insulin for every 25 grams of carbohydrate	
Grams of Carbohydrates	Units of Insulin
12-38	0.5
39-63	1
64-88	1.5
89-113	2
114-138	2.5
139-163	3
164-188	3.5
189-213	4
214-238	4.5
239-263	5
264-288	5.5

Insulin to Carbohydrate Ratio: ½:30 ½ unit of insulin for every 30 grams of carbohydrate	
Grams of Carbohydrates	Units of Insulin
15-45	0.5
46-75	1
76-105	1.5
106-135	2
136-165	2.5
166-195	3
196-225	3.5
226-255	4
256-285	4.5
286-315	5
316-345	5.5

Insulin to Carbohydrate Ratio: ½:35 ½ unit of insulin for every 30 grams of carbohydrate	
Grams of Carbohydrates	Units of Insulin
18-52	0.5
53-87	1
88-122	1.5
123-157	2
158-192	2.5
193-227	3
228-262	3.5
263-297	4
298-332	4.5
333-367	5
368-402	5.5

Insulin to Carbohydrate Ratio: ½:40 ½ unit of insulin for every 40 grams of carbohydrate	
Grams of Carbohydrates	Units of Insulin
21-60	0.5
61-100	1
101-140	1.5
141-180	2
181-220	2.5
221-260	3
261-300	3.5
301-340	4
341-380	4.5
381-420	5
421-460	5.5

Insulin to Carbohydrate Ratio: 1:5 1 unit of insulin for every 5 grams of carbohydrate	
Grams of Carbohydrates	Units of Insulin
3-7	1
8-12	2
13-17	3
18-22	4
23-27	5
28-32	6
33-37	7
38-42	8
43-47	9
48-52	10
53-57	11
58-62	12
63-67	13
68-72	14
73-77	15
78-82	16
83-87	17
88-92	18

Insulin to Carbohydrate Ratio: 1:6 1 unit of insulin for every 6 grams of carbohydrate	
Grams of Carbohydrates	Units of Insulin
3-9	1
10-15	2
16-21	3
22-27	4
28-33	5
34-39	6
40-45	7
46-51	8
52-57	9
58-63	10
64-69	11
70-75	12
76-81	13
82-87	14
88-93	15
94-99	16
100-105	17
106-111	18

Insulin to Carbohydrate Ratio: 1:7 1 unit of insulin for every 7 grams of carbohydrate	
Grams of Carbohydrates	Units of Insulin
4-10	1
11-17	2
18-24	3
25-31	4
32-38	5
39-45	6
46-52	7
53-59	8
60-66	9
67-73	10
74-80	11
81-87	12
88-95	13
96-102	14
103-109	15
110-116	16
117-124	17
125-132	18

Insulin to Carbohydrate Ratio: 1:8 or 2:15 1 unit of insulin for every 8 grams of carbohydrate, or 2 units of insulin for every 15 grams of carbohydrate	
Grams of Carbohydrates	Units of Insulin
5-11	1
12-19	2
20-27	3
28-35	4
36-43	5
44-51	6
52-59	7
60-67	8
68-74	9
75-83	10
84-89	11
90-99	12
100-104	13
105-115	14

Insulin to Carbohydrate Ratio: 1:10 1 unit of insulin for every 10 grams of carbohydrate	
Grams of Carbohydrates	Units of Insulin
6-15	1
16-25	2
26-35	3
36-45	4
46-55	5
56-65	6
66-75	7
76-85	8
86-95	9
96-105	10
106-115	11
116-125	12
126-135	13
136-145	14

Insulin to Carbohydrate Ratio: 1:12 1 unit of insulin for every 12 grams of carbohydrate	
Grams of Carbohydrates	Units of Insulin
10-18	1
19-30	2
31-42	3
43-54	4
55-66	5
67-78	6
79-90	7
91-102	8
103-114	9
115-126	10
127-138	11
139-150	12
156-162	13

Insulin to Carbohydrate Ratio: 1:15 1 unit of insulin for every 15 grams of carbohydrate	
Grams of Carbohydrates	Units of Insulin
7-22	1
23-37	2
38-52	3
53-67	4
68-82	5
83-97	6
98-112	7
113-127	8

Insulin to Carbohydrate Ratio: 1:18 1 unit of insulin for every 18 grams of carbohydrate	
Grams of Carbohydrates	Units of Insulin
9-27	1
28-45	2
46-63	3
64-81	4
82-99	5
100-117	6
118-135	7
136-153	8

Insulin to Carbohydrate Ratio: 1:20 1 unit of insulin for every 20 grams of carbohydrate	
Grams of Carbohydrates	Units of Insulin
11-30	1
31-50	2
51-70	3
71-90	4
91-110	5
111-130	6
131-150	7
151-170	8

Insulin to Carbohydrate Ratio: 1:25 1 unit of insulin for every 25 grams of carbohydrate	
Grams of Carbohydrates	Units of Insulin
10-35	1
36-60	2
61-85	3
86-110	4
111-159	5
160-185	6

Insulin to Carbohydrate Ratio: 1:30 1 unit of insulin for every 30 grams of carbohydrate	
Grams of Carbohydrates	Units of Insulin
15-45	1
46-75	2
76-105	3
106-135	4
136-165	5
166-195	6

Insulin to Carbohydrate Ratio: 1:35 1 unit of insulin for every 35 grams of carbohydrate	
Grams of Carbohydrates	Units of Insulin
17-52	1
53-87	2
88-122	3
123-157	4
158-192	5
192-227	6

Insulin to Carbohydrate Ratio: 1:40 1 unit of insulin for every 40 grams of carbohydrate	
Grams of Carbohydrates	Units of Insulin
21-60	1
61-100	2
101-140	3
141-180	4
181-220	5
221-260	6

Insulin to Carbohydrate Ratio: 1:45 1 unit of insulin for every 45 grams of carbohydrate	
Grams of Carbohydrates	Units of Insulin
22-68	1
69-113	2
114-158	3
159-204	4
205-249	5
250-294	6

Source:

Bell KJ, King BR, Shafat A, Smart CE. The relationship between carbohydrate and the mealtime insulin dose in type 1 diabetes. J Diabetes and Its Complications. 2015;29:1323-29.

King AB, Kuroda A, Matsuhisa M, Hobbs T. A review of insulin-dosing formulas for continuous subcutaneous insulin infusion (CSII) for adults with type 1 diabetes. 2016;16(83):1-8.

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Document Approvals

Approved Date: 12/13/2019, PRO-19-00045 Version 4

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