XP-8121-120 Protocol Cover Page

Study Title:	A Phase 2, Multicenter, Non-Randomized, Open-Label, Single Arm, Self-controlled Study of XP-8121 For the Treatment of Adult subjects with Hypothyroidism
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1. TITLE PAGE

A Phase 2, Multicenter, Non-Randomized, Open-Label, Single Arm, Self-controlled Study of XP-8121 For the Treatment of Adult Subjects with Hypothyroidism

Study Number:	XP-8121-120
Phase:	2
IND Number:	153502
Study Drug:	XP-8121 (Levothyroxine Sodium)
Sponsor:	Xeris Pharmaceuticals, Inc. Chicago, IL USA 60607
Medical Monitor:	Valentina Conoscenti, MD
Date of Protocol:	Version 1.0: 06 February 2023 Amendment 1 (Version 2.0): 08 March2023 Amendment 2 (Version 3.0): 07 May 2023
GCP Statement:	This study is to be performed in full compliance with International Council for 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.

SUMMARY OF REVISIONS: PROTOCOL VERSION 2.0 TO VERSION 3.0

This protocol was amended to clarify information in the protocol in response to an advice/information request by the Division of General Endocrinology at the Center for Drug Evaluation and Research at the United States Food and Drug Administration (US FDA) dated 20 April 2023. Additional clarifications have been made to support consistent conduct of the study.

Affected Sections/Tables	**Summary of Revisions Made**	**Rationale**
General	Minor formatting updates and clarifications. Updated wording to increase specificity of procedures and timing.	Administrative update.
Section 1	Added new protocol version. Updated address ZIP code.	Administrative update.
Summary of Revisions Appendix F	Replaced description of changes made to the protocol with the changes included for Protocol Version 2.0 to Version 3.0. Moved prior revisions for Protocol Version 1.0 to Version 2.0 to Appendix F.	Administrative update.
Section 2	Synopsis was updated to align with changes in main body of protocol.	Administrative update.
Table 2	Added footnote ‘n’ to the procedure of “XP-8121 administration” and removed from the individual assessments.	Clarification of guidance on the timing of XP-8121 dose administration.
Table 2, footnote ‘c’	Included a reference to the weekly visits to be conducted every 7 days. Clarified that assessments at the weekly visits includes the administration of XP-8121.	Procedural clarification.
Table 2, footnote ‘g’ Section 8.1, Inclusion Criterion (IC) #8 Section 12.3 Section 12.8.4 Appendix B	Specified that heart rate/pulse is measured in triplicate and that the average resting heart rate/pulse is to be used to assess eligibility. Clarified terminology to refer to heart rate/pulse.	Clarified terminology in protocol for heart rate/pulse as the same measurement and that it should be performed in triplicate.

Affected Sections/Tables	Summary of Revisions Made	Rationale
Table 2, footnote 'i' Table 2, footnote 'o' Section 7.1 Section 7.4.2 Section 8.1, IC#3 Section 8.1, IC#4 Section 11.1 Section 11.3.1	Included the study reference ranges for free T4 and TSH, as applicable.	Recommended FDA update.
Table 2, footnote 'j'	Switched location of footnote to 'XP-8121 administration' rather than 'Free and total T4'.	Administrative update.
Table 2, footnote 'k' Section 8.2, Exclusion Criterion (EC) #23 Section 12.8.8	Aligned language with the update to the EC#23 exception for prescription benzodiazepines.	Clarification of eligibility criteria, as prescription benzodiazepines are not a prohibited medication.
Table 2, footnote 'n'	Clarified information referencing the dose titration and adjustment criteria.	Administrative update.
Table 2, footnote 'n' Section 10.5 Appendix A	Updated with the timing of the administration of XP-8121. It is to occur every 7 days, within ±2 hours of the time of administration of the XP-8121 SC initiation dose.	Clarification of guidance on the timing of XP-8121 dose administration.
Section 5.5 Section 7.1 Section 7.4.1 Section 7.4.2 Section 7.4.3 Section 11.2 Section 13.5.1 Section 13.5.1.1 Appendix A	Clarified description of dose conversion to specify that the dose conversion factor will be based on µg of the daily oral levothyroxine and weekly XP-8121 SC.	Recommended FDA update.
Section 6.1.3	Clarified description of exploratory objectives to include both the Titration and Maintenance Periods	Recommended FDA update.

Affected Sections/Tables	Summary of Revisions Made	Rationale
Section 7.1	Included a summary of the total duration of treatment at the stable dose of XP-8121 (eg, 6 weeks).	Clarification of study design to address FDA recommendation/comment.
Section 8.2, EC#25	Included additional guidance for exclusion of patients with a history of clinically significant or uncontrolled conditions that could jeopardize the safety of the subject or impact the validity of the study results.	Recommended FDA update.
Section 8.4	Clarified the description of the subject withdrawal criteria.	Clarified to improve clarity of the unique withdrawal criteria in this study related to achieving an adequate and tolerable replacement dosage.
Section 11.1	Included guidance for potential to re-screen subjects with Medical Monitor approval.	Updated to include procedure for the management of re-screening potential subjects.
Section 11.1	Included guidance to align with the eligibility requirement for normalized TSH for at least 3 months prior to Screening (documented by local laboratory).	Procedural clarification.
Section 11.1 Section 12.8.7	Included guidance for the potential to repeat Screening visit laboratory assessments for clinical safety with Medical Monitor approval.	Updated to include procedure for management of potential subjects with abnormal Screening visit laboratory assessments for clinical safety.
Section 12.8.4	Clarified that each of the triplicate measurements for blood pressure and heart rate are to be entered in the eCRF.	Procedural clarification.
Section 13.4	Clarified definition of Completer Population to include subjects who exhibit normalized TSH throughout the Maintenance Period.	Recommended FDA update.

Affected Sections/Tables	Summary of Revisions Made	Rationale
Section 13.5.1.1	Updated to clarify population to be included in the analysis of the primary endpoints will be those in the Completer population with primary hypothyroidism only. And to reference that additional sensitivity analysis (if applicable) will be described in the statistical analysis plan.	Clarification to align with FDA recommendation/comment.
Section 13.5.2	Updated endpoints to include a separate endpoint for the proportion of subjects enrolled with normalized TSH throughout the Maintenance Period. Endpoint clarified to indicate that the blood thyroid hormone concentrations would be assessed during the Titration and Maintenance Periods.	Clarification to align with FDA recommendation/comment.
Section 13.5.2.1	Clarified that the secondary endpoints will be analyzed for the safety population for subjects with hypothyroidism only and for all subjects, as applicable. In addition, the analysis will be performed for subjects with normalized TSH throughout the Maintenance Period and at the End of Maintenance Period	Clarification to align with FDA recommendation/comment.
Section 13.5.3.1	Clarified that the exploratory endpoints will be analyzed for the safety population for subjects with primary hypothyroidism only and for all subjects, as applicable.	Clarification to align with FDA recommendation/comment.
Section 13.7.1	Removed reference to the collection of frequency information for a specific AE report.	AE frequency is assessed at the overall level of occurrence during the study. The study does not include an investigator assessment of frequency of occurrence for each AE reported by a subject.

INVESTIGATOR'S AGREEMENT

I have received and read the protocol for XP-8121-120 and associated documents 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	Email Address & Telephone Number
Medical monitor & 24-hr emergency contact	Valentina Conoscenti, MD Medical Director Clinical Research Xeris Pharmaceuticals, Inc.	[redacted]

2. SYNOPSIS

Name of Sponsor/ Company:	Xeris Pharmaceuticals, Inc.
Name of Investigational Product:	XP-8121
Name of Active Ingredient:	Levothyroxine Sodium
Title:	A Phase 2, Multicenter, Non-Randomized, Open-Label, Single Arm, Self-controlled Study of XP-8121 For the Treatment of Adult Subjects with Hypothyroidism
Study number	XP-8121-120
Sites	Multicenter study conducted in the United States (US)
Clinical phase	2
Study background & rationale	Xeris Pharmaceuticals, Inc. (Xeris) is developing a novel formulation of levothyroxine, XP-8121, for subcutaneous (SC) injection. XP-8121 was developed to mitigate many of the challenges associated with oral formulations of levothyroxine. XP-8121 is expected to provide patients with a therapy that will require less frequent dosing, thereby potentially improving treatment adherence, and that will bypass the gastrointestinal (GI) tract, thereby mitigating limitations of oral therapy (eg, drug-food and drug-drug interactions, GI conditions affecting drug absorption, intact swallowing function). In the first Phase 1 study of XP-8121 in healthy subjects conducted by Xeris (XP-8121-101), the pharmacokinetic (PK) of XP-8121 as a single dose of 300 µg following SC administration was evaluated. XP-8121 PK was compared to that of intravenous (IV) administration of 300 µg levothyroxine sodium and oral (PO) administration of 300 µg Eltroxin® (levothyroxine sodium) tablets (3 × 100 µg). Interpretation of the study results obtained from this study were limited as only estimations for maximum plasma concentration (C_{max}), time to maximum concentration (T_{max}), and area under the drug concentration-time curve (AUC) across the sample collection period (0-312 hours (hr)) could be considered interpretable. The 300-µg dose of levothyroxine administered to healthy subjects as XP-8121 (SC), or via IV and PO routes was not sufficient to allow estimation of the baseline-corrected elimination constant and half-life. Xeris shared the results from Study XP-8121-101 with the Food and Drug Administration (FDA), and based upon feedback received, Study XP-8121-108 was conducted to characterize additional doses, to allow more robust understanding of the XP-8121 absorption and elimination kinetics and to allow an evaluation of dose proportionality. Following FDA evaluation of the XP-8121-108 safety and PK data obtained following SC administration of 600 µg and 1200 µg XP-8121, FDA permitted additional dose of XP-8121 1500 µg to be evaluated to characterize dose proportionality across the potential range of clinical doses. In Study XP-8121-108, no notable differences in the safety results between the 600 µg, 1200 µg, and 1500 µg doses of XP-8121 were observed, and no XP-8121 studied dose was different from Synthroid® 600 µg PO with respect to the safety results. Predicted geometric mean AUC at steady state for XP-8121 at 1200 µg was similar to the predicted geometric mean AUC at steady state for Synthroid at 300 µg. Based on PK modeling, an XP-8121 SC weekly dose of 4 times the daily Synthroid PO dose is estimated to provide similar exposure (AUC). Therefore, this study will use a 4X conversion factor to calculate the target µg dose for weekly XP-8121 SC from the µg dose for daily levothyroxine PO. Based upon the known safety and toxicity profile of levothyroxine, published use of oral levothyroxine as a weekly dose regimen, and observed and expected PK profile of XP-8121, the doses proposed in this investigation are safe for use in the clinical trial setting and are appropriate to determine the dose range of XP-8121 to normalize Thyroid Stimulating Hormone (TSH).

Objectives:	**Primary Objective** • To assess the safety and tolerability of XP-8121 after once-weekly SC injections in adult subjects with hypothyroidism • To determine a target dose conversion factor from stably dosed oral levothyroxine to XP-8121 in patients with hypothyroidism **Secondary Objectives** • To determine a dose range of XP-8121 capable of maintaining normalized TSH following a switch from stable replacement therapy with oral levothyroxine • To evaluate a safe initiation dose of XP-8121 based on the prior stable dose of oral levothyroxine • To evaluate a safe titration scheme for dosing XP-8121 to TSH target **Exploratory Objectives** • To characterize the dynamics of thyroid hormones and TSH in blood during and after titration (ie, Titration and Maintenance Periods) with XP-8121 • To characterize the PK of plasma thyroid hormones following multiple once-weekly XP-8121 SC injections in adult subjects with hypothyroidism • To compare patient treatment satisfaction between daily oral levothyroxine and once-weekly XP-8121 SC injections
Endpoints:	**Primary endpoints:** • Safety endpoints collectively include incidence, frequency, severity, and relationship to study drug of treatment-emergent adverse events (TEAEs), including clinically significant vital sign measurements, safety laboratory test results, electrocardiograms (ECGs), and physical examinations • Tolerability assessments include Modified Draize Scale and Injection Site Discomfort assessments • Geometric mean ratio of the weekly dose of XP-8121 SC (in μg) to the daily dose of oral levothyroxine (aka dose conversion factor), where the XP-8121 dose corresponds to the administration immediately preceding collection of blood TSH used to determine normalization at the end of Maintenance Period **Secondary endpoints:** • Proportion of subjects enrolled with normalized TSH throughout the Maintenance Period • Proportion of subjects enrolled with normalized TSH at the end of Maintenance Period • Blood thyroid hormone concentrations (total thyroxine, free thyroxine (fT4) and TSH) following the first dose of XP-8121 and after titration (ie, during the Titration and Maintenance Periods) **Exploratory Endpoints:** • Observed values and changes from baseline values in thyroid hormones (total and fT4) and TSH during the Titration and Maintenance Periods • Pharmacokinetic profile of plasma thyroid hormones (thyroxine [T4] and triiodothyronine [T3]) during the 168-hr PK period (PK substudy only): – T_{max} – C_{max} and C_{max} normalized by dose (C_{max}/Dose) – AUC from time 0 to 168 hr post-dose ($AUC_{0\text{-}168hr}$) and $AUC_{0\text{-}168hr}$ normalized by dose ($AUC_{0\text{-}168hr}$ /Dose) – If supported by the data, the following additional parameters may be calculated: – Total apparent clearance (CL/F) • Comparison of the score of Convenience, Overall Satisfaction, and Effectiveness domain of the Treatment Satisfaction Questionnaire for Medication (TSQM-9) between oral levothyroxine and once-weekly XP-8121 SC treatments

	• Summary of results from the Subject Preference Survey
Number of subjects:	A total of up to approximately 44 subjects who meet all the inclusion criteria and none of the exclusion criteria will be enrolled into the study. Approximately 12 subjects will be enrolled in the PK substudy.
Duration of subject participation:	Participation will last for up to approximately 16 weeks (~4 months).
Study design:	This is a non-randomized, open-label, single arm, self-controlled study of XP-8121 to determine a target dose conversion factor from stably dosed oral levothyroxine to XP-8121 in patients with hypothyroidism and to assess the safety and tolerability of XP-8121 after once-weekly SC injections. This study includes the following periods: Screening, Titration Period, and Maintenance Period. The study will conclude with an End of Maintenance Visit or Early Termination (ET) Visit. Screening will be performed within 28 days of the planned start of the Titration Period. Subjects will be required to be on a stable dose of oral levothyroxine (Synthroid or an FDA-approved generic equivalent), or in the PK substudy, Synthroid only, for at least 3 months prior to Screening. Subjects will also be required to have a normal TSH documented during Screening via the central laboratory (study reference range: 0.47 to 4.68 μIU/mL) and for at least 3 months prior to Screening according to local laboratory reference ranges. If a potential subject does not meet the eligibility requirements described in the protocol on initial Screening, they may be eligible to re-screen only if their medical condition has changed and increases the likelihood that they would meet the study eligibility criteria. Such re-screenings will be exceptional circumstances, and all re-screenings require prior permission of the study Medical Monitor before they begin. Repeating Screening visit laboratory assessments for clinical safety (with Medical Monitor approval) and repeating a Screening test (eg, fT4 and/or TSH) that has been found to be technically flawed will not be considered re-screening. The XP-8121 initiation dose will correspond to 50% of the target dose (in μg) of weekly XP-8121 SC, which is calculated as the current daily oral levothyroxine dose (in μg) multiplied by 4, rounded up to the nearest 50 μg. During the Titration Period, subjects will come into the clinic once a week for 2 through up to 8 weeks, as applicable, for dosing administration. Based on free thyroxine (fT4) levels, XP-8121 will be titrated biweekly (every other week) by intervals of 25% of the target dose. TSH and T4 (free and total) will be checked weekly. A safety check will be completed 72 hr after the initial dose and each escalation during the Titration Period. If fT4 exceeds the upper limit of normal during titration, the XP-8121 dosage will be lowered and held at the previously tolerated dose. Otherwise, titration will continue as scheduled. Titration should not be stopped or interrupted prior to the target dosage unless the Investigator is concerned about the possibility of overdosage or a drug-related adverse event occurs. In such cases, the Investigator and Medical Monitor should confer prior to establishment of the Maintenance dose. Once subjects have completed the Titration Period, they will continue at the same dose of XP-8121 in the Maintenance Period for 4 weeks, returning to the Clinical Research Unit (CRU) on a weekly basis for dosing. An End of Maintenance Visit will be performed at Day 29 (1 week after the last XP-8121 dose). Subjects not achieving an adequate fT4 at ≤125% of the target dose or the maximum weekly dose of 1500 μg may also continue into the Maintenance Period at the discretion of the Investigator and after conferring with the Medical Monitor. During Week 4 of the Maintenance Period, a subgroup of subjects (~12) who have been on a stable dose of Synthroid for at least 3 months prior to Screening and who have maintained adequate trough fT4 and total T4 levels will participate in a PK substudy. Subjects will be housed in the CRU for 9 days and 8 nights to undergo PK sample collections at specified timepoints.

	After completing the Maintenance Period, subjects will complete the study with the End of Maintenance Visit and will subsequently restart their previous daily levothyroxine PO dose that they were taking before the study. Adverse events (AEs) that are ongoing at the End of Maintenance Visit will be recorded on the CRF and followed until resolution or maximally up to 14 days after the End of Maintenance Visit or Early Termination Visit. For subjects who dropped out or have been discontinued from the study, an ET Visit will occur 14 days (±2 days) after the last dose of XP-8121.
Diagnosis and main entry criteria:	**Inclusion Criteria** To be eligible, a subject must meet all the following inclusion criteria: 1. Provide written informed consent. 2. Male or female between the ages of 18 and 65 years (inclusive) at Screening, with chronic hypothyroidism and on a stable dose of oral levothyroxine (Synthroid or an FDA-approved generic equivalent to Synthroid) or, if in the PK substudy, Synthroid only for at least 3 months. 3. TSH within the normal range at Screening (study reference range: 0.47 to 4.68 µIU/mL) and at least 3 months prior to Screening (documented by local laboratory). 4. Free T4 within the normal range at Screening (study reference range: 0.78 to 1.42 ng/dL). 5. Women of childbearing potential (WOCBP) must have a negative urine pregnancy test at Screening and agree to use medically accepted contraception (except for contraceptives containing estrogen for PK substudy subjects only), or abstinence throughout the study. 6. Body mass index (BMI) 18 to 40 kg/m² at Screening. 7. Average triplicate blood pressure (BP) reading for systolic BP >90 mmHg and <150 mmHg and diastolic BP >40 mmHg and <100 mmHg at Screening. 8. Average triplicate resting heart rate/pulse >40 bpm or <100 bpm at Screening. 9. Agrees to return to the CRU for all study visits, and if a part of the substudy PK group, remain at the CRU to comply with all required study procedures. **Exclusion Criteria** To be eligible a subject must not meet any of the following exclusion criteria: 1. History of hypersensitivity to levothyroxine (any formulation). 2. Current dose of oral levothyroxine based on body weight >2 µg/kg/day. 3. Current levothyroxine total daily dose either <50 µg or >375 µg. 4. Current use of combined thyroid treatment (i.e., Synthroid plus liothyronine or Synthroid plus Armour Thyroid) and/or any other levothyroxine aside from those used in the study. 5. Has renal insufficiency (serum creatinine > 3.0 mg/dL) or end-stage renal disease requiring renal replacement therapy. 6. Has any diagnosed hepatic disease affecting liver functionality or serum ALT or AST >3 times the upper limit of normal (ULN) 7. Has hepatic synthetic insufficiency (eg, serum albumin <3.0 g/dL). 8. Has hematocrit of <33.5% for females and <38.7% for males. 9. Has hemoglobin of <10.8 g/dL for females and <12.8 g/dL for males. 10. Has clinically significant ECG abnormalities at Screening. 11. Has congestive heart failure, New York Heart Association (NYHA) Class III or IV. 12. Has history of myocardial infarction, unstable angina, or revascularization within 6-months prior to Screening. 13. Has history of a cerebrovascular accident within 6 months prior to Screening with major neurological deficits. 14. Has active malignancy within 5 years prior to Screening (except: basal cell or squamous cell skin cancers). 15. Has had major surgical operation within 60 days prior to Screening or planned surgical operation during the study. 16. Has a current bleeding disorder or platelet count <50 $\times 10^9$/L. 17. Has donated blood or plasma within 7 days prior to Screening Visit or plans to donate within 7 days prior to Screening or during the study. 18. Use of supplements containing biotin within 7 days prior to Screening and during the study.

	19. Participated in a clinical study within 30 days or 5 half-lives of the study drug prior to Screening. 20. Current use or history of using anticoagulants 14 days prior to Screening (Use of aspirin greater than 325 mg/day is excluded). 21. Hemoglobin A1C (HbA1c) >8% at Screening. 22. History of active substance or alcohol abuse within the 12 months prior to Screening. Abuse of alcohol defined as an average weekly intake of >21 units (1 unit is equivalent to a half pint of beer, 1 serving of hard liquor, or 1 glass of wine). 23. Positive urine drug screen (except: if the results are positive for a benzodiazepine that is being taken as a prescribed concomitant medication, as defined and documented in accordance with the protocol). 24. Positive blood screen for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C antibodies at Screening. 25. Has a history of clinically significant or uncontrolled gastrointestinal, neurologic, hematologic, endocrine (with the exception of hypothyroidism), oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease, or any other condition which would jeopardize the safety of the subject or impact the validity of the study results, **OR** Any reason the Investigator or designee deems exclusionary. 26. **For PK substudy only:** Use of any estrogen-containing compound within 14 days prior to Day 1 of the Titration Period and throughout the study. 27. **For PK substudy only**: On medical examination (at Screening) by the Investigator or designee, has inadequate or difficult venous access that may jeopardize the quality or timing of the PK samples.
Treatment(s):	Subjects will receive single doses of XP-8121 on a weekly basis. The XP-8121 SC initiation dose (in µg) will correspond to 50% of the target weekly XP-8121 SC dose, which is calculated as the current daily oral levothyroxine dose (in µg) multiplied by 4, rounded up to the nearest 50 µg. XP-8121 will be titrated biweekly by intervals of 25% of the target dose, based on each subject's adequate trough fT4 level, up to a maximum of 125% of the target dose or 1500 µg (whichever is lower).
Investigational product:	XP-8121 (levothyroxine sodium) 100 to 1500 µg SC injection
Comparator/ Reference therapy:	N/A
PK parameters (if appropriate):	PK parameters will be derived from the approximately 12 subjects who participate in the PK substudy from total T4 and total T3 plasma concentrations and will include C_{max}, T_{max}, $AUC_{0\text{-}168hr}$, and other PK parameters, as appropriate.
Statistical methods:	Descriptive statistics will be calculated for continuous variables, including number of non-missing observations (N), arithmetic mean, standard deviation (SD), median, minimum, and maximum, and where applicable for PK parameters, the percent coefficient of variation (CV%), geometric mean, and geometric CV%. Descriptive statistics for categorical variables will consist of counts and percentages. The statistical models that will be used to analyze the primary endpoint of dose conversion factor and exploratory endpoint of TSQM-9 domain scores are described below; additional details of the testing procedures not included here, including handling of missing data, will be described in the Statistical Analysis Plan (SAP).
Sample size determination	Assuming a between-subject coefficient of variation of 0.5 and a within-subject, between measurements correlation of 0.5, a sample size of 38 subjects will have 80% power to reject the null hypothesis that the dose conversion factor is less than 3.2X or more than 5X, in favor of the alternative hypothesis that the dose conversion factor is between 3.2X and 5X (in another words, within 80% and 125% of the proposed 4X conversion factor derived from population pharmacokinetic (PPK) modeling). For the exploratory endpoint of TSQM-9, assuming a standard deviation of differences of 20, a sample size of 34 subjects will have 80% power to detect a difference of 10 in means (domain scores range from 0 to 100) with a 5% two-sided significance level (α=0.05). Taking into consideration study non-completers and non-normalizers of TSH at study end, a total of 44 subjects will be enrolled.

Analysis sets:	**Safety Population:** All subjects who receive at least 1 dose of XP-8121. **Completer Population:** All subjects who complete the Maintenance Period and exhibited normalized TSH throughout the Maintenance Period while on a stable dose for approximately 6 weeks. **PK Population:** All safety population subjects who participated in the PK substudy, who do not have any major protocol deviations affecting the PK endpoints and for whom a sufficient number of samples is available to determine at least one PK parameter.
Endpoint analysis:	The final dose conversion factor will be assessed by comparing the ln-transformed final XP-8121 dose (in µg) that maintains normalized TSH throughout the Maintenance Period to the ln-transformed daily oral levothyroxine dose (in µg) the subject was taking before the study, using a linear mixed effects model with treatment as fixed effects, and subject as random effect. Geometric least square means (LSMs), geometric mean ratios, and 90% confidence intervals (CIs) will be presented. This endpoint will be analyzed using the Completer population for subjects with primary hypothyroidism only. Additional sensitivity analyses that include subjects with secondary/tertiary hypothyroidism, subjects with dose adjustment, and/or subjects that maintain normal free T4 may be conducted. The details of the sensitivity analyses will be described in the SAP. Analysis of safety endpoints will be described in the section below. Secondary endpoints will be analyzed for the safety population, for subjects with primary hypothyroidism only and for all subjects, if applicable. Subjects with normalized TSH throughout the Maintenance Period and at the end of Maintenance Period will be presented by number and percentage of subjects referenced to the safety population and the number of subjects entering the Maintenance Period, along with corresponding 95% CIs. TSH, total and free T4 measures following the first dose of XP-8121 will be summarized using descriptive statistics. Number and percentage of subjects with results outside the normal ranges will be tabulated. All exploratory endpoints will be analyzed for the safety population, for subjects with primary hypothyroidism only and for all subjects, if applicable, except for PK endpoints which will be analyzed for the PK population only. TSH, total and free T4 measures and changes from baseline will be summarized by each protocol-specified timepoint using descriptive statistics. Total plasma concentrations and plasma PK parameters will be summarized for all subjects in the PK Population, using descriptive statistics (N, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%). The analysis of the exploratory endpoint of TSQM-9 domain scores will be gated on results from the primary endpoint analysis. The three domain scores will be hierarchically analyzed to ensure control of the family-wise type I error rate at the 0.05 level, with the Convenience score first, Overall Satisfaction score second, and Effectiveness third. Hypothesis tests for the three domain scores will be based on null hypotheses that assume no difference between oral levothyroxine and once-weekly XP-8121 SC treatments. Each domain score will be compared between the two treatments using a paired t-test. Subject counts and percentages for each answer to each question from the Subject Preference Survey will also be presented.
Safety analyses:	All safety and tolerability analyses will be performed on the Safety Population. Safety data will be collected and summarized by study period (Titration Period, Maintenance Period). No formal hypotheses will be tested on safety data. Adverse events will be summarized by the number and percentage of subjects who experienced at least one AE of the following categories in each study period: any AE, any TEAE, any drug-related TEAE, any severe 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. Laboratory evaluations, vital sign measurements, and ECG assessments will be summarized by study period and protocol-specified timepoint within each study period. Local tolerability (using Modified Draize Scale and Injection Site Discomfort questionnaires) will be summarized by protocol-specified timepoint following SC injections of XP-8121.

Table 2: Schedule of Assessments

Study Period	Screening Period [m]	Titration Period		Maintenance Period [a]		ET [b]
Study/Period Day	-28 to -1	Once a week for 2 to 8 weeks as applicable [c]	72 hr (±1 day) Post Initial Dose and Up-Titration Visit [d]	Maintenance Day 1, Day 8, Day 15, Day 22	End of Maintenance Visit Day 29 [m]	ET 14 (±2) days after last dose of XP-8121
Informed consent	X					
Inclusion/exclusion criteria	X					
Medical history and concomitant medication review	X					
Complete physical examination [e]	X				X	X
Abbreviated physical examination [e]		X	X			
Height	X					
Weight	X				X	X
BMI	X					
12-lead ECG [f]	X		X		X	X
Vital signs [g]	X	X	X		X	X
Serology (HCV, HBsAg, & HIV)	X					
Clinical safety laboratory tests [h]	X			X	X	X
Free and total T4 [i]	X	X	X	X	X	X
TSH	X	X	X	X	X	X
Urine drug screen [k]	X					
Urine pregnancy test [l]	X	X		X	X	X
XP-8121 administration [n]		X		X [j]		
PK blood sample collection for substudy subjects only [o]				X	X	
Modified Draize Scale [p]		X		X		
Injection Site Discomfort Evaluations [q]		X		X		
Subject Preference Survey					X [r]	X [r]
TSQM-9 [s]		X		X		
Monitoring of AEs & non-study medications [t]	X	X	X	X	X	X

Abbreviations: AE = adverse event; BMI = body mass index; BP = blood pressure; CRU = Clinical Research Unit; ECG =electrocardiogram; eCRF = electronic case report form; ET = Early Termination; fT4 = free thyroxine; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PK = pharmacokinetic; SC = subcutaneous; T4=Thyroxine; TSH = thyroid-stimulating hormone; TSQM-9 = Treatment Satisfaction Questionnaire for Medication - 9 items

a: Dose changes will only be allowed as outlined in Section 7.4.3 during the Maintenance Period.

b: **Early Termination:** Subjects who withdraw prematurely from the study will be encouraged to return to the CRU for an ET Visit 14 (±2) days after their last dose of XP-8121.

c: Subjects will return to the clinic weekly (every 7 days) for assessments (including administration of XP-8121). XP-8121 will be titrated biweekly as needed. Once subjects have completed the Titration Period, they will continue at the same dose of XP-8121 in the Maintenance Period for 4 weeks (Section 7.4.2)

d: Following the initial dose and any up-titration, subjects will be required to return for an outpatient visit 72 hr [±1 day] after the up-titration has occurred for the following assessments: ECG, vital signs, abbreviated physical examination, T4 and TSH collections and monitoring of AEs and non-study medications.

e: See Section 12.8.2 for details on complete and abbreviated physical examinations.

f: **12-lead ECG** to be assessed prior to vital signs and blood draws. ECGs will be taken after remaining in the supine position for at least 10 minutes. Note that at Screening only, the order of ECGs, vital signs, and blood draw procedures are allowed to vary. All potentially clinically significant automated ECG readings should be repeated within 5 minutes of the reading. If potentially clinically significant reading is confirmed, then the ECG will be sent to a local cardiologist for review (Section 12.8.5). See Section 11.5 for further details on procedure order. Table 3 outlines windows for assessment timepoints.

g: **Vital signs:** triplicate measurements of systolic and diastolic BP and heart rate/pulse will be taken at intervals of 1 to 2 minutes after being in a supine position for at least 10 minutes. Respiratory rate and oral body temperature will also be measured. When the time of scheduled vital sign measurements coincide with a blood draw, vital sign measurements are to be performed before the blood draw where possible, ensuring the blood draw is within the window specified in the protocol. See Section 11.5 for further details on procedure order. Table 3 outlines windows for assessment timepoints.

h: **Clinical Safety Laboratory evaluation** (hematology, chemistry, and urinalysis): Clinical safety laboratory testing will be performed at Screening, the beginning and the end of the Maintenance Period, and the ET Visit, if needed. Subjects are required to fast from all food and drink except water for ≥10 hr prior to collection when glucose values will be obtained. Fasting will not be required for the other safety laboratory testing, and when a safety recheck is deemed necessary and the glucose value is not included. See Section 11.5 for further details on procedure order.

i: Each subject's qualification fT4 level must be within the normal range (study reference range: 0.78 to 1.42 ng/dL) at Screening. During the Titration Period, subjects will come into the clinic once a week for 2 up to 8 weeks, as applicable, for dosing administration. Based on fT4 levels, XP-8121 will be titrated biweekly by intervals of 25% of the target dose. See Section 7.4.2 for further details on dose titration and adjustment criteria during the Titration Period. Table 3 outlines windows for assessment timepoints.

j: Once subjects have completed the Titration Period, they will continue at the same dose of XP-8121 in the Maintenance Period for 4 weeks unless the conditions described in Section 7.4.3 are met.

k: **Urine drug screen**: Repeat urine drug screens are permitted for suspected false positive results. If results of the drug screen are positive for a prescribed benzodiazepine, then the subject is eligible to participate in the study. See Section 12.8.8 for description of urine drug screen.

l: A urine pregnancy test is required during the Screening Period to confirm eligibility for women of childbearing potential only. A urine pregnancy test also will be performed every 2 weeks (ie, Weeks 1, 3, 5 and 7) during the Titration Period, at Day 1 (Week 1) of the Maintenance Period, at the End of Maintenance Visit and, if applicable, at the ET Visit. If the urine pregnancy test results are positive, a serum pregnancy test will be performed for confirmation.

m: **Oral levothyroxine administration**: Subjects must be receiving a stable dose of oral levothyroxine (Synthroid or an FDA-approved generic equivalent to Synthroid) or, if in the PK substudy, Synthroid for at least 3 months prior to Screening to be eligible for trial. During Screening subjects will continue their prescribed daily dose of oral levothyroxine. After all other procedures at the End of Maintenance Visit, subjects will restart their previously prescribed daily oral levothyroxine, at the dose they were taking before the study.

n: **XP-8121 administration**: The XP-8121 SC initiation dose will correspond to 50% of the target XP-8121 dose, which is calculated as the current daily oral levothyroxine dose multiplied by 4, rounded up to the nearest 50 µg. Based on fT4 levels XP-8121 will be titrated biweekly by intervals of 25% of the target dose. See Section 7.4.2 and Section 7.4.3 for further details about dose titration and dose adjustment criteria during the Titration and Maintenance Periods, respectively. The time of weekly (every 7 days) XP-8121 SC dose administration will remain consistent throughout the study and will occur within ±2 hours of the time of the XP-8121 SC initiation dose (Section 10.5).

o: A subgroup of subjects (~12), who have been on Synthroid for at least 3 months prior to Screening and who have maintained adequate trough T4 (free and total) levels in the Maintenance Period will participate in a PK substudy. The study reference ranges for T4 (free and total) and TSH are: 0.78 to 1.42 ng/dL (fT4), 5.53 to 10.96 µg/dL (total T4), and 0.47 to 4.68 µIU/mL (TSH). During Week 4 of the Maintenance Period, subjects will be housed in the CRU for 9 days and 8 nights to undergo PK sample collections at specified timepoints as outlined in Table 5. Subjects will be admitted to the CRU on Maintenance Day 21 (day prior to XP-8121 administration and initiation of PK sampling) and discharged from the CRU on Maintenance Day 29 (168 hr PK sample).

p: **Modified Draize Scale:** Injection site erythema and edema will be assessed using Modified Draize Scales 30 (±5) minutes after injection of XP-8121. If the Draize score is >1 at 30 minutes, the subject will be discharged, and a follow up visit will be scheduled at 24 (±3) hr post-dose to allow the Investigator or designee to complete an assessment of the injection site using the Modified Draize Scale.

q: **Injection Site Discomfort evaluations:** Injection site discomfort will be assessed at 10 (±2) minutes) after injection of XP-8121 using the Numeric Rating Scale for Injection Discomfort, and subjects will complete a Site Discomfort Description and Duration Questionnaire 10 (±2) minutes after injection.

r: **Subject Preference Survey:** Survey will be completed during the End of Maintenance Visit or Early Termination Visit.

s: **TSQM-9**: During first visit of the Titration Period prior to dosing, subjects will be asked to complete the questionnaire regarding their oral levothyroxine use. Subjects will also complete on Maintenance Day 22 after the last administration of XP-8121.

t: All **AEs and non-study medications** must be recorded on the subjects' eCRF from the time of consent and followed until resolution or maximally up to 14 days after the End of Maintenance. Medications used prior to the time of informed consent will be recorded as prior medications.

Table 3: Timing Window Allowances for T4 and TSH, Electrocardiogram, and Vital Sign Measurements

Timepoint[a]	Tolerance Window
T4 and TSH Sampling	
Titration Period: Predose	within 10 minutes of dosing
Titration Period: 72 hr	72 hr (±1 day) following initial dose and up titration
Maintenance Period: Predose	within 10 minutes of dosing
Early Termination Visit	14 (±2) days following last dose of XP-8121
Electrocardiogram	
Titration Period: 72 hr	72 hr (±1 day) following initial dose and up titration
Early Termination Visit	14 (±2) days following last dose of XP-8121
Vital Sign Measurements	
Titration Period: Predose	within 10 minutes of dosing
Titration Period: 72 hr	72 hr (±1 day) following initial dose and up titration
Early Termination Visit	14 (±2) days following last dose of XP-8121

Abbreviations: T4 = thyroxine; TSH = thyroid stimulating hormone
a Timepoints are not all inclusive of all required samples needed in study as some visits do not have associated windows

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 4: Abbreviations and Specialist Terms

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the drug concentration-time curve
$AUC_{0\text{-last}}$	Area under the drug concentration-time curve from time 0 to time of the last measured concentration
$AUC_{0\text{-12hr}}$	Area under the drug concentration-time curve from time 0 to 12 hr
$AUC_{0\text{-24hr}}$	Area under the drug concentration-time curve from time 0 to 24 hr
$AUC_{0\text{-48hr}}$	Area under the drug concentration-time curve from time 0 to 48 hr
$AUC_{0\text{-72hr}}$	Area under the drug concentration-time curve from time 0 to 72 hr
$AUC_{0\text{-132hr}}$	Area under the drug concentration-time curve from time 0 to 132 hr
$AUC_{0\text{-144hr}}$	Area under the drug concentration-time curve from time 0 to 144 hr
$AUC_{0\text{-168hr}}$	Area under the drug concentration-time curve from time 0 to 168 hr
BMI	Body mass index
BP	Blood pressure
bpm	Beats Per Minute
cGMP	Current Good Manufacturing Practices
CI	Confidence interval
CL/F	Total Apparent Clearance
C_{max}	Maximum plasma concentration
CRF	Case report form
CRU	Clinical research unit
CSR	Clinical study report
CV	Coefficient of variation
DMSO	Dimethyl sulfoxide
ECG	Electrocardiogram
eCRF	Electronic case report form
ET	Early termination
FDA	Food Drug and Administration
fT4	Free (protein-unbound) thyroxine
GCP	Good Clinical Practice
GI	Gastrointestinal
HbA1C	Hemoglobin A1C
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
hr	Hour or Hours
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IM	Intramuscular
IRB	Institutional Review Board
IV	Intravenous
LSM	Least square mean

Abbreviation	Definition
MDMA	3,4-Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numeric Rating Scale
NYHA	New York Heart Association
OAE	Other Adverse Event
OTC	Over the counter
PK	Pharmacokinetic
PO	Oral administration
PPK	Population pharmacokinetic
PT	Preferred term
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SOC	System organ classification
T3	Triiodothyronine
T4	Thyroxine
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum concentration
TMF	Trial master file
TSH	Thyroid-stimulating hormone
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
WOCBP	Women of childbearing potential
Xeris	Xeris Pharmaceuticals

5. INTRODUCTION

Xeris Pharmaceuticals, Inc. (Xeris) has developed a novel formulation of levothyroxine, XP-8121 (levothyroxine sodium for subcutaneous (SC) injection) to mitigate challenges associated with oral (PO) formulations of levothyroxine, which can include interference with absorption (e.g., simultaneous ingestion with calcium, iron, certain foods, other drugs, and conditions that impair gastric acidification or intestinal absorption, such as celiac disease). For this reason, patients are usually instructed to ingest oral levothyroxine on an empty stomach 30 to 60 minutes before food intake. Further, a once weekly dosing schedule, as provided by XP-8121, could improve adherence that is adversely affected by unintentionally missed daily doses. Finally, SC administration of XP-8121 could alleviate burdens associated with swallowing difficulties or other barriers to taking daily medication.

The first Phase 1 study of XP-8121 in healthy subjects conducted by Xeris (XP-8121-101) evaluated the safety and pharmacokinetics (PK) of XP-8121 300 µg following SC administration of a single dose as compared with identical doses of intravenous (IV) and oral levothyroxine sodium (Eltroxin, 3 x 100 µg). XP-8121 was well tolerated with treatment-emergent adverse events (TEAEs) similar in incidence and severity across treatment arms. Estimations of maximum plasma concentration (C_{max}), time to maximum concentration (T_{max}), and area under the drug concentration-time curve (AUC) across the sample collection period (0 to 312 hr) were considered interpretable. As expected, XP-8121, levothyroxine IV, and Eltroxin PO were not bioequivalent, i.e.., C_{max} and AUC from time 0 to time of the last measured concentration ($AUC_{0\text{-last}}$) geometric least-squares mean (LSM) ratios did not satisfy absolute or relative bioavailability criteria for bioequivalence. See Section 5.4.1.1 for additional details.

In the second Phase 1 study (XP-8121-108), single SC doses of XP-8121 600 µg, 1200 µg, and 1500 µg were compared with a single oral dose of Synthroid 600 µg. TEAEs in the XP-8121 arms were typically mild and similar in frequency and severity across dose groups. Overall, there were no relevant safety finding differences between the three XP-8121 doses, nor between XP-8121 and Synthroid. Baseline-adjusted plasma levothyroxine levels analyzed by noncompartmental analysis showed that compared to oral Synthroid, XP-8121 was associated with slower absorption (ie, longer T_{max}), lower C_{max}, and greater overall exposure ($AUC_{0\text{-last}}$) to thyroxine. Plasma thyroxine mean C_{max} after oral Synthroid 600 µg was approximately 2.2-fold higher than following XP-8121 600 µg SC, while being roughly equivalent to the mean C_{max} after XP-8121 1500 µg SC. See Section 5.4.1.2 for additional details.

Population pharmacokinetics (PPK) modeling based on the above data suggested that at steady-state, approximately equivalent mean plasma exposure to levothyroxine could be achieved in healthy volunteers by converting a daily oral dose to a once-weekly dose of XP-8121 as follows (daily levothyroxine PO dose x 4 = once weekly target dose XP-8121). Study XP-8121-120 will determine whether a target conversion factor when switching from daily oral levothyroxine replacement therapy with Synthroid or a generic equivalent to weekly XP-8121 is approximately 4.

5.1. Hypothyroidism

The thyroid gland is responsible for the synthesis, storage, and release of the thyroid hormones, thyroxine (T4) and triiodothyronine (T3) [Colucci et al, 2013]. These hormones are nuclear

receptor-activating and regulate critical metabolic processes that are vital for normal growth, development, and health throughout life.

Deficiency of circulating T4 or T3 is known as hypothyroidism. Most commonly in developed countries, the primary cause of hypothyroidism is autoimmune destruction of the glands responsible for thyroid hormone synthesis, also known as Hashimoto's disease or autoimmune thyroiditis. Other causes of primary hypothyroidism (thyroid hormone production/release deficits) include other forms of thyroid inflammation, iatrogenic causes (surgery and radiation sequelae and certain medications, iodine deficiency, et al). Uncommonly, thyroid synthesis is impaired at birth (congenital). Hypothyroidism can also result from problems with TSH production/secretion or action (secondary hypothyroidism, most commonly because of pituitary tumor or trauma) or from hypothalamic dysregulation of pituitary function (tertiary hypothyroidism). Rare syndromes of resistance to the actions of thyroid hormone can also resemble more typical hypothyroidism [Laurent et al, 2018; Winther et al, 2016; Colucci et al, 2013].

Regardless of etiology, inadequate thyroid hormone that manifests clinically should be treated, i.e., thyroid hormone replacement. Treatment is often chronic, most commonly lifelong. The goal of replacement therapy is restoration of the euthyroid state, with reversal of the clinical manifestations of hypothyroidism. In most developed countries, replacement most commonly consists of levothyroxine monotherapy and in most guidelines, TSH is currently recommended as the sole biomarker of replacement adequacy.

5.2. Existing Parenteral Replacement

Oral and IV levothyroxine products have exhibited acceptable safety profiles and have been in use for many decades. Currently, there are no approved levothyroxine products indicated for SC administration for the treatment of hypothyroidism. The extremely low water solubility of levothyroxine (approximately 0.1 mg/mL) has hindered the development of ready-to-use aqueous commercial formulations. Approved use of lyophilized powders of levothyroxine for reconstitution as aqueous IV formulations in myxedema coma are also used off-label as intramuscular (IM) and SC injections. However, such use requires large injection volumes, and the formulation is pharmaceutically unstable, rendering such use unsuitable for a broad patient application.

5.3. Limitations with Levothyroxine Administered Orally

Levothyroxine is a drug with a narrow therapeutic index [Vita et al, 2014]. It has been reported, however, that nearly 40% of patients undergoing treatment with levothyroxine are either over- or under-treated [Laurent et al, 2018] due to factors that include but are not limited to drug formulation, drug-food interaction, drug-drug interaction, adherence, gastrointestinal (GI) malabsorption, and other preexisting medical conditions. Levothyroxine absorption issues are frequently based on concurrent absorption of interfering substances in the digestive tract [Skelin et al, 2017]. When co-administered with a standard test breakfast, levothyroxine absorption is impaired about 40% [Hennessey, 2017]; oral levothyroxine sodium labeling recommends avoidance of food around the time of dosing.

Because of these limitations, there is an unmet need for levothyroxine formulations that circumvents the GI tract and the need for daily drug administration.

5.4. XP-8121 for Subcutaneous Injection

XP-8121 is a ready-to-use, liquid formulation of levothyroxine sodium intended for SC administration once-weekly. XP-8121 is made possible via use of XeriSol™ formulation technology that uses dimethyl sulfoxide (DMSO) as an excipient. The toxicology, pharmacology, and metabolic properties of DMSO have been studied extensively. DMSO possesses a low degree of toxicity to humans via oral and parenteral routes [McKim et al, 2008]. Notably, DMSO, at a similar concentration as used in XP-8121, is used in a concentrated, liquid-stable formulation of glucagon [Gvoke®; Xeris Pharmaceuticals, 2021] approved for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes ages 2 years and above.

Toxicology data for the XeriSol formulation were obtained as part of a 26-week SC toxicity and toxicokinetic study supporting Gvoke (Report 8394785, data on file). In male and female rats, no adverse clinical findings or safety signals were observed. The incidence of injection site reactions (minimal to marked erosion/ulcer; minimal to moderate mixed cell inflammation, hemorrhage, exudate, epithelial hyperplasia, and/or fibrosis; and minimal to slight thrombus) were comparable among animals administered XeriSol vehicle or active XeriSol glucagon. All XeriSol glucagon-related clinical observations were considered non-adverse as they did not affect the overall health of the animals and were reversible during recovery phase.

5.4.1. Clinical Experience

Xeris has recently completed 2 Phase 1 XP-8121 clinical trials. Study XP-8121-101 was designed to evaluate the safety, PK, and absolute and relative bioavailability of levothyroxine sodium after a single SC dose of XP-8121 300 µg compared to reference IV and PO formulations of levothyroxine sodium of the same dose in 30 healthy adult subjects (mean age of 28.5 years, 73% male). Study XP-8121-108 was a single-center, randomized, open-label, crossover study to evaluate XP-8121 in 60 healthy subjects (mean age of 40.4 years, 42% male) designed to characterize the absorption and elimination kinetics of XP-8121 600 µg, 1200 µg, and 1500 µg following SC administration in healthy volunteers. The study evaluated dose proportionality across the potential range of clinical doses and the relative bioavailability of XP-8121 600 µg SC versus levothyroxine 600 µg PO. Results are described briefly below.

5.4.1.1. Study XP-8121-101

A single SC dose of XP-8121 was well-tolerated in healthy volunteers with reported TEAEs similar in incidence and severity across arms. Overall, TEAEs were mild to moderate in severity, self-limited, and required no intervention. No deaths or other serious adverse events (SAEs) were reported, and no subject was withdrawn due to TEAE. Headache (30% of subjects) and catheter site pain (13% of subjects) were the only TEAEs reported for more than 10% of subjects overall. Headache was the sole TEAE assessed as related to study drug that was reported for more than 10% of subjects overall. Headache is an adverse reaction listed in approved product labels of IV and oral levothyroxine [Abbott Laboratories, 2001; AbbVie Inc, 2018].

Within each study arm, the most frequently reported TEAEs were:

- For PO levothyroxine, headache (10.7% of subjects), catheter site pain (7.1%), and oropharyngeal pain (7.1%).
- For IV levothyroxine, headache (7.1%), catheter site pain (7.1%), and infusion site erythema (7.1%).

- For XP-8121, headache (22.2%), nausea (7.4%), and injection site reaction (7.4% of subjects).

With respect to other safety findings, there was no evidence of mean population changes during the study and, while a few individual results changed across the normal range boundaries, none was found to be of clinical significance.

Interpretation of the PK results is limited to estimations for C_{max}, T_{max}, and AUC across the sample collection period (0 - 312 hr), as the 300-µg doses did not allow estimation of baseline-corrected levothyroxine elimination-phase PK parameters (inadequate for determining the elimination constant and half-life).

- Absorption of XP-8121 was slower; median T_{max} approximately 30 hr slower than either IV or PO;
- C_{max} mean for XP-8121 was reduced compared to IV or PO; mean values 27.6 (±15.74) ng/mL, 70.4 (±37.72) ng/mL and 32.8 (±23.18) ng/mL, respectively;
- AUC means for XP-8121 compared to IV and PO were lower across the early portion of the assessment period [area under the drug concentration-time curve from time 0 to 12 hr (AUC_{0-12hr}), area under the drug concentration-time curve from time 0 to 24 hr (AUC_{0-24hr}), and area under the drug concentration-time curve from time 0 to 48 hr (AUC_{0-48hr})], indicating slower absorption of XP-8121 as compared to the other routes of administration;
- Comparable AUC values were obtained between XP-8121 and oral levothyroxine for area under the drug concentration-time curve from time 0 to 144 hr ($AUC_{0-144hr}$), while the Area under the drug concentration-time curve from time 0 to 312 hr ($AUC_{0-312hr}$) was slightly greater for XP-8121. All values for AUC levothyroxine IV were greater than those of either XP-8121 or oral.

5.4.1.2. Study XP-8121-108

5.4.1.2.1. Safety

In Study XP-8121-108, single SC doses of XP-8121 600 µg, 1200 µg, and 1500 µg were well-tolerated in healthy volunteers with reported TEAEs similar in incidence and severity across study arms. Overall, TEAEs were mild to moderate in severity and self-limited. No deaths or other SAEs were reported, and no subjects were withdrawn due to TEAE.

Overall, TEAEs reported in more than 2 subjects were constipation (10/60; 16.7%), dermatitis contact (10/60 subjects; 16.7%), headache (5/60; 8.3%) and pruritis (4/30; 13.3%).

With respect to other safety findings, there was no evidence of clinically relevant mean population changes during the study and, while a few individual results changed across the normal range boundaries, none was found to be of clinical significance. No clinically significant mean changes from baseline were observed in any safety assessment. Importantly, with respect to electrocardiogram (ECG) findings, there were no observations of any major cardiovascular manifestation (e.g., atrial fibrillation, tachycardia, myocardial ischemia, arrhythmias) that have been associated with levothyroxine overdosage. Two subjects reported telemetry-related adverse event (AE) findings that were considered related to study drug (atrial tachycardia following treatment with XP-8121 600 µg SC and ventricular extrasystoles with XP-8121 1500 µg SC). Both events were considered mild in severity and resolved prior to end of study. No AEs were

reported in the subject with the highest reported C_{max} value after administration of XP-8121 1500 µg.

Overall, there were no notable differences in the safety results between doses of XP-8121 nor between XP-8121 and Synthroid 600 µg PO.

5.4.1.2.2. Pharmacokinetics

Baseline-adjusted plasma levothyroxine levels analyzed by noncompartmental analysis showed that subjects receiving XP-8121 SC have slower absorption, lower peak plasma concentration, and higher extended exposure of levothyroxine compared to Synthroid PO at the comparable dose of 600 µg. Peak levothyroxine exposure, as measured by mean C_{max} was highest for subjects receiving levothyroxine 600 µg PO and was 55% lower at 600 µg XP-8121 SC, 22% lower at 1200 µg XP-8121 SC, and 1% lower at 1500 µg XP-8121 SC.

While plasma levothyroxine exposure over 72 hr as measured by mean area under the drug concentration-time curve from time 0 to 72 hr (AUC_{0-72}) was higher for Synthroid PO than XP-8121 at comparable doses of 600 µg, exposure was approximately 35% higher for XP-8121 with respect to mean AUC_{0-last}. The relationship of XP-8121 dose and PK parameters (AUC_{0-last} and C_{max}) was assessed with a power model. The 95% confidence intervals (CIs) for the slope of the model are (0.78, 1.32) for AUC_{0-last} and (0.67, 1.06) for C_{max}, respectively. Both 95% CIs contain 1, indicating dose proportionality.

A PPK model estimated that an XP-8121 SC weekly dose equivalent to 4 times a daily Synthroid PO dose will provide similar exposure (AUC) to thyroxine.

5.5. Current Study (XP-8121-120) Design and Dose Range Rationale

Following the above-described studies in healthy volunteers, Xeris received guidance from Food and Drug Administration (FDA) on a proposed registration path for XP-8121. The current study was designed, incorporating FDA guidance, to provide information on weekly use of XP-8121 in stably treated subjects with hypothyroidism. The goals of the study are to determine safe starting doses, safe and feasible titration schedules, and the effective dose range of XP-8121, wherein effectiveness is determined by maintenance of normalized TSH. The dose conversion target was considered the primary objective and serves as the basis for hypothesis testing and sample size determination. Pharmacokinetics will also be characterized in a subset of subjects to determine any differences from modeled chronic PK using data from healthy volunteers. The findings from this study will inform a future clinical efficacy and safety demonstration.

This is a non-randomized, open-label, single arm, self-controlled study (i.e., subjects serve as their own controls based on baseline assessment of thyroid function). The design is appropriate because replacement of deficient T4 with levothyroxine is necessary and sufficient to treat hypothyroidism. A comparator is not necessary for an initial assessment of the ability of SC administered levothyroxine to maintain normalized TSH in stably treated subjects, as efficacy is not being established by this study. Blinding is not necessary since all subjects receive active therapy and there is no comparator. Furthermore, the primary outcome measure, TSH, is objective, and compliance (adherence) with therapy will be assessed.

The XP-8121 initiation dose will correspond to 50% of the target weekly dose of XP-8121 SC, which is defined, per study hypothesis, as the baseline daily oral levothyroxine dose (in µg) multiplied by 4, rounded up to the nearest 50 µg. The lowest initiation dose to be studied is

100 µg. The highest dose to be studied is 1500 µg weekly, selected based on the known safety and toxicity profile of levothyroxine, published use of oral levothyroxine as a weekly dose regimen, and the observed and expected PK profile of XP-8121. This dose is not expected to result in overdosage using the proposed biweekly titration-to-target scheme with careful safety monitoring as described below.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Objectives

6.1.1. Primary Objective

- To assess the safety and tolerability of XP-8121 after once-weekly SC injections in adult subjects with hypothyroidism
- To determine a target dose conversion factor from stably dosed oral levothyroxine to XP-8121 in patients with hypothyroidism

6.1.2. Secondary Objectives

- To determine a dose range of XP-8121 capable of maintaining normalized TSH following a switch from stable replacement therapy with oral levothyroxine
- To evaluate a safe initiation dose of XP-8121 based on the prior stable dose of oral levothyroxine
- To evaluate a safe titration scheme for dosing XP-8121 to TSH target

6.1.3. Exploratory Objectives

- To characterize the dynamics of thyroid hormones and TSH in blood during and after titration (ie, Titration and Maintenance Periods) with XP-8121
- To characterize the PK of plasma thyroid hormones following multiple once-weekly XP-8121 SC injections in adult subjects with hypothyroidism
- To compare patient treatment satisfaction between daily oral levothyroxine and once-weekly XP-8121 SC injections

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

This is a non-randomized, open-label, single arm, self-controlled study of XP-8121 to determine a target dose conversion factor from stably dosed oral levothyroxine to XP-8121 in patients with hypothyroidism and to assess the safety and tolerability of XP-8121 after once-weekly SC injections.

This study includes the following periods: Screening, Titration Period, and Maintenance Period. The study will conclude with an End of Maintenance or Early Termination (ET) Visit. Subjects will be maintained on a stable dose of XP-8121 for a total of 6 weeks; subjects are required to be on a stable dose of XP-8121 for the last 2 weeks of the Titration Period, enter the Maintenance Period on the same dose, and continue at the same dose during the 4-week duration of the Maintenance Period.

Screening will be performed within 28 days of the planned start of the Titration Period. Subjects will be required to be on a stable dose of oral levothyroxine (Synthroid or an FDA-approved generic equivalent), or in the PK substudy, Synthroid only, for at least 3 months prior to Screening. Subjects will also be required to have a normal TSH documented during Screening via the central laboratory (study reference range: 0.47 to 4.68 µIU/mL) and for at least 3 months prior to Screening according to local laboratory reference ranges.

The XP-8121 initiation dose will correspond to 50% of the target weekly dose of XP-8121 SC (in µg), which is calculated as the current daily oral levothyroxine dose (in µg) multiplied by 4, rounded up to the nearest 50 µg.

During the Titration Period, subjects will come into the clinic once a week for 2 through up to 8 weeks, as applicable, for dosing administration. Based on free thyroxine (fT4) levels, XP-8121 will be titrated biweekly (every other week) by intervals of 25% of the target dose. TSH and T4 (free and total) will be checked weekly. A safety check will be completed 72 hr after the initial dose and each escalation during the Titration Period. If fT4 exceeds the upper limit of normal during titration, the XP-8121 dosage will be lowered and held at the previously tolerated dose.

Once subjects have completed the Titration Period, they will continue at the same dose of XP-8121 in the Maintenance Period for 4 weeks, returning to the Clinical Research Unit (CRU) on a weekly basis for dosing. An End of Maintenance Visit will be performed at Day 29 (1 week after the last XP-8121 dose). Subjects not achieving an adequate fT4 at ≤125% of the target dose or the maximum weekly dose of 1500 µg may also continue into the Maintenance Period at the discretion of the Investigator and after conferring with the Medical Monitor. Titration details are outlined in Appendix A.

During Week 4 of the Maintenance Period, a subgroup of subjects (~12) who have been on a stable dose of Synthroid for at least 3 months prior to Screening and who have maintained adequate trough fT4 and total T4 levels will participate in a PK substudy. Subjects will be housed in the CRU for 9 days and 8 nights to undergo PK sample collections at specified timepoints as outlined in Table 5.

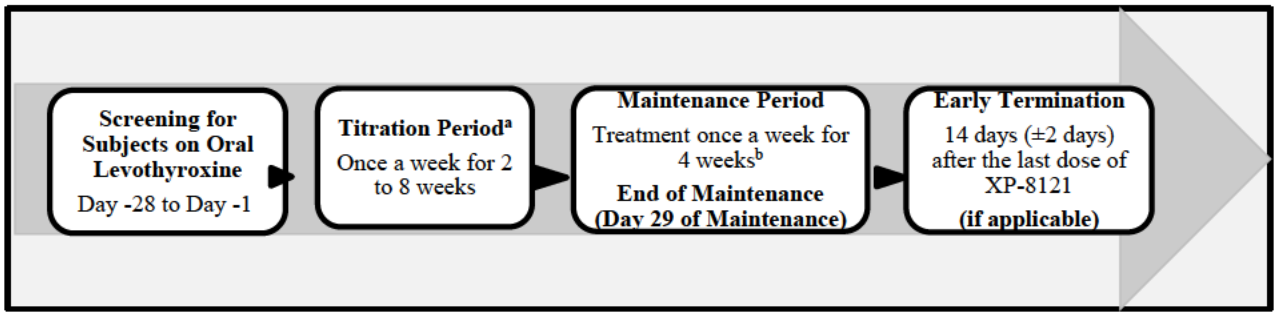
After completing the Maintenance Period, subjects will complete the study with the End of Maintenance Visit and will subsequently restart their previous daily levothyroxine PO dose that they were taking before the study. AEs that are ongoing at the End of Maintenance Visit will be

recorded on the case report form (CRF) and followed until resolution or maximally up to 14 days after the End of Maintenance Visit or ET Visit.

For subjects who dropped out or have been discontinued from the study, an ET Visit will occur 14 days (±2 days) after the last dose of XP-8121.

Figure 1 includes an overview of the study design schema.

Figure 1: Study Design Schema



a: Titration details are outlined in Appendix A.
b: A subgroup of subjects (~12), who have been on Synthroid for at least 3 months prior to Screening and who have maintained adequate trough T4 (free and total) levels in the Maintenance Period will participate in a PK substudy. During Week 4 of the Maintenance Period, subjects will be housed in the CRU for 9 days and 8 nights to undergo PK sample collections at specified timepoints as outlined in Table 5.

7.2. Number of Subjects

A total of up to approximately 44 subjects who meet all the inclusion criteria and none of the exclusion criteria will be enrolled into the study. Approximately 12 subjects will be enrolled in the PK substudy.

7.2.1. Subject Replacement

Subjects who withdraw from the study for any reason will not be replaced.

7.3. Treatment Assignment

All subjects receive open-label XP-8121 at a starting dose corresponding to 50% of the target XP-8121 dose (4x the daily oral levothyroxine dose, rounded up to the nearest 50 µg).

7.4. Dose Titration and Adjustment Criteria

7.4.1. Target XP-8121 Dose Definition and Calculation

Predicted geometric mean AUC at steady state for XP-8121 1200 µg was similar to the predicted geometric mean AUC at steady state for Synthroid 300 µg. Based on PK modeling, an XP-8121 SC weekly dose of 4 times the daily oral levothyroxine dose is estimated to provide similar exposure (AUC). Thus, the target weekly dose of XP-8121 SC (in µg) is calculated as the current daily oral levothyroxine dose (in µg) multiplied by 4 rounded up to the nearest 50 µg.

7.4.2. Titration Period

The XP-8121 SC initiation dose will correspond to 50% of the target weekly dose of XP-8121 SC (in µg). During the Titration Period, XP-8121 will be titrated at a rate intended to mitigate potential adverse effects of thyroid hormone excess, while avoiding prolonged under-replacement. The response to titration will be carefully monitored to avoid these effects.

During the Titration Period, XP-8121 will be titrated based on individual response to therapy (using blood fT4 trough concentration as a fast-response marker) at intervals no more frequent than every other week and in dosage increments corresponding to 25% of the target dose, up to a maximum of 125% of the target dose or 1500 µg (whichever is lower).

Operationally, each week subjects will return to the CRU for dosing and to have trough fT4 concentrations measured. Based on the fT4 concentration, the Titration Period will proceed as follows:

- If fT4 concentration is below or within normal range (study reference range: 0.78 to 1.42 ng/dL), and no signs/symptoms of thyroid hormones excess are present, the dose of XP-8121 SC will be increased by 25% of the target dose (eg, if fT4 concentration levels drawn at Week 2 of Titration Period are confirmed to be within the normal range at Week 3 of Titration Period, XP-8121 will be increased to 75% of the target weekly XP-8121 SC dose). If a drug-related AE is reported or if overdosage is a concern, the Investigator should consult with the Medical Monitor before up-titrating.
- If fT4 is in the normal range with presence of signs/symptoms of thyroid excess, then XP-8121 titration will occur at the discretion of the Investigator and in discussion with the Medical Monitor.
  - Signs/symptoms of thyroid excess have differing dynamics (ie, start and worsen at varying time and rates) and are non-specific when assessed individually. Therefore, clinical judgment is needed to interpret them in the scenario of acute response to changes in the replacement levothyroxine dose using XP-8121. Investigators should determine whether solicited symptom(s) or observed sign(s) warrant a presumptive determination of thyroid excess (or intolerance of replacement therapy). Such determination should be made conservatively, considering the potential impact of the signs/symptoms on the subject well-being during the subsequent Maintenance Period (See Appendix B for a list of positive signs/symptoms of thyroid excess).
- If fT4 concentration exceeds the upper limit of normal (regardless of signs/symptoms of thyroid hormones excess), then XP-8121 titration will end, **and** the XP-8121 dosage will be lowered and held at the highest previously tolerated dose for the remainder of the study.

Once subjects have completed the Titration Period, they will continue at the same dose of XP-8121 in the Maintenance Period for 4 weeks (see Appendix A for details on titration algorithm).

7.4.3. Maintenance Period

Subjects will remain on the dose of XP-8121 used at the end of the Titration Period.

If, during Maintenance Period, biochemical hyperthyroidism is present, as evidenced by elevated trough fT4 and/or low TSH, the Investigator may reduce the weekly dose of XP-8121 SC by one dose level (ie, 25% of the target dose) and maintain the lowered dose throughout the remainder of the study as tolerated. If multiple signs/symptoms of thyroid excess are present without definitive biochemical evidence of hyperthyroidism, the Investigator should confer with the Medical Monitor. If the Investigator and Medical Monitor agree to a XP-8121 dose reduction, the dose should be reduced by one dose level and held at the lowered dose for the remainder of the study, as tolerated.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

To be eligible, a subject must meet all the following inclusion criteria:

1. Provide written informed consent.
2. Male or female between the ages of 18 and 65 years (inclusive) at Screening, with chronic hypothyroidism and on a stable dose of oral levothyroxine (Synthroid or an FDA-approved generic equivalent to Synthroid) or, if in the PK substudy, Synthroid only for at least 3 months.
3. TSH within the normal range at Screening (study reference range: 0.47 to 4.68 μIU/mL) and at least 3 months prior to Screening (documented by local laboratory).
4. Free T4 within the normal range at Screening (study reference range: 0.78 to 1.42 ng/dL).
5. Women of childbearing potential (WOCBP) must have a negative urine pregnancy test at Screening and agree to use medically accepted contraception (except for contraceptives containing estrogen for PK substudy subjects only), or abstinence throughout the study.
6. Body Mass Index (BMI) 18 to 40 kg/m² at Screening.
7. Average triplicate blood pressure (BP) reading for systolic BP >90 mmHg and <150 mmHg and diastolic BP >40 mmHg and <100 mmHg at Screening.
8. Average triplicate resting heart rate/pulse >40 beats per minute (bpm) or <100 bpm at Screening.
9. Agrees to return to the CRU for all study visits, and if a part of the substudy PK group, remain at the CRU to comply with all required study procedures.

8.2. Subject Exclusion Criteria

To be eligible a subject must not meet any of the following exclusion criteria:

1. History of hypersensitivity to levothyroxine (any formulation).
2. Current dose of oral levothyroxine, based on body weight >2 μg/kg/day.
3. Current levothyroxine total daily dose either <50 μg or >375 μg.
4. Current use of combined thyroid treatment (ie, Synthroid plus liothyronine or Synthroid plus Armour Thyroid) and/or any other levothyroxine aside from those used in the study.
5. Has renal insufficiency (serum creatinine >3.0 mg/dL) or end-stage renal disease requiring renal replacement therapy.
6. Has any diagnosed hepatic disease affecting liver functionality or serum ALT or AST >3 times the upper limit of normal (ULN)
7. Has hepatic synthetic insufficiency (eg, serum albumin <3.0 g/dL).
8. Has hematocrit of <33.5% for females and <38.7% for males.
9. Has hemoglobin of <10.8 g/dL for females and <12.8 g/dL for males.
10. Has clinically significant ECG abnormalities at Screening.
11. Has congestive heart failure, New York Heart Association (NYHA) Class III or IV.
12. Has history of myocardial infarction, unstable angina, or revascularization within 6 months prior to Screening.
13. Has history of a cerebrovascular accident within 6 months prior to Screening with major neurological deficits.
14. Has active malignancy within 5 years prior to Screening (except: basal cell or squamous cell skin cancers).

15. Has had major surgical operation within 60 days prior to Screening or planned surgical operation during the study.
16. Has a current bleeding disorder or platelet count <50 $\times 10^9$/L.
17. Has donated blood or plasma within 7 days prior to Screening Visit or plans to donate within 7 days prior to Screening or during the study.
18. Use of supplements containing biotin within 7 days prior to Screening and during the study.
19. Participated in a clinical study within 30 days or 5 half-lives of the study drug prior to Screening.
20. Current use or history of using anticoagulants 14 days prior to Screening. (Use of aspirin greater than 325 mg/day is excluded).
21. Hemoglobin A1C (HbA1c) >8% at Screening.
22. History of active substance or alcohol abuse within the 12 months prior to Screening. Abuse of alcohol defined as an average weekly intake of >21 units (1 unit is equivalent to a half pint of beer, 1 serving of hard liquor, or 1 glass of wine).
23. Positive urine drug screen (except: if the results are positive for a benzodiazepine that is being taken as a prescribed concomitant medication, as defined and documented in accordance with the protocol).
24. Positive blood screen for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C antibodies at Screening.
25. Has a history of clinically significant or uncontrolled gastrointestinal, neurologic, hematologic, endocrine (with the exception of hypothyroidism), oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease, or any other condition which could jeopardize the safety of the subject or impact the validity of the study results,
    OR
    Any reason the Investigator or designee deems exclusionary.
26. **For PK substudy only:** Use of any estrogen-containing compound within 14 days prior to Day 1 of the Titration Period and throughout the study.
27. **For PK substudy only:** On medical examination (at Screening) by the Investigator or designee, has inadequate or difficult venous access that may jeopardize the quality or timing of the PK samples.

8.3. Duration of Subject Participation

Subject participation in this study will last for up to approximately 16 weeks (~4 months).

8.4. Subject Withdrawal Criteria

Subjects may withdraw their consent to participate in the study at any time. If a subject withdraws consent, the date and reason for consent withdrawal should be documented. Wherever possible, the tests and evaluations described for the Early Termination Visit in Section 11.4 should be performed for all subjects who discontinue prior to the completion of the study. Subject data, including the results of sample testing, will be included in the analysis up to the date of the withdrawal of consent. The reason for withdrawal must be specified on the appropriate electronic case report form (eCRF), including further specification if the category of 'Other' is selected.

Individual subjects will be advised verbally and in the written informed consent form (ICF) that they have the right to withdraw from the study at any time. The Investigator or sponsor may discontinue a subject from the study in the event of an intercurrent illness, adverse event, death,

positive pregnancy test at any time during the study, other reasons concerning the health or well-being of the subject, or in the case of lack of cooperation, non-compliance, protocol deviations, or other administrative reasons. In addition, potential reasons for early termination from the study include:

- Inability to achieve an adequate replacement dosage
- Inability to achieve a tolerable replacement dosage

If a subject is withdrawn from the study, a replacement subject will not be enrolled (Section 7.2.1).

8.5. Study Termination

This study may be suspended or prematurely terminated by Xeris. Reasons for this may include the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

8.6. Lifestyle Considerations

8.6.1. Contraception

For WOCBP (ie, women who are not postmenopausal or who have not had bilateral oophorectomy or hysterectomy), there is a requirement for a negative urine pregnancy test at all assessment timepoints and for agreement to use medically accepted contraception (eg, non-hormonal or estrogen- or progestin-containing hormonal intrauterine device, surgical sterilization of the partner, physical barrier with spermicide for at least 14 days prior to first dosing and throughout the study, bilateral tubal ligation or salpingectomy) or abstinence from heterosexual intercourse for at least 28 days prior to first dosing and throughout the study. *Note*: estrogen-containing compounds are exclusionary for subjects entering the PK substudy. A female subject who becomes sexually active during the course of the study must agree to use a physical barrier method (eg, condom, diaphragm) with spermicide from the time of the start of sexual activity and throughout the study.

8.6.2. Other Restrictions

8.6.2.1. Alcohol Consumption

For only those subjects participating in the PK substudy, subjects must agree to abstain from alcohol intake from 48 hr before study drug administration on Day 22 of the Maintenance Period until the end of the inpatient period (Maintenance Day 29).

8.6.2.2. Fasting

Subjects will be required to fast from all food and drink except water for at least 10 hrs prior to the collection of blood when a glucose evaluation is planned. Fasting will not be required for other safety laboratory testing or when a safety recheck is deemed necessary and glucose assessment is not included.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

9.1.1. XP-8121

XP-8121 is supplied as a sterile, nonpyrogenic, preservative-free, liquid for injection of levothyroxine sodium 10 mg/mL packaged in single-use glass vials. XP-8121 will be administered using a sterile-packaged, 0.3 mL Covidien™ (now Cardinal Health™) Monoject™ Insulin Syringe. XP-8121 is manufactured using XeriSol formulation technology that includes DMSO, trehalose, mannitol, and sulfuric acid.

Further details relating to preparation, storage, and administration of XP-8121 will be provided in the Pharmacy Manual.

9.2. Concomitant Medications

Medication (eg, prescription drugs, over the counter (OTC) drugs, vaccines, topical medications, herbal remedies) used by a subject from 30 days or 5 half-lives (whichever is the longer) before Screening and for the duration of the study will be recorded on the subject's eCRF, including the medication name, total daily dose, route, frequency of dosing, and indication for use.

9.2.1. Prohibited Medications

The following medications are prohibited:

- Administration of an investigational product in another trial within 30 days prior to the Screening, or five half-lives, whichever is longer.
- Use of any levothyroxine (other than XP-8121) or any combined thyroid hormone preparation (eg, Synthroid plus liothyronine or Synthroid plus Armour Thyroid) and/or any other non-approved oral thyroid replacement.
- Use of any estrogen-containing compound within 14 days prior to Day 1 of the Titration Period and throughout the study (subjects in PK substudy only).
- Use of any supplements containing biotin within 7 days prior to Screening and during the study.
- Use or history of using anticoagulants 14 days prior to Screening.
- Use of aspirin greater than 325 mg/day prior to Screening and during the study.

9.3. Treatment Compliance

All doses of XP-8121 will be administered at the CRU. Study drug administration during Titration and Maintenance Periods will be recorded on the drug accountability log.

9.4. Randomization and Blinding

This is an open-label, non-randomized study.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

The Sponsor will supply XP-8121 to the investigational site. The XP-8121 provided for this study will be manufactured under current Good Manufacturing Practices (cGMP) and will be suitable for human use.

10.2. Study Drug Packaging and Labeling

XP-8121 is supplied as a sterile, nonpyrogenic, preservative-free, liquid for injection as levothyroxine at 10 mg/mL. The formulation is a clear, colorless-to-yellow solution packaged in single-use glass vials. The Sponsor is responsible for the preparation and labeling of XP-8121, and for providing details such as batch numbers, safety, and stability data.

XP-8121 will be labeled in accordance with applicable regulatory requirements and will be shipped under temperature monitored conditions at a temperature of 2 °C to 8 °C (35-46 °F).

10.3. Study Drug Storage

The Investigator or an approved member of the study staff will ensure that 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 condition must be documented (including minimum and maximum temperature excursions as well as an 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 an appropriate course of action taken, regarding the future use of the study drugs, upon consultation with Xeris.

The Investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational drug product.

Further details are provided in the Pharmacy Manual.

10.3.1. XP-8121 Storage

Vials containing XP-8121 should be stored at 2 °C to 8 °C (35-46 °F).

10.4. Study Drug Preparation

Procedures relating to study drug preparation and dispensing are outlined in the Pharmacy Manual.

10.5. Administration and Dose

Subjects will receive single doses of XP-8121 on a weekly basis (every 7 days). The time of the weekly XP-8121 dose administration will remain consistent throughout the study and will occur within ±2 hours of the time of the XP-8121 SC initiation dose. The SC injections of the XP-8121 will be performed within the periumbilical region of the abdomen.

The Investigator and/or delegate is responsible for the education of study staff as to the correct timing and procedure for administration of the study drug. Further details are provided in the Pharmacy Manual.

10.6. Study Drug Accountability

A record will be maintained by the investigational site that will account for all dispensing and return of any used and unused study drug. At the end of the study, the study drug will be reconciled, and a copy of the record will be included in the Trial Master File (TMF).

10.7. Study Drug Handling and Disposal

On completion of the study, any study drug surplus will be destroyed, in accordance with the procedures of the investigational site and following receipt of written approval from the Sponsor unless otherwise specified. Documented evidence of the destruction of any surplus study drug will be included in the TMF. If no supplies remain, this will be documented in the accountability record.

11. STUDY SCHEDULE

A Schedule of Assessments is provided in Table 2. See Table 3 for a table of timing window allowances for T4 and TSH sampling, ECG collections and vital sign measurements.

This study includes the following periods: Screening, Titration Period, and Maintenance Period. The study will conclude with an End of Maintenance Visit or, if applicable, the ET Visit.

11.1. Screening (Day -28 to Day -1)

Prior to enrolling and before performance of any procedures, potential subjects will arrive at the CRU for Screening, at which time they will be provided with complete information about the study assessments and procedures. They will also be provided with an ICF, be given time to review it and will be encouraged to discuss questions with the site staff prior to being asked to sign.

After the ICF is signed, Screening assessments will be carried out as follows:

- Review of inclusion and exclusion criteria
- Review of concomitant medications and medical history which should include adequate historical data on the etiology of hypothyroidism and prior treatments (e.g., prior surgeries and radiation therapies, including radioactive iodine)
- Complete physical examination (See Section 12.8.2 for details)
- Measurement of height and weight (See Section 12.8.3 for details)
- Calculation of BMI (weight (kg) / [height (m)]^2) (See Section 12.8.3 for details)
- 12-lead ECG (See Section 12.8.5 for details)
- Vital sign measurements (See Section 12.8.4 for details)
- Serology sample collection (hepatitis C virus (HCV), HBsAg, & HIV)
- Clinical safety laboratory testing (hematology, chemistry, and urinalysis). See Section 12.8.7 for details. See Section 8.6.2.2 for fasting requirements.
- Free and total T4 and TSH measurements
- Urine drug screen (See Section 12.8.8 for details)
- Urine pregnancy test (WOCBP only) (See Section 12.8.9 for details)

During the Screening Period, subjects will continue their prescribed daily dose of oral levothyroxine.

At Screening, subjects must have TSH and fT4 clinical laboratory values within the normal range (study reference range for TSH and fT4 are 0.47 to 4.68 µIU/mL and 0.78 to 1.42 ng/dL, respectively). (Note: TSH is also required to be within the normal range for at least 3 months prior to Screening [documented by local laboratory].)

If a potential subject does not meet the eligibility requirements described in the Section 8 on initial Screening, they may be eligible to re-screen only if their medical condition has changed and increases the likelihood that they would meet the study eligibility criteria. Such re-screenings will be exceptional circumstances, and all re-screenings require prior permission of the study Medical Monitor before they begin. Repeating Screening visit laboratory assessments for clinical

safety (with Medical Monitor approval) and repeating a Screening test (eg, fT4 and/or TSH) that has been found to be technically flawed will not be considered re-screening.

Note: AEs and changes in medications will be recorded from the time of informed consent. Repeat urine drug screens will be permitted for suspected false positive results. A repeat of the Screening visit laboratory assessments for clinical safety (hematology, chemistry, and urinalysis) may be permitted after consultation with the Medical Monitor.

11.2. Titration Period

The XP-8121 initiation dose will correspond to 50% of the target weekly dose of XP-8121 SC (in µg), which is calculated as the current daily oral levothyroxine dose (in µg) multiplied by 4 and rounded up to the nearest 50 µg.

XP-8121 will be titrated biweekly, as needed, by intervals of 25% of the target dose, up to a maximum of 125% of the target or 1500 µg (whichever is lower). Titration algorithm details are outlined in Appendix A. See Section 7.4, Dose Adjustment Criteria, for further details.

The following procedures will be conducted once a week for 2 up to 8 weeks as applicable or unless otherwise noted:

- Abbreviated physical examination (See Section 12.8.2 for details)
- Vital sign measurements (See Section 12.8.4 for details)
- Free and total T4 and TSH measurements
- Urine pregnancy test (WOCBP only) will be done every 2 weeks (ie, Weeks 1, 3, 5 and 7) during this period (See Section 12.8.9 for details)
- XP-8121 administration (See Section 10.5)
- Modified Draize Scale to be completed 30 (±5) minutes after each XP-8121 injection. If the Draize score is >1 at 30 minutes, the subject will be discharged, and a follow up visit will be scheduled at 24 (±3) hrs post-dose to allow the Investigator or designee to complete an assessment of the injection site using the Modified Draize Scale. See Appendix E for details.
- Injection Site Discomfort Evaluations to be completed (See Appendix C): Numeric Rating Scale for Injection Site Discomfort to be done 10 (±2) minutes after injection as well as Injection Site Discomfort Description and Duration Questionnaire completed 10 (±2) minutes after each XP-8121 injection.
- Treatment Satisfaction Questionnaire for Medication (TSQM-9) to be completed during the first visit of the Titration Period prior to XP-8121 administration.
- Review of AEs and changes in concomitant medication

Following the initial XP-8121 dose and any up-titrations, subjects will be required to return for an outpatient visit 72 hr (±1) day. The following procedures will be conducted:

- Abbreviated physical examination (See Section 12.8.2 for details)
- 12-lead ECG (See Section 12.8.5 for details)
- Vital sign measurements (See Section 12.8.4 for details)
- Free and total T4 and TSH measurements

- Review of AEs and changes in concomitant medication

11.3. Maintenance Period

Once subjects have completed the Titration Period, they will continue at the same dose of XP-8121 in the Maintenance Period for 4 weeks. All subjects will return to the CRU weekly for dosing before having an End of Maintenance Visit.

The following procedures will be conducted once a week for 4 weeks (Day 1, Day 8, Day 15, and Day 22), as applicable, unless specified differently below:

- Clinical safety laboratory testing (hematology, chemistry, and urinalysis) on Day 1 (Week 1 Maintenance Period). See Section 12.8.7 for details. See Section 8.6.2.2 for fasting requirements.
- Free and total T4 and TSH measurements every week
- Urine pregnancy test (WOCBP only) on Day 1 (Week 1 Maintenance Period) (See Section 12.8.9 for details)
- XP-8121 administration (See Section 10.5)
- Modified Draize Scale to be completed 30 (±5) minutes after each XP-8121 injection. If the Draize score is >1 at 30 minutes, the subject will be discharged, and a follow up visit will be scheduled at 24 (±3) hr post-dose to allow the Investigator or designee to complete an assessment of the injection site using the Modified Draize Scale. See Appendix E for details.
- Injection Site Discomfort Evaluations to be completed (see Appendix C): Numeric Rating Scale for Injection Site Discomfort to be done 10 (±2) minutes after injection as well as Injection Site Discomfort Description and Duration Questionnaire completed 10 (±2) minutes after each XP-8121 injection.
- TSQM-9 questionnaire to be completed on Maintenance Day 22 after last administration of XP-8121.
- Review of AEs and changes in concomitant medication

11.3.1. XP-8121 Pharmacokinetic Substudy

During Week 4 of the Maintenance Period, a subgroup of subjects (~12) who have been on Synthroid for at least 3 months prior to Screening and who have maintained adequate trough T4 (free and total) concentration levels (study reference ranges: 0.78 to 1.42 ng/dL and 5.53 to 10.96 µg/dL, respectively) in the Maintenance Phase will participate in a PK substudy. Subjects will be housed in the CRU for 9 days and 8 nights to undergo PK sample collections at specified timepoints as outlined in Table 5.

Subjects will be admitted to the CRU on Maintenance Day 21 (day prior to XP-8121 administration and initiation of PK sampling) and discharged from the CRU on Maintenance Day 29 (168 hr PK sample). During the inpatient period, subjects are to be fed standardized meals according to the clinic schedule. In addition to PK sample collections at the specified timepoints noted below, all procedures required for Maintenance Day 22 and Maintenance Day 29 are to be completed per protocol. There are no additional procedures required during the inpatient period.

Venous blood samples (approximately 5 mL) will be collected for the determination of plasma T4 and T3 concentrations.

Table 5 outlines the PK sampling timepoints. The actual collection time of each sample must be recorded in the source data documentation and in the eCRF. The PK sample on Day 29 should be drawn before administration of previous oral levothyroxine. A deviation will be recorded if the collection time falls outside of the allowed time windows. Instructions for the collection and handling of the PK samples will be provided. The samples will be analyzed utilizing a validated assay of appropriate sensitivity and specificity.

Table 5: Pharmacokinetic Sample Timepoints

XP-8121 Pharmacokinetic Sampling	
Day 22: Predose	within 10 minutes of dosing
Day 22: 1, 6, 12, and 18 hr post dose	±5 minutes for 1-hour timepoint; ±10 minutes for 6, 12, and 18 hr timepoints
Days 23-29: 24,36,48,60,72,84,96,108, 120,144 and 168 hr post Day 22 dose	±10 minutes

11.3.2. End of Maintenance Visit

An End of Maintenance Visit will be performed on Maintenance Day 29, 1 week after the last XP-8121 dose. At the End of Maintenance Visit, the following procedures will be conducted:

- Complete physical examination (See Section 12.8.2 for details)
- Weight (See Section 12.8.3 for details)
- 12-lead ECG (See Section 12.8.5 for details)
- Vital sign measurements (See Section 12.8.4 for details)
- Clinical safety laboratory testing (hematology, chemistry, and urinalysis). See Section 12.8.7 for details. See Section 8.6.2.2 for fasting requirements.
- Free and total T4 and TSH measurements
- Urine pregnancy test (WOCBP only) (See Section 12.8.9 for details)
- Restart previously prescribed daily oral levothyroxine medication
- Subject Preference Survey (Appendix D)
- Review of AEs and changes in concomitant medication. AEs that are ongoing at the End of Maintenance Visit will be recorded on the CRF and followed until resolution or maximally up to 14 days after the End of Maintenance.

11.4. Early Termination Visit

An ET Visit will be performed 14 (±2) days after the last dose of XP-8121. Subjects who withdraw prematurely from the study will be encouraged to complete an ET Visit to assess safety.

The following procedures will be conducted at the Early Termination Visit:

- Complete physical examination (See Section 12.8.2 for details)
- Weight (See Section 12.8.3 for details)
- 12-lead ECG (See Section 12.8.5 for details)
- Vital sign measurements (See Section 12.8.4 for details)
- Clinical safety laboratory testing (hematology, chemistry, and urinalysis). See Section 12.8.7 for details. See Section 8.6.2.2 for fasting requirements.
- Free and total T4 and TSH measurements
- Urine pregnancy test (WOCBP only) – if urine pregnancy test result is positive, a serum pregnancy test must be conducted to confirm results.
- Subject Preference Survey (Appendix D)
- Review of AEs and changes in concomitant medication. AEs that are ongoing at the ET Visit will be recorded on the CRF and followed until resolution or maximally up to 14 days after the ET Visit.

11.5. Order of Procedures

When applicable, all procedures are to be performed pre-dose except for the Modified Draize Scale and Injection Site Discomfort Evaluations, unless otherwise stated. Where possible, assessments should be conducted in order of least invasive to most invasive. When ECGs, vital signs measurement, and/or blood draws are required at the same visit, they should be performed in the aforementioned order.

Note that at Screening only, the order of ECGs, vital signs, and blood draw procedures are allowed to vary.

12. ASSESSMENT OF SAFETY

Safety assessments include evaluations of AEs/SAEs, physical examinations, vital sign measurements, clinical safety laboratory evaluations, ECGs, and injection site assessments. Safety assessments will be performed at specified timepoints as defined in Table 2 and Table 3. All spontaneously volunteered and enquired for, as well as observed AEs, will be recorded in the subject's source documentation and the eCRF. Additional unscheduled safety assessments may be performed at other times if deemed necessary by the Investigator.

12.1. Adverse and Serious Adverse Events

12.1.1. Definition of Adverse Events

12.1.1.1. Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

12.1.1.2. Serious Adverse Event

A SAE is an AE occurring during any study period and at any dose of the study drug that fulfils one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

All SAEs that occur after any patient/subject has been enrolled, before treatment, during treatment, or within 14 days following the cessation of treatment, whether or not they are related to the study, must be recorded on forms provided by Xeris.

12.1.1.3. Other Adverse Event (OAE)

OAEs will be identified by the Drug Safety Physician and if applicable also by the Clinical Study Team Physician during the evaluation of safety data for the Clinical Study Report (CSR). Significant AEs of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient/subject from the study, will be classified as OAEs. For each OAE, a narrative may be written and included in CSR.

12.2. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the study drug for each AE (Unrelated, Possibly Related, Probably Related or Definitely Related).

The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the study drug. If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the study drug and the occurrence of the AE, then the AE should be considered "related."

If the relationship between the AE/SAE and the study drug is determined to be "possible" or "probable" the event will be considered to be related to the study drug for the purposes of expedited regulatory reporting.

12.3. Recording Adverse Events

Adverse events spontaneously reported by the patient/subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, BP, and heart rate/pulse also need to be reported as AEs. Disease -related events will be recorded as AEs if the events occur with greater frequency, severity or duration than expected. Information about AEs will be collected from the signing of consent form and followed until resolution or maximally up to 14 days after the End of Maintenance. Serious Adverse Event information will be collected from time of consent and followed until resolution. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. An AE of severe intensity may not be considered serious.

Should a pregnancy occur, it must be reported within 24 hrs of the first awareness of the event and recorded on Xeris' pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

12.4. Reporting Adverse Events

Adverse events including SAEs will be reported for all subjects from the time of consent until the completion of the End of Maintenance Visit. AEs that are ongoing at the End of Maintenance

Visit will be recorded on the CRF and followed until resolution or maximally up to 14 days after the End of Maintenance Visit or ET Visit.

Any SAEs considered possibly or probably related to the study drug and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to Xeris within 24 hr of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy to Xeris via email to both ClinicalPV@xerispharma.com and Xerispharma.pharmacovigilance@propharmagroup.com.

Additional follow-up information, if required or available, should all be sent to Xeris via email to both ClinicalPV@xerispharma.com and Xerispharma.pharmacovigilance@propharmagroup.com within 24 hrs of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

Xeris is responsible for notifying the relevant regulatory authorities of certain events. It is the Investigator's responsibility to notify the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

12.5. Adverse Event Reporting Requirements to Regulatory Authorities

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

An Investigator must notify the IRB/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.

12.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments Reported as Adverse Events and Serious Adverse Events

Abnormal laboratory findings (eg, serum chemistry, hematology, and urinalysis) or other abnormal assessments (eg, ECG and vital signs) per se are not reported as AEs. However, those abnormal findings that are deemed **clinically significant** by the Investigator and/or delegate or are associated with signs/symptoms must be recorded as AEs if they meet the definition of an AE (and recorded/reported as an SAE if they meet the criteria of being serious) as previously described. Clinically significant abnormal laboratory or other clinically significant abnormal findings that are detected after consent or that are present at Screening and worsen after consent are included as AEs (and SAEs if serious).

12.7. Subject Monitoring

Subjects will be monitored for AEs throughout the study by the CRU staff. The Investigator or designated sub-Investigator will be available during onsite drug administration. The Investigator or designated sub-Investigator will also be available (eg, "on call") for the subject as needed.

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 before taking any medicines or undergoing any medical procedure.

12.8. Other Safety Parameters

12.8.1. Subject Blood Volumes to be Drawn Over the Course of the Study

The approximate amount of blood drawn over the course of the study for each subject is presented below in Table 6 and Table 7.

Table 6: Number and Volume of Blood Collections for Subjects Not Participating in Pharmacokinetic Substudy

Sample Type	Volume Per Sample (mL)	Total Volume (mL)			
		Screening Period	Titration Period	Maintenance Period	ET
Clinical Chemistry	7.5	7.5	0	15	7.5
Free and total T4	2	2	6-24	10	2
TSH	3.5	3.5	10.5-42	17.5	3.5
Hematology	3	3	0	6	3
Serology	5	5	0	0	0
Cumulative Sample Volume	21	21	16.5-66	48.5	16
		Total Volume (mL) for Study through End of Maintenance Period: 86-135.5			

Abbreviations: ET= Early termination; mL = milliliter; TSH = thyroid-stimulating hormone, T4 = thyroxine

Table 7: Number and Total Volume of Blood Collections for Subjects Participating in Pharmacokinetic Substudy

Sample Type	Volume Per Sample (mL)	Total Volume (mL)			
		Screening Period	Titration Period	Maintenance Period	ET
Clinical Chemistry	7.5	7.5	0	15	7.5
Free and total T4	2	2	6-24	10	2
TSH	3.5	3.5	10.5-42	17.5	3.5
Hematology	3	3	0	6	3
Serology	5	5	0	0	0
Substudy PK	4	0	0	64	0
Cumulative Sample Volume	25	21	16.5-66	112.5	16
		Total Volume (mL) for Study through End of Maintenance Period: 150-199.5			

Abbreviations: ET= Early termination; mL = milliliter; PK = pharmacokinetic; TSH = thyroid-stimulating hormone, T4 = thyroxine

12.8.2. Physical Examination

Complete and abbreviated physical examinations will be performed by the Investigator or appropriately trained, delegated designee at the timepoints specified in the Schedule of Assessments (Table 2).

Complete physical examinations include general appearance, head, ears, eyes, nose, throat, dentition, thyroid, respiratory, cardiovascular, abdomen, skin, neurological, musculoskeletal, and lymph nodes.

Abbreviated physical examinations include head, ears, eyes, nose, throat, respiratory, cardiovascular, abdomen, skin, musculoskeletal, and lymph nodes and any pertinent system based on any prior findings.

12.8.3. Weight, Height, BMI

Body height (centimeters) and body weight (kilograms) will be measured at Screening and will be used to calculate BMI (kg/m^2). Body weight and height will be obtained with the subject's shoes and jacket removed.

12.8.4. Vital Sign Measurements

Vital signs (systolic and diastolic BP, heart rate/pulse, respiratory rate, oral temperature) will be measured as described in the Schedule of Assessments (Table 2). Three readings of BP and heart rate/pulse should be taken at intervals of 1 to 2 minutes. The three readings of each will be recorded on the eCRF and assessed to determine eligibility for inclusion into the study and throughout the study (Section 8.1).

Subjects should be resting for at least 10 minutes in a supine position prior to measurement of BP and heart rate/pulse. See Table 3 for timing window allowances with respect to measurement collection. Where possible, assessments should be conducted in order of least invasive to most invasive (See Section 11.5 for details).

12.8.5. Electrocardiogram

12-lead ECGs are to be performed prior to vital signs with subjects in a supine position at least 10 minutes before the reading is taken. See Table 3 for timing window allowances with respect to measurement collection.

All ECG tracings will be reviewed and assessed by the Investigator or designee. All potentially clinically significant automated ECG readings should be repeated within 5 minutes of the reading. If potentially clinically significant reading is confirmed, then the ECG will be sent to a local cardiologist for review.

12.8.6. Local Tolerability

Local tolerability will be assessed following SC injection as follows:

- The Investigator/qualified designee will use the Modified Draize Scale (Appendix E) to assess erythema and edema formation at the injection site at 30±5 minutes after injection of XP-8121. Note: If the Draize score is >1 at 30 minutes, the subject will be discharged, and a follow up visit will be scheduled at 24 (±3) hrs after injection in order for the Investigator or designee to complete an assessment of the injection site using the Modified Draize Scale.

- To assess injection site discomfort, subjects will complete an 11-point Numeric Rating Scale (NRS) questionnaire and an Injection Site Discomfort Description and Duration Questionnaire 10 (±2) minutes after injection of XP-8121 (Appendix C).

12.8.7. Clinical Safety Laboratory Assessments

Safety laboratory tests will be performed at the timepoints specified in the Schedule of Assessments (Table 2). Additional laboratory tests may be performed at other times, if deemed necessary by the Investigator. A repeat of the Screening visit laboratory assessments for clinical safety (hematology, chemistry, and urinalysis) may be permitted after consultation with the Medical Monitor.

The central laboratory will perform hematology, chemistry, and urinalysis tests. Blood and urine samples for hematology, chemistry, and urinalysis will be prepared using standard procedures. Laboratory panels are defined as listed in Table 8.

Table 8: Clinical Safety Laboratory Tests

Hematology	Serum Chemistry	Urinalysis (Dipstick)	Virology
• Erythrocytes (red blood cells [RBC]) • Hematocrit • Hemoglobin • Leukocytes with differential (including eosinophils, neutrophils, basophils, monocytes, lymphocytes, and reticulocytes) • Mean platelet volume • Platelets	• ALT • Albumin • Alkaline phosphatase • AST • Bicarbonate • Calcium • Chloride • Creatine kinase • Creatinine • Globulin • Glucose (fasting laboratory assessments only) • HbA1c • Phosphate • Potassium • Sodium • Thyroid-stimulating hormone • T4 • Total and direct bilirubin • Urate • Urea	• Blood • Glucose • Ketones • Leukocytes • Nitrite • pH • Protein • Specific gravity • Total bilirubin • Urobilinogen • If abnormality is noted for protein, blood, nitrite or leukocyte esterase, a microscopic examination of RBC, white blood cell (WBC), bacteria, and casts will be performed	• Hepatitis C • Hepatitis B • HIV

Abnormalities in clinical laboratory tests that are considered clinically significant are to be recorded on the AE eCRF page. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as an SAE (see Section 12.4).

12.8.8. Urine Drug Screen

A urine drug screen will be performed at Screening and will include the following:

- Tetrahydrocannabinol

- Cocaine
- Amphetamines
- Barbiturates
- Benzodiazepines
- Opiates
- Methadone
- Methamphetamines
- Ecstasy (3,4-Methylenedioxymethamphetamine [MDMA])
- Phencyclidine

Repeat assessments may be performed in the event of a suspected false positive result.

If the results are positive for a benzodiazepine that is being taken as a prescribed concomitant medication, as defined and documented in accordance with Section 9.2, then the assessment would not have to be repeated.

12.8.9. Pregnancy Testing

A urine pregnancy test is to be performed all timepoints specified in the Schedules of Assessments (Table 2). If a urine pregnancy test returns a positive result, a serum pregnancy test must be performed in order to confirm the result. If confirmed positive, subjects should be withdrawn and pregnancy reported to Sponsor within 24 hr. See Section 12.3 for reporting requirements for pregnancies.

13. STATISTICS

Detailed methodology for PK descriptive and inferential statistical analyses of the data collected in this study will be documented in the Statistical Analysis Plan (SAP). This SAP will be used for both clinical parameters from the eCRF and the PK parameters derived from bioanalytical analysis data. Procedures outlined in the SAP will supersede protocol-specified statistical methods in the event of divergence.

Descriptive statistics will be used to summarize clinical and laboratory data. Continuous data will be represented by n (number of subjects), mean, median, standard deviation (SD), and range. Categorical variables will be presented by number and percentage of subjects (n [%]). Additional details of the testing procedures not included here, including handling of missing data, will be described in the SAP.

If not otherwise stated, baseline will be determined by the last evaluable assessment prior to dosing in each period. Measurement of specific baseline values will be described in the SAP.

13.1. Sample Size Determination

Assuming a between-subject coefficient of variation of 0.5 and a within-subject, between measurements correlation of 0.5, a sample size of 38 subjects will have 80% power to reject the null hypothesis that the dose conversion factor is less than 3.2X or more than 5X, in favor of the alternative hypothesis that the dose conversion factor is between 3.2X and 5X (in another words, within 80% and 125% of the proposed 4X conversion factor derived from PPK modeling). For the exploratory endpoint of TSQM-9, assuming a SD of differences of 20, a sample size of 34 subjects will have 80% power to detect a difference of 10 in means (domain scores range from 0 to 100) with a 5% two-sided significance level (α=0.05). Taking into consideration study non-completers and non-normalizers of TSH at study end, a total of 44 subjects will be enrolled.

13.2. Subject Disposition

The number of subjects enrolled, included in each analysis population, who complete the study, and who prematurely discontinue, along with reason for discontinuation will be summarized.

13.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for all subjects. Summary statistics will be generated for continuous variables and the number and percentage of subjects within each category will be presented for categorical variables.

13.4. Analysis Populations

Safety Population: All subjects who receive at least 1 dose of XP-8121.

Completer Population: All subjects who complete the Maintenance Period and exhibit normalized TSH throughout the Maintenance Period while on a stable dose for approximately 6 weeks.

PK Population: All safety population subjects who participate in the PK substudy, who do not have any major protocol deviations affecting the PK endpoints and for whom a sufficient number of samples is available to determine at least one PK parameter.

13.5. Study Endpoints

13.5.1. Primary Endpoints

- Safety endpoints collectively include incidence, frequency, severity, and relationship to study drug of TEAEs, including clinically significant vital sign measurements, safety laboratory test results, ECGs, and physical examinations
- Tolerability assessments include Modified Draize Scale and Injection Site Discomfort questionnaires
- Geometric mean ratio of the weekly dose of XP-8121 SC (in μg) to the daily dose of oral levothyroxine (aka dose conversion factor), where the XP-8121 dose corresponds to the administration immediately preceding collection of blood TSH used to determine normalization at the end of Maintenance Period

13.5.1.1. Analysis of Primary Endpoint (Dose Conversion Factor)

The final dose conversion factor will be assessed by comparing the ln-transformed final XP-8121 SC dose (in μg) that maintains normalized TSH throughout the Maintenance Period to the ln-transformed daily oral levothyroxine dose (in μg) the subject was taking before the study, using a linear mixed effects model with treatment as fixed effects, and subject as random effect. Geometric LSMs, geometric mean ratios, and 90% CIs will be presented. This endpoint will be analyzed using the Completer population for subjects with primary hypothyroidism only. Additional sensitivity analyses that include subjects with secondary/tertiary hypothyroidism, subjects with dose adjustment, and/or subjects that maintain normal free T4 may be conducted. The details of the sensitivity analyses will be described in the SAP.

Analysis of safety endpoints will be described in Section 13.7.

13.5.2. Secondary Endpoints

The secondary endpoints of the study are as follows:

- Proportion of subjects enrolled with normalized TSH throughout the Maintenance Period
- Proportion of subjects enrolled with normalized TSH at the end of Maintenance Period
- Blood thyroid hormone concentrations (total thyroxine, fT4 and TSH) following the first dose of XP-8121 and after titration (ie, during the Titration and Maintenance Periods)

13.5.2.1. Analysis of Secondary Endpoints

Secondary endpoints will be analyzed for the safety population, for subjects with primary hypothyroidism only and for all subjects, if applicable. Subjects with normalized TSH throughout the Maintenance Period and at the end of Maintenance Period will be presented by number and percentage of subjects referenced to the safety population and the number of subjects entering the Maintenance Period, along with corresponding 95% CIs. TSH, total and free T4 measures following the first dose of XP-8121 will be summarized using descriptive statistics. Number and percentage of subjects with results outside the normal ranges will be tabulated.

13.5.3. Exploratory Endpoints

- Observed values and changes from baseline values in thyroid hormones (total and fT4) and TSH during the Titration and Maintenance Periods
- Pharmacokinetic profile of plasma thyroid hormones (T4 and T3 during the 168-hr PK period (PK substudy only):
  - T_{max}
  - C_{max} and C_{max} normalized by dose (C_{max}/Dose)
  - $AUC_{0\text{-}168hr}$ and $AUC_{0\text{-}168hr}$ normalized by dose ($AUC_{0\text{-}168hr}$/Dose)
  - If supported by the data, the following additional parameters may be calculated:
    - Total apparent clearance (CL/F)
- Comparison of the score of Convenience, Overall Satisfaction, and Effectiveness domain of the TSQM-9 between oral levothyroxine and once-weekly XP-8121 SC treatments
- Summary of results from the Subject Preference Survey

13.5.3.1. Analysis of Exploratory Endpoints

All exploratory endpoints except for PK endpoints will be analyzed for the safety population, for subjects with primary hypothyroidism only and for all subjects, if applicable. TSH, total and free T4 measures and changes from baseline will be summarized by each protocol-specified timepoint using descriptive statistics. Analysis of PK endpoints will be described in Section 13.6.

The analysis of the exploratory endpoint of TSQM-9 domain scores will be gated on results from the primary endpoint analysis. The three domain scores will be hierarchically analyzed to ensure control of the family-wise type I error rate at the 0.05 level, with the Convenience score first, Overall Satisfaction score second, and Effectiveness third. Hypothesis tests for the three domain scores will be based on null hypotheses that assume no difference between oral levothyroxine and once-weekly XP-8121 SC treatments. Each domain score will be compared between the two treatments using a paired t-test.

Subject counts and percentages for each answer to each question from the Subject Preference Survey will also be presented.

13.6. Pharmacokinetics

Plasma PK parameters will be summarized for all subjects in the PK Population, using descriptive statistics (number of non-missing observations (N), arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%).

Total plasma concentration of thyroxine and triiodothyronine will be summarized by collection timepoint within the PK period for all subjects in the PK Population using descriptive statistics (N, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%).

13.7. Safety and Tolerability

All safety analyses will be performed using the Safety population. Safety data will be collected and summarized by study period (Titration Period, Maintenance Period). No formal hypotheses will be tested on safety data.

13.7.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or higher. Listings of all AEs, treatment-emergent SAEs, and TEAEs leading to study discontinuation will be provided by subject, study period, verbatim term, MedDRA System Organ Classification (SOC) and Preferred Term (PT), start and end dates, seriousness, severity, relationship to study drug, action taken with study treatment, 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 study period: any AE, any TEAE, any drug-related TEAE, any severe 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 study period and overall (while taking XP-8121) will be tabulated by SOC and PT; by SOC, PT, and severity (mild, moderate, and severe); and by SOC, PT, and relationship to study drug.

The number and percentage of subjects reporting an SAE or reporting a TEAE leading to premature discontinuation of study drug in each study period and overall will be summarized by SOC and PT.

13.7.2. Laboratory Evaluations, Vital Sign Measurements, and Electrocardiograms

Laboratory evaluations (including TSH), vital signs, and ECG assessments will be summarized by study period, and protocol-specified collection timepoint within each period using descriptive statistics. A summary of change from baseline at each protocol-specified timepoint will also be presented.

Listings of clinically significant abnormal laboratory values will be presented. Individual laboratory results will be listed indicating values outside normal range. Vital signs and electrocardiogram results will be listed.

13.7.3. Prior and Concomitant Medications

Prior and concomitant medications will be mapped to a World Health Organization (WHO) drug classification using WHO Drug Dictionary (WHO-DD) and summarized for anatomical therapeutic chemical (ATC), and PT.

Prior and concomitant medication will be summarized for all subjects. A listing of prior and concomitant medications will be provided for the safety population.

13.7.4. Local Tolerability

Local tolerability (incidence of injection site discomfort and erythema/edema) will be summarized by protocol-specified timepoint following SC injections of XP-8121. Specifically, subjective injection site discomfort as reported by the NRS and Discomfort Description and Duration Questionnaire will serve as the data basis. The incidence of any injection site discomfort (score >0 on the ordinal rating scale) will be analyzed descriptively. Descriptive statistics also will be provided for time of onset and duration (of discomfort), and discomfort description (i.e., pain, irritation, itching, etc.).

In addition, erythema and/or edema formation at the injection site will be assessed using the Modified Draize Scale. Counts and percentages of each category on the erythema/edema spectrum will be presented for each scheduled timepoint.

13.7.5. Physical Examinations

Findings on the physical examinations will be listed by subject, and abnormal findings will be flagged for clinical significance based on the investigator's judgment.

13.8. Other Assessments

The following assessments will be listed by subject:

- Medical history (coded using MedDRA)
- Pregnancy test
- Urine drug screen

13.9. Statistical Issues

13.9.1. Missing or Imputed Data

No statistical adjustments for missing data will be conducted.

13.9.2. Interim Analysis

No interim analysis will be conducted.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of Xeris will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Xeris or its representatives. This will be documented in a Clinical Study Agreement between Xeris and the Investigator.

During the study, a monitor from Xeris or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that study drug accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to Xeris.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Xeris and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

The Medical Monitor will review each proposed subject prior to entering into the Titration Period of the study. The Investigator or designee will complete the Enrollment Authorization Request Form which will detail out the key eligibility criteria and submit to the medical monitor for review and approval.

14.2. Audits and Inspections

Authorized representatives of Xeris, a regulatory authority, an IRB or IEC may visit the site to perform audits or inspections, including source data verification. The purpose of a Xeris audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, International Council for Harmonization Good Clinical Practice (GCP) guidelines, and any applicable regulatory requirements. The Investigator should contact Xeris and the IRB/IEC immediately if contacted by a regulatory agency about an inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, Xeris may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to Xeris before he or she can enroll any patient/subject into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. Xeris will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)/GCP, applicable regulatory requirements and the Xeris' policy on Bioethics.

16.3. Written Informed Consent

The Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study procedures.

The Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

17. DATA MANAGEMENT

Electronic CRFs (eCRFs) will be employed for this study. Data will be entered into the eCRFs by the study site unless transmitted to Xeris or designee electronically (eg, laboratory data). Queries will be issued for any inconsistencies, omissions, and discrepancies and will be resolved by the appropriate parties. The PI or authorized designee will ensure that all information derived from the source documentation is consistent with the source information and accurately reflected in the CRF. By signing the eCRFs, the PI confirms that the information is complete and correct.

All medical history conditions and AEs will be coded using MedDRA. Concomitant medications will be coded using the current WHO-DD. Data management details will be outlined in a separate data management plan. Following database lock, archive media will be created and forwarded to the clinical site, and the clinical database will be archived.

18. DATA HANDLING AND RECORDKEEPING

18.1. Inspection of Records

Xeris will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

18.2. Retention of Records

The Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Xeris or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

19. PUBLICATION POLICY

All data generated from this study are the property of Xeris and shall be held in strict confidence along with all information furnished by Xeris. Independent analyses and/or publication of these data by an Investigator or any member of his/her staff is not permitted without prior written consent of Xeris.

Any formal presentation or publication of data from this trial will be considered as a joint publication by the Investigator(s) and appropriate Xeris personnel. Authorships will be determined chiefly by merit, with rights of final authorship decisions to be held by Xeris, unless superseded by an agreement stipulating otherwise. Factors determining merit will include active participation in study design and conduct, as well as interest and ability to participate meaningfully in analyzing or interpreting, writing, or presenting study results. The venue(s) selected for publication will be determined jointly by the publication authors. The first publication will be based on data from all study centers and analyzed as stipulated in the protocol and SAP. Investigators participating in multicenter studies agree not to present data gathered from one study center or a subset of centers before the first full publication, unless formally agreed by Xeris in advance. Written permission to Investigators to publish subset or secondary results will be contingent on prior review by Xeris of the proposed methodology and analytical plan. Any Investigator-led publication or presentation will provide for nondisclosure of Xeris confidential or proprietary information. In all cases, parties planning to publish data agree to submit all draft manuscripts or abstracts to Xeris and other relevant parties at least 60 days prior to publication submission. This will enable involved parties to protect proprietary information and to provide comments to authors.

Further details on the publication process may be provided in individual contractual agreements signed by the Investigators and Xeris.

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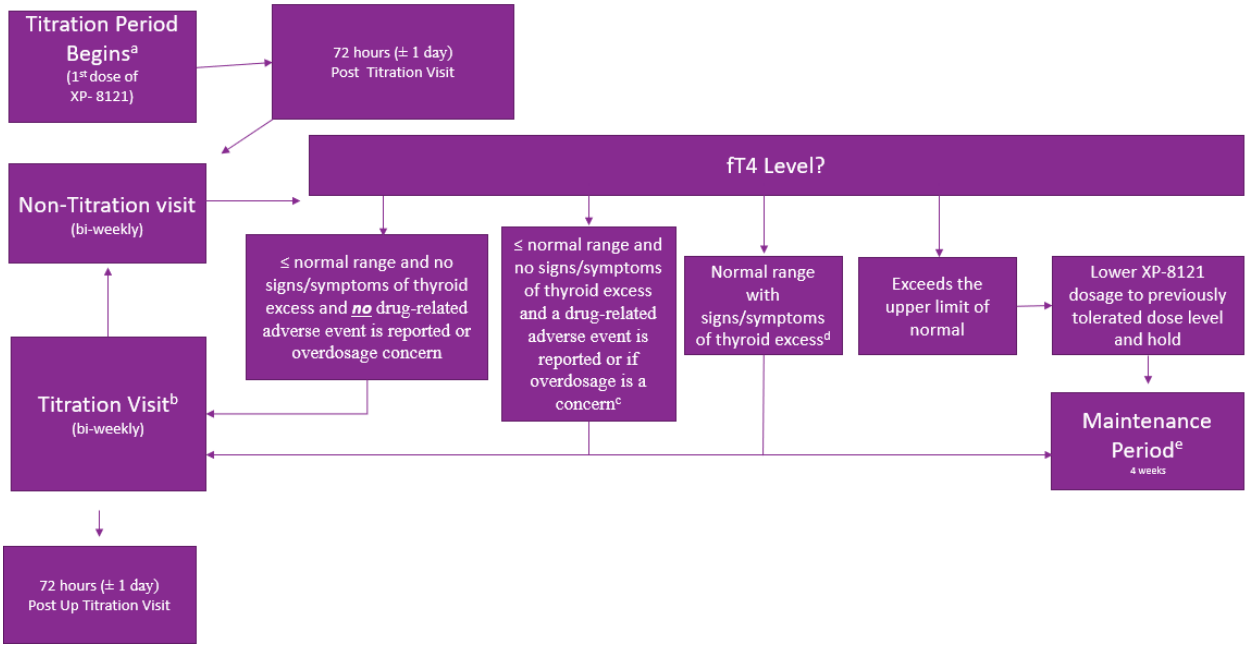
21. APPENDICES

APPENDIX A. TITRATION ALGORITHM



a. Corresponds to 50% of the target weekly dose of XP-8121 (in µg), which is calculated as the current daily oral levothyroxine dose (in µg) multipled by 4 rounded up to the nearest 50 µg.
b. During the Titration Period, XP-8121 will be titrated based on individual response to therapy (using blood free T4 [fT4] trough concentration as a fast-response, interim biomarker of replacement adequacy) at intervals no more frequent than every other week and in dosage increments corresponding to 25% of the target dose, up to a maximum of 125% of the target dose or 1500 µg (whichever is lower).
c. If a drug-related adverse event is reported or if overdosage is a concern, the Investigator should consult with the Medical Monitor before up-titrating.
d. Dosing titration decsions should be made after conferring with the Medical Monitor.
e. Once subjects have completed the Titration Period they will continue at the same dose and time of administration of XP-8121 in the Maintenance Period.

Note: Subjects not achieving an adequate fT4 at ≤125% of the target dose or the maximum weekly dose of 1500 µg may also continue into the Maintenance Period at the discretion of the Investigator and after conferring with the Medical Monitor.

APPENDIX B. SIGNS AND SYMPTOMS OF HYPERTHYROIDISM

This table includes an overview of the most common symptoms and signs for the diagnosis of hyperthyroidism. The presence of several of the following signs/symptoms may be indicative of hyperthyroidism and should be further investigated.

Table 9: Signs/Symptoms of Indicative of Hyperthyroidism

Heat intolerance
Hyperkinesis
Atrial fibrillation
Excessive sweating
Increased Appetite
Decreased Weight
Casual heart rate/pulse >90 bpm
Palpitations
Tiredness
Nervousness
Hot hands
Shortness of breath
Moist hands
Tremor
Increased frequency of bowel movements
Urinary frequency and nocturia

APPENDIX C. INJECTION SITE DISCOMFORT ASSESSMENT

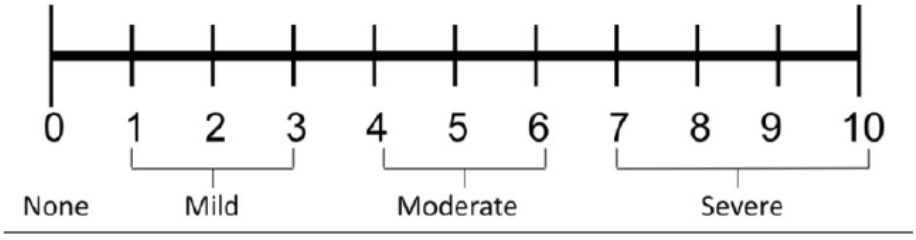
Numeric Rating Scale for Injection Site Discomfort

Investigative Site Instructions: The subject should complete the 11-point NRS for Injection Site Discomfort at 10 (±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 timepoint, 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.



Source: Downie et al, 1978

Injection Site Discomfort Description and Duration Questionnaire

Study Personnel Instructions: Question 1 should be completed by the subject at 10 (± 2) minutes after study drug injection. If the answer to Question 1 is 'Yes' then complete the following:

i. Questions 1a and 1b should be assessed at 10 (±) 2 minutes after study drug injection and,

ii. Question 1c only should be assessed once discomfort has fully resolved.

If the answer to Question 1 is 'No', then questions 1a, 1b, and 1c should not be assessed.

The goal is for the subject to report if they had any discomfort and if there was discomfort, the qualitative nature and duration of discomfort associated with the delivery of study drug, ignoring any transient pain associated with injection of study drug.

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 the questions below.

1. Did you have any discomfort from the study drug administration?

_____ Yes ____ No

If yes,

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

_____Pain (e.g., throbbing, soreness, muscle ache)

_____Itching

_____Tingling, twitching or numbness

_____Irritation (e.g., burning, stinging)

_____Other (specify): _____

1b. About how long after the study drug administration did the discomfort start?

(Please enter a number) _____ minutes

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

Source: Downie et al, 1978

APPENDIX D. SUBJECT PREFERENCE SURVEY

By participating in this study (XP-8121-120), you have now received thyroid replacement therapy in two different ways:

1. A once-daily oral pill (e.g., Synthroid) that should be taken every day at the same time before breakfast with only water and on an empty stomach and then wait for at least 30 minutes before eating, drinking, or taking any other medications.
2. A once-weekly injectable medication administered under the skin that can be taken at any time of day.

Please think back to your participation in this study (XP-8121-120) and consider your life and what works best for you. Think about the treatment itself, rather than the doctor's office or study personnel. There are no right or wrong answers.

If you had the choice between these two medications for thyroid replacement therapy, which one would you choose?

a. once-daily oral pill
b. once-weekly injection
c. no preference

If you prefer one of the administration methods, how strong is the preference?

a. Very strong
b. Fairly strong
c. Slightly strong
d. Not very strong

If you prefer one of the administration methods, what are the main reason(s) for your preference? Choose all that apply.

a. Convenience
b. Ease of administration
c. Frequency of administration
d. My level of compliance with therapy
e. Confidence in my therapy
f. Other

APPENDIX E. MODIFIED DRAIZE SCALE

Draize Scales

g. *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.
h. The injection site should be examined by the Investigator/qualified designee for formation of both erythema and edema and results recorded in the eCRF at the timepoint noted in the Schedule of Assessments.
i. If the Draize score is >1 at 30 minutes, the subject will be discharged, and a follow up visit will be scheduled at 24 (±3) hrs post-dose to allow the Investigator or designee to complete an assessment of the injection site using the Modified Draize Scale.

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
Slight erythema (Edges of area well defined by definite raising)	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

Source: FDA, 1999; Draize et al, 1944

APPENDIX F. SUMMARY OF PRIOR CHANGES TO PROTOCOL

Rationale and Summary of Changes from Protocol Version 1.0 to Version 2.0

This protocol was amended to update the minimum current daily dose of oral levothyroxine permitted for enrollment into the study to a level that would permit subjects to start at a dose of 100 µg XP-8121. The minimum laboratory values for hematocrit and hemoglobin were also updated to reflect the lower limit of the normal range for the central laboratory being used for the study. In the preparation of this amendment, other minor updates were made and are included in the following table.

Affected Sections/Tables	Summary of Revisions Made	Rationale
General	Minor formatting updates and clarifications. Updated wording to increase specificity of procedures and timing.	Administrative update.
Section 1	Added new protocol version.	Administrative update.
Summary of Revisions	Added description of changes made to the protocol with the amendment.	Administrative update.
Procedures in Case of Emergency	Removed reference to direct phone number.	Administrative update.
Section 2	Synopsis was updated to align with changes in main body of protocol.	Administrative update.
Table 2	Removed study procedure for oral levothyroxine administration during Screening and at the End of Maintenance Visit.	Oral levothyroxine administration is part of the eligibility assessments performed during the Screening Period and at the End of Maintenance it is a return to standard of care for the subject.
Table 2	Moved clinical safety laboratory assessment from the end of the Titration Period to the beginning of the Maintenance Period.	Clarified timing of clinical safety laboratory assessment from the end of the Titration Period, as it is unknown at the time of the visit if it is the last visit in the Titration Period; therefore, the laboratory assessments for this need to be performed at the beginning of the Maintenance Period.
Table 2	Clarified timing of urine pregnancy test during Titration Period as Weeks 1, 3, 5 and 7.	Administrative update.
Table 2	ECG footnote updated to include handling of potentially clinically significant ECG readings, as defined in Section 12.8.5.	Administrative update.

Affected Sections/Tables	Summary of Revisions Made	Rationale
Table 2 Section 11.2 Section 11.3 Section 12.8.6 Appendix E	Clarified description of the assessment of the injection site, if required 24 (±3) hrs post-dose to be completed using the Modified Draize Scale.	Administrative update
Section 5.5	Updated lowest dose of XP-8121 administered to 100 µg.	Updated the lowest dose to 100 µg to correspond to the initiation dose required for the lowest dose of oral levothyroxine.
Section 5.5	Updated lowest daily dose of oral levothyroxine permissible for enrollment to 50 µg.	Updated to ensure that the lowest dose of oral levothyroxine aligned with the conversion criteria being applied for the minimum starting dose of XP-8121 (eg, 4 times 50 µg, is 200 µg, and the 50% starting dose would be the minimum dose of 100 µg XP-8121).
Section 8.2	Exclusion Criteria #3 updated lowest dose of oral levothyroxine permissible for enrollment to 50 µg.	Updated to ensure that the lowest dose of oral levothyroxine aligned with the conversion criteria being applied for the minimum starting dose of XP-8121 (eg, 4 times 50 µg, is 200 µg, and the 50% starting dose would be the minimum dose of 100 µg XP-8121).
Section 8.2	Exclusion Criteria #8 updated the minimum hematocrit level allowed for enrollment to 33.5% for females and 38.7% for males.	Updated to align with the normal range for the central laboratory being used for the study.
Section 8.2	Exclusion Criteria #9 updated the minimum hemoglobin level allowed for enrollment to 10.8 g/dL for females and 12.8 g/dL for males.	Updated to align with the normal range for the central laboratory being used for the study.
Section 9.1	Removed description of unit markings on syringe.	Administrative update.
Section 11.2	Clarified timing of urine pregnancy test during Titration Period as Weeks 1, 3, 5 and 7. Removed clinical safety laboratory assessments from the end of the Titration Period.	Administrative update.
Section 11.3	Added clinical safety laboratory assessments to the beginning of the Maintenance Period	

Affected Sections/Tables	**Summary of Revisions Made**	**Rationale**
Section 11.2.1 Table 6 Table 7	Updated volume of blood drawn in the Titration and Maintenance Periods.	Updated to align with the shift of clinical laboratory assessments from the end of the Titration Period to the beginning of the Maintenance Period, maximum total volume remained unchanged. Updated to clarify minimum volume requirements for minimum free and total T4 sample collections.
Appendix C	Clarified question to align with the qualitative nature and duration of the potential discomfort associated with the delivery of study drug.	Administrative clarification.