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Phase 1 Study Evaluating the Pharmacokinetics, Dose Proportionality, Bioavailability, and Tolerability of Subcutaneous Levothyroxine Sodium (XP-8121)

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ABSTRACT

Levothyroxine sodium has been the cornerstone of hypothyroidism management worldwide, with daily oral administration (PO) recognized as standard of care. Oral administration of levothyroxine, however, poses challenges due to variability in pharmacokinetics (PK), influenced by factors such as gastrointestinal absorption, food/drug interactions, and patient adherence. XP-8121 (levothyroxine for subcutaneous administration) is a ready-to-use, subcutaneous (SC) injection formulation of levothyroxine in Phase 3 development. This Phase 1, single-center, 2-part study aimed to characterize the PK and dose proportionality of XP-8121 SC compared to 600 μg oral Ievothyroxine in healthy adults. Additionally, the study evaluated the safety and tolerability of XP-8121 and incorporated population pharmacokinetic (PPK) modeling to support future development. Part 1 was a randomized, open-label, crossover, fixed-sequence study ($n = 30$). Dose linearity was evaluated by escalating XP-8121 SC doses up to 1200 μg. Part 2 was an open-label, single-period study ($n = 30$) evaluating PK characteristics of a single dose of XP-8121 SC (1500 μg), potential clinical exposure range, and dose proportionality. After oral levothyroxine administration, baseline-adjusted levothyroxine concentration increased rapidly in plasma (T_{max} median: 3.1 h); absorption for all XP-8121 SC doses was slower compared to 600 μg oral levothyroxine, and levels remained elevated for 4–5 days before decreasing. Dose proportionality was confirmed, and safety results were similar between all groups. PPK analysis results suggested that weekly doses of XP-8121 SC at four times the daily oral levothyroxine dose provide similar exposure at steady state (AUC_{ss}). Overall, these data for XP-8121 provide adequate predictive performance to inform future phase 2 studies.

1 | Introduction

Levothyroxine (T4), a synthetic form of thyroxine, is the standard of care for hypothyroidism treatment worldwide [1]. However, the daily oral administration of T4 poses challenges due to the significant bioavailability limitations, influenced by factors such as gastrointestinal (GI) absorption, food and drug interactions, and patient adherence. T4 absorption occurs predominantly in the jejunum and ileum, with an estimated bioavailability of 60%–80%, which is influenced by pH, gastric transit time, and the presence of food or certain medications (e.g., calcium, iron supplements, proton pump inhibitors, and bile acid sequestrants) [1, 2].

To optimize bioavailability, clinical guidelines from the American Thyroid Association recommend administering T4 on an empty stomach, at least 30–60 min before food, or at least 3 h after a meal [1]. Despite these recommendations, many patients experience challenges with the timing of administration or avoiding interfering substances, often leading to suboptimal

Summary

- What is the current knowledge on the topic?
  - Alternative hypothyroidism treatments that avoid the challenges of oral therapy are needed by a subset of individuals with persistently elevated thyroid-stimulating hormone levels, especially those affected by comorbid conditions that require diet modifications and medications known to interfere with gastric levothyroxine absorption.
- What question did this study address?
  - This Phase 1 study in healthy adult participants assesses pharmacokinetics (PK), safety, exploratory efficacy, and population PK model information on XP-8121 to inform dosing in future Phase 2 studies.
- What does this study add to our knowledge?
  - The PK profile of XP-8121 demonstrated a lower maximum concentration (C_{max}), longer time to maximum concentration (T_{max}) with a sustained exposure profile relative to oral T4 and suggested that weekly doses of XP-8121 SC at four times the daily oral T4 dose provide similar exposure at steady state (AUC_{ss}).
- How might this change clinical pharmacology or translational science?
  - Results of this study inform on the PK and dose conversion of XP-8121 SC, an investigational levothyroxine formulation, compared with oral levothyroxine sodium in addition to a population PK analysis.

control of thyroid stimulating hormone (TSH) levels, under- or over-treatment, and safety issues. Both overtreatment and undertreatment of hypothyroidism with T4 are associated with significant long-term risks, including increased cardiovascular mortality and heart disease, as well as a higher incidence of fractures in older adults [3, 4].

Efforts to address these limitations have led to the development of alternative T4 formulations, including liquid and soft-gel capsules, designed to minimize variability in pharmacokinetic (PK) profiles, particularly in populations with known absorption challenges [5]. However, even these formulations remain susceptible to factors affecting GI absorption and patient adherence. Malabsorption of tablet formulations of T4 can occur from either hindered gastric dissolution of the tablet or binding of T4 by sequestrants in the intestinal lumen [6]. Patients with swallowing issues and those with GI disorders including celiac disease, lactose intolerance, *Helicobacter pylori* infections, and atrophic gastritis have difficulties achieving optimal blood T4 concentrations with oral formulations [7]. Food consumption and certain beverages (e.g., coffee, cow's milk) also inhibit T4 absorption [8, 9]. When co-administered with a standard test breakfast, studies have documented a 38%–40% reduction of absorption of T4 [7]. In addition, less T4 is physiologically absorbed in approximately 20%–40% of elderly patients who take five or more medications [6]. Certain medications (e.g., iron, calcium, proton pump inhibitors, and certain estrogens) are known to significantly reduce the absorption of T4, effectively lowering its concentration, altering TSH levels, and thereby diminishing therapeutic outcomes [10, 11]. Such interactions disproportionately affect older adults, who are more likely to take multiple medications that can alter T4 metabolism or absorption [6]. These challenges underscore the need for alternative administration routes to improve therapeutic outcomes. XP-8121, a novel formulation of levothyroxine sodium for subcutaneous (SC) administration, offers a potential solution by bypassing the GI tract and delivering more predictable PK and thyroxine levels. This approach could significantly benefit patients struggling to consistently achieve TSH targets despite escalating oral doses.

The present study aimed to characterize the PK and dose proportionality of XP-8121 compared to 600 μg oral (PO) Synthroid (T4; Ievothyroxine sodium, Abbvie, Chicago, IL, USA) in healthy adults. Additionally, the study evaluated the safety and tolerability of XP-8121 and incorporated population pharmacokinetics (PPK) modeling to simulate T4 concentrations at steady state, comparing weekly XP-8121 SC with oral T4, to support future development.

2 | Materials and Methods

The Institutional Review Board (IRB) (ADVARRA; initial approval date: 21 July 2021) was a properly constituted board operating in accordance with 21 Code of Federal Regulations (CFR) part 56, "Institutional Review Boards." This study was conducted at Celerion Inc. in Tempe, AZ in full compliance with the protocol, Good Clinical Practice (GCP) principles, current United States (US) Food and Drug Administration (FDA) regulations, International Council for Harmonization (ICH) guidelines, GCP guidelines, Good Laboratory Practices (GLP) guidelines, local ethical and regulatory requirements, including the Federal Food, Drug, and Cosmetic Act, US applicable CFR (Title 21), and IRB/IEC requirements relative to clinical studies. All participants signed a written informed consent form.

2.1 | Study Design

2.1.1 | Phase 1 Study Design

This was a 2-part, single-center, dose escalation Phase 1 study. Part 1 was a randomized, open-label, crossover, fixed-sequence

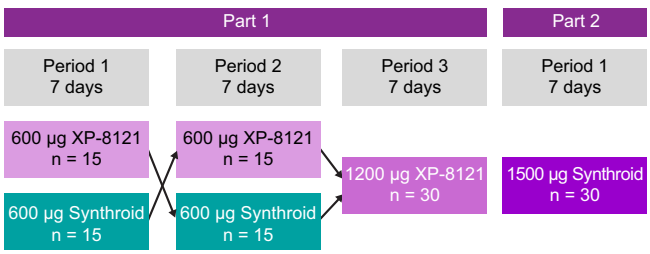

FIGURE 1 | Schematic overview of the study design of the two-part Phase 1 study. Part 1 was a randomized, open-label, PK study in 30 healthy participants composed of three periods: Periods 1 and 2 utilized a crossover design between 600 μg XP-8121 SC and 600 μg oral T4 to assess relative bioavailability. Period 3 was a dose escalation of XP-8121 to 1200 μg SC in all study participants. Part 2 was an open-label PK study in 30 healthy participants, composed of a single period which evaluated the PK characteristics of a single dose of 1500 μg XP-8121 SC.

study in 30 healthy participants (Figure 1). An evaluation of escalating XP-8121 SC doses, up to 1200 μg, was also assessed to determine dose linearity, and safety was evaluated at all doses of XP-8121. Part 1 of the study was comprised of three periods. Periods 1 and 2 utilized a crossover design between 600 μg XP-8121 SC and 600 μg oral T4 to assess relative bioavailability. Period 3 was a dose escalation of XP-8121 SC to 1200 μg in all study participants. A minimum washout of 42 days (but not > 45 days) occurred between study drug administration within each period during part 1. Part 2 was an open-label, single period, PK study in 30 healthy participants which evaluated the PK characteristics of a single dose of 1500 μg XP-8121 SC, characterized the potential clinical exposure range for XP-8121, and assessed dose proportionality.

Screening was done within 28 days of the planned start of treatment. PK samples for measurement of total T4 and triiodothyronine (T3) in plasma were collected at the following timepoints: Pre-dose (−0.50, −0.25, and 0 h) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 48, 72, 96, 120, 144, 168 (part 2 only), 240 (part 2 only), 312, 384 (part 2 only), 480, and 648 h post-dose. Plasma samples for TSH measurement were collected at screening, Day −1, pre-dose (within 2 h of study drug administration) and 4, 24, 48, 96, 144 (part 1 only), 168 (part 2 only), 240 (part 2 only), 312, 384 (part 2 only), 480, and 648 h post-dose.

2.1.2 | Noncompartmental PK Analysis

Standard methods were used for assessments of noncompartmental PK parameters (Data S1).

2.1.3 | Population PK (PPK) Analysis

Standard methods were used for PPK Analysis (Data S1).

2.1.4 | Study Participants

Study participants were healthy adults (aged 18–55 years at screening) who met all eligibility criteria (Data S2). The collection of self-reported race and ethnicity data was based on current FDA guidance.

2.1.5 | End Points

Primary end points for part 1 and part 2 included the assessment of plasma T4 baseline-corrected PK for C_{max}, T_{max}, partial AUC (not shown) and AUC from time 0 to last quantifiable concentration (AUC_{0-last}). If supported by the data, the following additional parameters were calculated: apparent terminal elimination rate constant (K_{el}); apparent terminal half-life ($t_{½}$); AUC from time 0 to infinity (AUC_{0-inf}); apparent total clearance (CL/F (PO and SC administration)); apparent volume of distribution (Vz/F (PO and SC administration)).

Additional primary end points included plasma T3 baseline-corrected PK end points for C_{max}, T_{max}, AUC_{0-last}; mean concentrations of thyroxine after XP-8121 SC doses and oral T4 by timepoint; and partial AUCs from time 0 to 12, 24-, 48-, 72-, and 96-h post-dose.

Secondary end points for safety and tolerability included: incidence, frequency, and severity of treatment-emergent adverse events (TEAEs), clinically significant vital sign measurements, laboratory test results including liver and renal function tests, physical examinations (PEs), and local tolerability assessments (modified Draize Scale and injection site discomfort questionnaires). The exploratory end point was an analysis of efficacy to determine any shifts in TSH from baseline.

2.2 | Statistical Analyses

2.2.1 | Phase 1 Study

Unless specified otherwise, the safety population (all participants who received any amount of study drug) was used for safety/tolerability analyses, and the PK population (safety population participants who had no important protocol deviations affecting the PK variables and had ≥ 3 samples to determine at least one PK parameter) used for PK statistical analyses. Missing data were not imputed. All analyses described in the statistical analysis plan (SAP) were considered a priori analyses in that they had been defined before locking the database.

Baseline-adjusted plasma concentrations of T4 and T3 were used for the calculation of plasma T4 and T3 PK parameters. Plasma PK parameters were summarized by treatment for all participants in the PK population, using descriptive statistics (number of non-missing observations (*N*), arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean (Geom Mean) and geometric CV% (Geom CV%)).

The mean concentration of thyroxine after XP-8121 SC doses and oral T4 was summarized by treatment and collection time point for all participants in the PK population using descriptive statistics (number of non-missing observations (*N*), arithmetic mean, SD, CV%, median, minimum, maximum, Geom Mean, and Geom CV%).

Ln-transformed PK parameter C_{max} for plasma T4 was compared to evaluate the bioavailability of 600 μg XP-8121 SC (Treatment A) versus 600 μg oral T4 (Treatment B) using a linear mixed effects model with treatment, period, and sequence as fixed effects and subject within sequence as a random effect. The inferential results (least squares means (LSMs), difference between LSMs, and 90% CIs of the difference) were exponentiated to the original scale. Geometric LSMs, geometric mean ratios (GMRs), and 90% CIs were presented.

Dose proportionality was assessed after doses of XP-8121 SC for the unadjusted and baseline-adjusted AUC_{0-last} and C_{max} with a power model using SAS PROC MIXED [12]:

$$\text{Parameter} = a * \text{Dose}^b,$$

which is equivalent to a linear regression model using ln-transformed parameters:

$$\ln(\text{Parameter}) = \ln(a) + b[\text{Ln}(\text{Dose})]$$

The AUC_{0-last} and C_{max} for the 1500 μg XP-8121 SC dose was calculated in two ways for the purpose of dose proportionality assessment, one with the concentrations from the additional timepoints in part 2 included and one with these concentrations excluded for matched sample frequency between part 1 and part 2. The latter approach was considered as the main analysis.

2.2.2 | PPK Study Data Analysis Platform

For information on model selection criteria, interindividual variability model, and residual error model, please refer to Data S1.

3 | Results

3.1 | Participants

A total of 60 healthy participants enrolled in the Phase 1, single-center, 2-part, crossover, PK study (Table 1 and Data S3). Twenty-eight of 30 participants completed part 1. All 30 participants completed part 2. One participant completed part 1, period 1 but was lost to follow-up; one participant completed part 1, periods 1 and 2 but was withdrawn by the principal investigator. Participants had a mean (SD) age of 40 years (10.4); mean (SD) body weight of 75 kg (12.7). There were 35 female participants (58%), and 53 participants (88%) identified as White.

3.2 | Pharmacokinetics of Levothyroxine

All 60 participants that received at least 1 dose of the study drug were included in the PK analysis. Noncompartmental analysis was applied to the baseline-adjusted T4 concentration. The oral T4 plasma concentration-time curve was characterized by a rapid rise, reaching C_{max} at a median time of 3.1 h, followed by a log-linear decrease. XP-8121 SC plasma T4 concentration-time curves were characterized by gradual absorption reaching C_{max} at a median post-dose time of 48.1 h for 600 μg, 72.0 h for 1200 μg, and 96.0 h for 1500 μg. Mean plasma T4 levels remained steady over 4 to 5 days before decreasing (Figure 2a,b). In addition to slower absorption, peak T4 exposure as measured by mean baseline-adjusted C_{max} with 600 μg XP-8121 SC (21.58 ng/mL) was 55% lower than with 600 μg oral T4 (47.59 ng/mL) (Table 2). The C_{max} was not comparable as the two-sided 90% CI for the GMR (42.95% [36.92%, 49.97%]) was outside the 80% to 125% interval. The mean C_{max} of the higher dose of XP-8121 SC at 1200 μg (37.10 ng/mL) was also 22% lower than oral T4 600 μg, while C_{max} at the 1500 μg dose of XP-8121 SC (46.91 ng/mL) was similar to oral T4 600 μg. Total exposure, as assessed by baseline-adjusted T4 AUC_{0-last} (mean) for doses of 600 μg XP-8121 SC (5392 ng h/mL), 1200 μg XP-8121 SC (8980 ng h/mL), and 1500 μg XP-8121 SC (12,720 ng h/mL), was all greater than oral T4 (4005 ng h/mL). At comparable doses, the mean AUC_{0-last} of 600 μg XP-8121 SC was 35% greater than with 600 μg oral T4.

3.3 | Dose Proportionality

The estimated slope was 1.0502 with a 95% CI of [0.7775, 1.3228] for AUC_{0-last}, and 0.8676 with a 95% CI of [0.6704, 1.0647] for C_{max}. Since both 95% CIs contained 1, dose proportionality was confirmed.

3.4 | Pharmacokinetics of Triiodothyronine

Noncompartmental analysis was applied to the baseline-adjusted plasma T3 concentration. After baseline adjustment, T3 concentrations above baseline were generally sparse and low in magnitude for some participants. Pharmacokinetic parameters were not calculated for participants with less than three consecutive post-dose concentrations greater than 0. Pharmacokinetic parameters (T_{max}, C_{max}, and AUC_{last}) were calculated for 17 participants administered 600 μg oral T4 and those administered XP-8121 SC ($n = 16$ for 600 μg, $n = 23$ for 1200 μg, and $n = 27$ for 1500 μg). Due to the low number of participants with PK parameters for T3, a meaningful evaluation of these parameters was limited. At the same dose of 600 μg, XP-8121 SC and oral T4 produced similar baseline-adjusted plasma T3 concentration over time curves, with XP-8121 SC reaching a median (range) T_{max} at 479.9 (1.51 to 648.19) hours and oral T4 at 480.2 (2.50 to 671.64) hours. Doses of 1200 μg and 1500 μg XP-8121 SC produced similar baseline-adjusted plasma triiodothyronine concentration over time curves, reaching a shorter median (range) T_{max} at 144.0 (1.49 to 647.31) hours for 1200 μg and 120.0 (0.62 to 648.14) hours for 1500 μg. However, the range of T_{max} values overlapped for all treatment groups. Peak T3 exposure, as indicated by C_{max} (mean (SD)), was 0.1733 (0.064034) ng/mL for 600 μg XP-8121 SC and 0.1550 (0.080817) ng/mL for 600 μg oral T4. The C_{max} was 0.1854 (0.071716) ng/mL for 1200 μg XP-8121 SC and 0.2059 (0.13551) ng/mL for 1500 μg XP-8121 SC. Inclusive of the entire sample time range, the T3 AUC_{0-last} (mean (SD)) was similar between all treatments: 44.70 (35.362), 48.64 (24.826), 52.54 (31.622), and 44.88 (46.720) ng hr/mL for 600 μg oral T4, 600 μg XP-8121 SC, 1200 μg XP-8121 SC, and 1500 μg XP-8121 SC, respectively.

3.5 | Exploratory Efficacy Analysis

The relationship between plasma T4 and TSH was explored after administration of oral T4 at 600 μg and XP-8121 SC at 600, 1200, 1500 μg. After administration of 600 μg oral T4, baseline-adjusted plasma T4 concentration levels increased to a median C_{max} of 47.59 ng/mL by 3.1 h, and TSH levels decreased with the rising T4 levels to a mean (SD) maximum decrease of 0.88 (0.479) μIU/mL measure at 48 h (Figure 3a). TSH levels returned to pre-dose levels by 312 h post-dose administration. The baseline-adjusted plasma T4 concentration levels after administration of XP-8121 SC reached a mean C_{max} of 21.58 ng/mL for doses of 600 μg at 48 h, 37.10 ng/mL for 1200 μg at 72 h, and 46.91 ng/mL for 1500 μg at 96 h. TSH levels decreased with rising T4 levels, reaching mean (SD) maximum decreases of 0.51 (0.425) μIU/mL for 600 μg XP-8121 SC at 96 h, 1.03 (0.622) μIU/mL for 1200 μg at 312 h, and 0.92 (0.469) μIU/mL for 1500 μg at 312 h (Figure 3b). At the comparable dose of 600 μg, oral T4 had a higher baseline-adjusted C_{max}

TABLE 1 | Summary of demographics (safety population).

		Part 1			Part 2	
		Randomized treatment sequence			Treatment	
Characteristic	**Category/statistics**	**ABC, $N=15$, n (%)**	**BAC, $N=15$, n (%)**	**Overall, $N=30$, n (%)**	**D, $N=30$, n (%)**	**Total, $N=60$, n (%)**
Sex	Female	6 (40.0%)	6 (40.0%)	12 (40.0%)	23 (76.7%)	35 (58.3%)
	Male	9 (60.0%)	9 (60.0%)	18 (60.0%)	7 (23.3%)	25 (41.7%)
Race	Asian	0 (0%)	0 (0%)	0 (0%)	1 (3.3%)	1 (1.7%)
	Black or African American	1 (6.7%)	1 (6.7%)	2 (6.7%)	3 (10.0%)	5 (8.3%)
	Multiple: White, Black or African American	0 (0%)	0 (0%)	0 (0%)	1 (3.3%)	1 (1.7%)
	White	14 (93.3%)	14 (93.3%)	28 (93.3%)	25 (89.3%)	53 (88.3%)
Ethnicity	Hispanic or Latino	11 (73.3%)	12 (80.0%)	23 (76.7%)	24 (80.0%)	47 (78.3%)
	Not Hispanic or Latino	4 (26.7%)	3 (20.0%)	7 (23.3%)	6 (20.0%)	13 (21.7%)
Age (years)	Mean (SD)	38.7 (11.0)	43.2 (10.6)	40.9 (10.9)	39.8 (10.1)	40.4 (10.4)
Weight (kg)	Mean (SD)	80.6 (13.5)	74.7 (12.3)	77.7 (13.1)	72.8 (12.0)	75.2 (12.7)
BMI (kg/m^2)	Mean (SD)	28.4 (3.4)	27.5 (3.2)	28.0 (3.3)	27.2 (3.2)	27.6 (3.2)

Note: Treatment A: A single dose of 600 μg XP-8121 SC. Treatment B: A single dose of 600 μg oral T4. Treatment C: A single dose of 1200 μg XP-8121 SC. Treatment D: A single dose of 1500 μg XP-8121 SC. Height and weight were collected at screening. Age was approximated by subtracting the year of birth from the year of informed consent. If "year of informed consent" − "year of birth" was less than the protocol minimum age, then the age approximation was "year of informed consent" − "year of birth + 1". If "year of informed consent" − "year of birth" was more than protocol maximum age, then the age was "year of informed consent" "year of birth − 1".
Abbreviations: BMI, body mass index calculated as weight (kg)/[height (m)]^2 using height and weight collected at screening; PO, oral(ly); SC, subcutaneous(ly); SD, standard deviation.

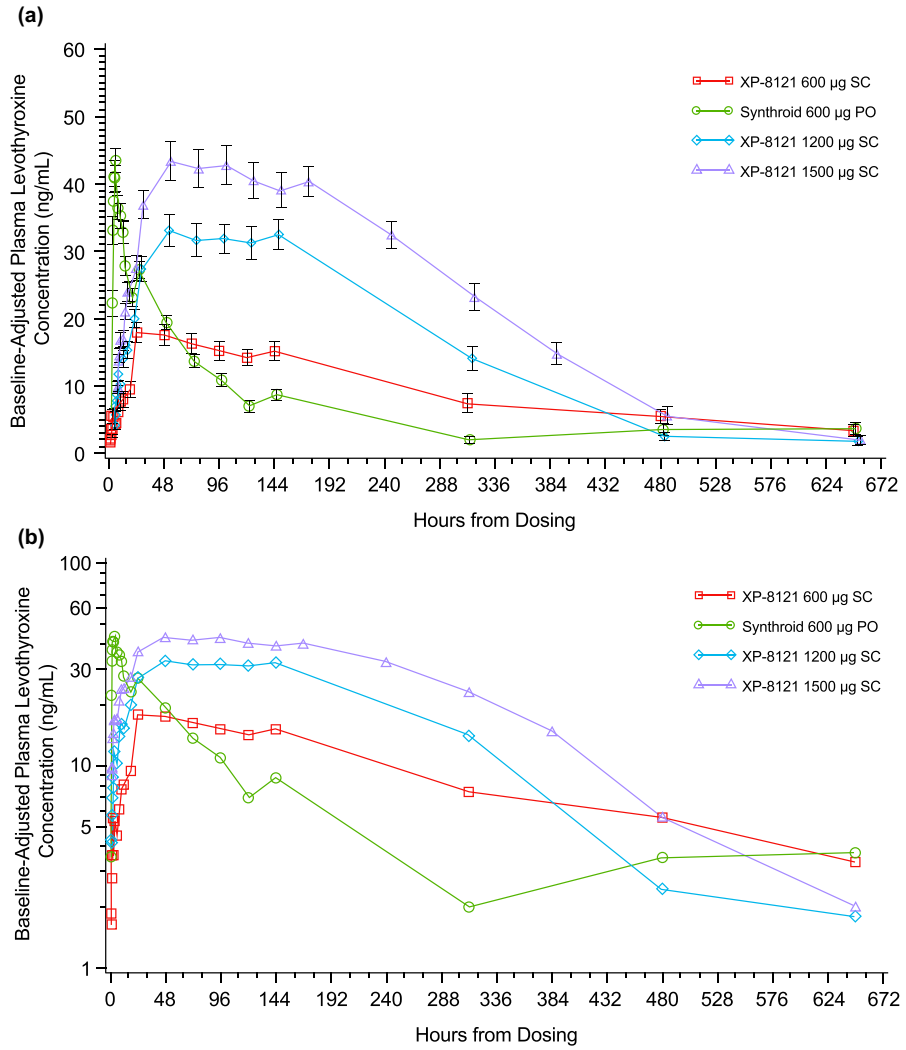

FIGURE 2 | (a) Mean (SE) baseline-adjusted plasma (ng/mL) levothyroxine concentration versus time profiles following single subcutaneous doses of XP-8121 and a single oral dose of T4: Linear scale. (b) Mean baseline-adjusted plasma levothyroxine concentration versus time profiles following single subcutaneous doses of XP-8121 and a single oral dose of T4: Semi-log scale.

and greater decrease in relative TSH levels compared to XP-8121 SC. However, TSH levels remained below baseline longer after administration of XP-8121 SC compared to oral T4. The differences in the magnitude and duration of TSH decreases between oral T4 and XP-8121 SC were related to peak (C_{max}) and duration of elevated T4 concentrations.

3.6 | Safety

The safety population included 30 participants who received at least one of the three treatments in part 1 and 30 participants who received 1500 µg XP-8121 SC in part 2 (Data S2: Tables S1 and S2). Of these 60 participants, TEAEs were mild to moderate in severity except for one severe TEAE of COVID-19-related pneumonia, which was not considered related to the 600 µg oral T4 treatment. No notable differences in the safety results were reported between any XP-8121 SC doses or between any XP-8121 SC dose and 600 µg oral T4. No participants withdrew from the study due to adverse events (AEs). No deaths or serious adverse events (SAEs) were reported. Single-dose administration of XP-8121 was safe and well-tolerated, and it supports XP-8121 as a future potential therapy in the treatment of hypothyroidism.

3.7 | Population Pharmacokinetic Model

A PPK model of XP-8121 SC and oral T4 was developed using baseline adjusted plasma T4 concentration-time data from all 60 participants to simulate and compare the relative exposure at the steady-state (ss) of XP-8121 SC administered weekly and oral T4 administered PO daily. The PPK of XP-8121 SC and oral T4 were characterized by a one-compartment disposition model with first-order elimination. Of the covariates assessed (age, body weight, BMI, body surface area (BSA), sex, race, ethnicity), only body weight was identified as a significant covariate on the clearance and volume of distribution for XP-8121 SC, with parameter estimates of 0.739 for clearance and 1.46 for volume of distribution.

The modeling was appropriate for adequate predictive performance for XP-8121 SC. The observed data were contained

TABLE 2 | Summary of baseline-adjusted plasma levothyroxine primary pharmacokinetic parameters by treatment (pharmacokinetic population).

Parameter	600 μg XP-8121 SC	600 μg oral LT4	1200 μg XP-8121 SC	1500 μg XP-8121 SC
	***N* = 29**	***N* = 29**	***N* = 28**	***N* = 30**
C_{max} (ng/mL)				
Mean	21.6	47.6	37.1	46.9
SD	7.8	10.2	12.4	14.9
Min-Max	5.57, 38.6	29.4, 69.7	11.6, 61.5	28.0, 89.4
T_{max} (h)				
Mean	79.2	3.6	87.0	103.6
SD	79. 2	1. 6	61.9	86.1
Min-Max	2.6, 312.7	1.5, 8.0	10.0, 312.0	10.0, 480.1
AUC_{last}				
Mean	5392	4005	8980	12,720
SD	3055	2033	3049	4470
Min-Max	850, 11,100	1340, 8620	3100, 16,000	5170, 24,100
	***N* = 12**	***N* = 13**	***N* = 16**	***N* = 23**
CL/F (L/h)				
Mean	0.17	0.19	0.13	0.11
SD	0.17	0.10	0.05	0.04
Min-Max	0.04, 0.64	0.03, 0.41	0.07, 0.28	0.05, 0.22
$t_{1/2}$ (h)				
Mean	176.7	144.0	112.2	120.1
SD	109.4	188.1	58.1	124.6
Min-Max	30.4, 456.4	33.2, 747.3	45.5, 237.7	42.2, 658.3
V_z/F (L)				
Mean	33.8	26.3	19.9	15.9
SD	28.7	14.1	10.4	10.5
Min-Max	8.8, 108	10.6, 60.2	7.9, 47.4	6.4, 45.7

Abbreviations: CL/F, apparent total plasma clearance after oral (extravascular) administration; C_{max}, maximum observed plasma concentration; Max, maximum; Min, minimum; PO, oral(ly); SC, subcutaneous(ly); SD, standard deviation; $t_{½}$, apparent first order terminal elimination half-life; T_{max}, time to reach C_{max}; V_z/F, apparent volume of distribution during the terminal elimination phase.

within the prediction intervals. The observed medians agreed well with the simulated data, although the peak concentrations (C_{max}) with oral T4 were slightly underestimated (Figure 4). Figure 5a demonstrates the overlap among the simulated concentration time profiles at ss from different doses of XP-8121 SC and 300 μg oral T4. The predicted geometric mean AUC_{ss}, C_{maxss}, and C_{minss} for weekly doses of XP-8121 SC at 1200 μg (11,941 ng h/mL, 85.9 ng/mL, 53.2 ng/mL) are similar to daily doses of 300 μg oral T4 (11,932 ng*h/mL, 80 ng/mL, 62.7 ng/mL), suggesting that weekly doses of XP-8121 SC at four times the oral daily dose of oral T4 are estimated to provide similar exposure (Figure 5b).

4 | Discussion

Levothyroxine sodium has been the cornerstone of hypothyroidism management since its approval in 1955, with daily oral administration recognized as the standard of care [1, 6]. However, despite its established safety and efficacy, T4 is a narrow therapeutic index drug that requires regular lab testing and frequent titration to achieve the desired biochemical effect and avoid morbidity associated with out-of-range TSH levels. The narrow therapeutic index of T4 is highlighted in clinical findings with 20% or more of treated patients not controlled when tested once, and 30% or more with TSH or T4 levels that vary over time or stay out of range [13–16].

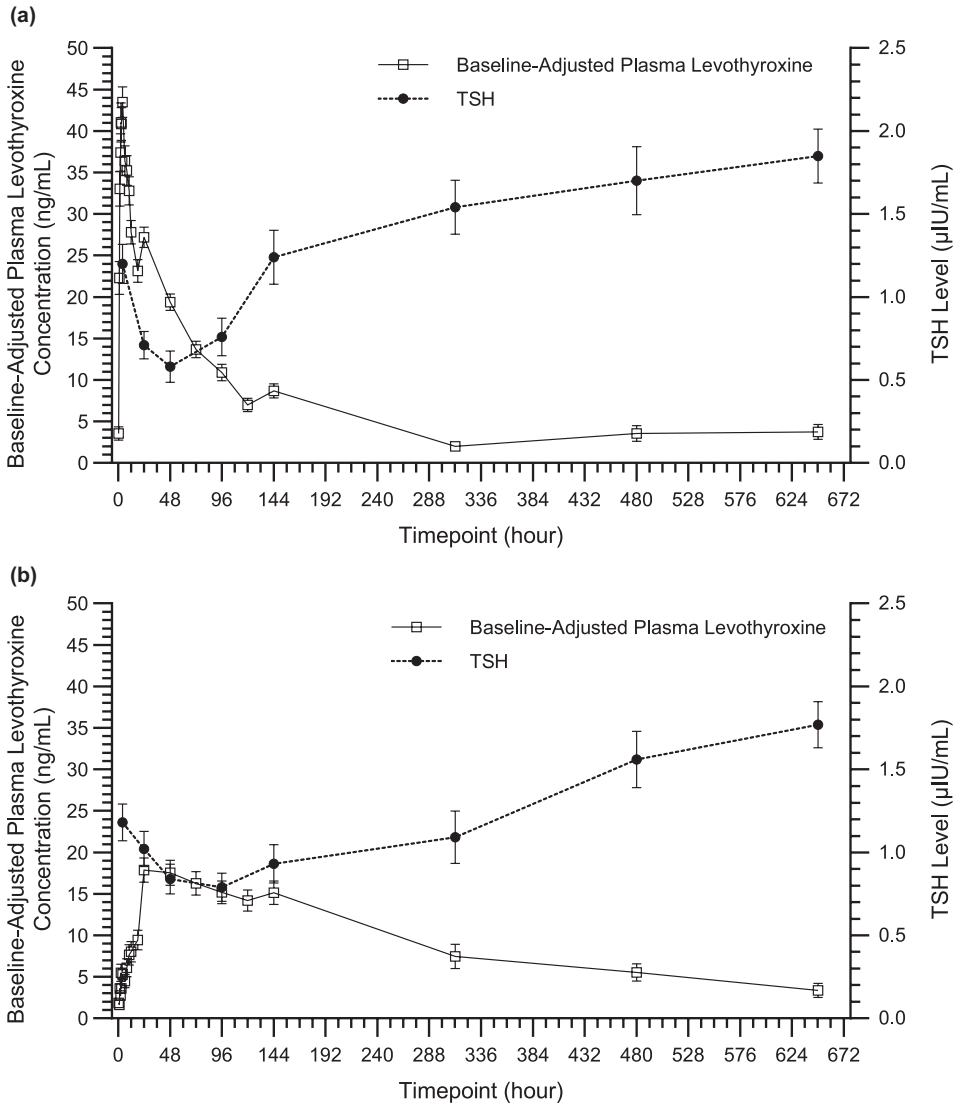

FIGURE 3 | (a) Time-matched baseline-adjusted plasma levothyroxine and thyroid stimulating hormone concentrations following a single oral dose of T4 600 μg from Day 0 to Day 28 (linear scale; safety population). (b) Time-matched baseline-adjusted plasma levothyroxine and thyroid stimulating hormone concentrations following a single subcutaneous dose of XP-8121 600 μg from Day 0 to Day 28 (linear scale; safety population).

In addition to challenges with T4 being a narrow therapeutic index drug, medication formulation, significant drug–food interactions, drug–drug interactions, medication adherence, GI malabsorption, and other preexisting medical conditions may contribute to inadequate management of hypothyroidism [6, 17]. Furthermore, several clinical conditions may cause oral T4 dosing complexity, including dose increases to compensate for reduced gastric absorption and more frequent dosing changes due to progression of underlying conditions and medications required to treat them. For example, individuals who are not able to consistently achieve normal TSH, including those with refractory hypothyroidism, especially those with GI malabsorption or facing unique dietary requirements, remain difficult to treat despite escalation in drug doses. Most T4 absorption issues are based on concurrent absorption of interfering substances in the digestive tract resulting in reduced T4 absorption [8]. In order to be fully compliant, patients may need to make lifestyle modifications, such as timing medication administration in relation to meals, which may be more difficult for patients taking multiple drugs and supplements that interfere with T4 absorption.

Daily oral administration of T4 can result in burdensome dosing challenges for patients due to food effects, variation in GI drug absorption, drug–drug interaction, and other factors, resulting in inconsistencies in medication adherence, under- or over-treatment, and safety issues. For example, in a review of hypothyroid patients who require more than the expected weight-based dose of T4, 21% took medication known to interfere with T4 absorption, and 17% admitted to compliance issues [18]. Additionally, the incidence of concomitant GI-related disease is common. In the CONTROL Surveillance Project, a comprehensive US patient-based survey conducted among 925 hypothyroid patients undergoing treatment, almost half (47%) of those receiving T4 had at least one comorbid condition that could adversely affect its absorption: gastroesophageal reflux

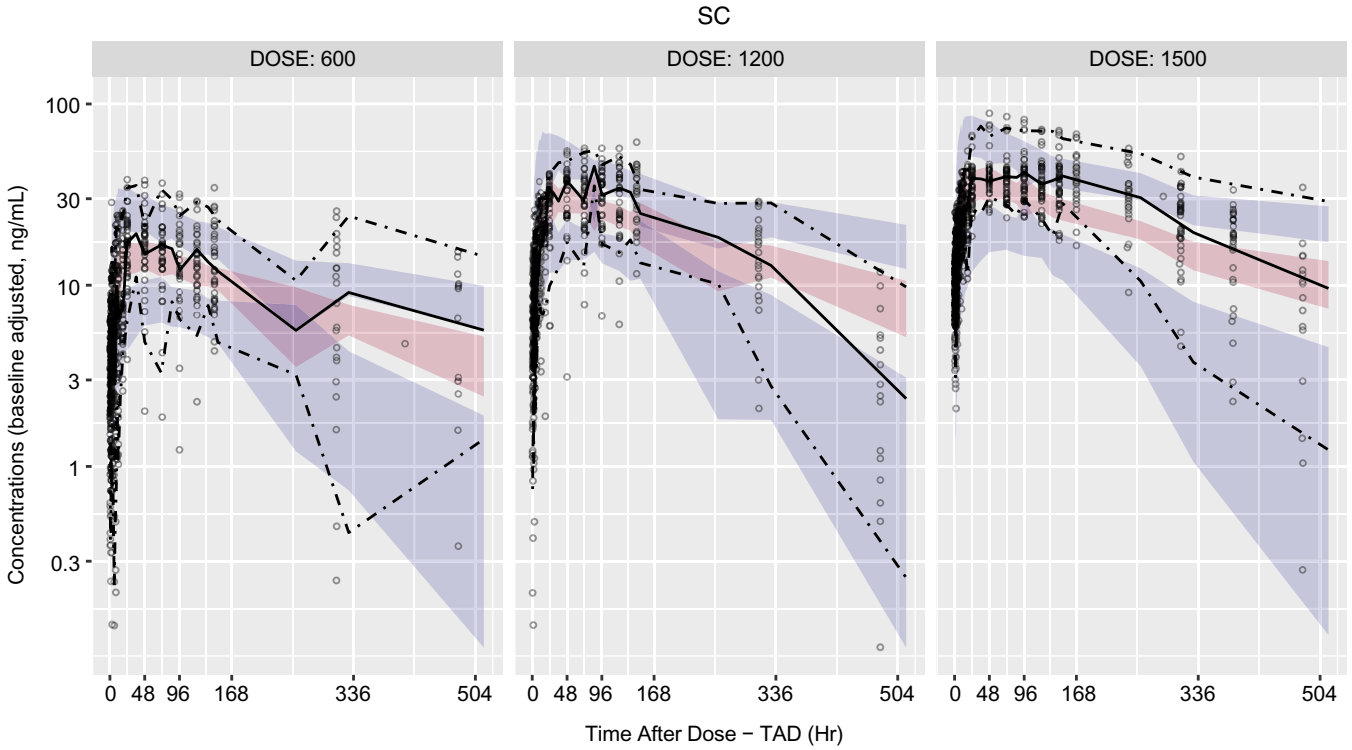

FIGURE 4 | Visual predictive check results.

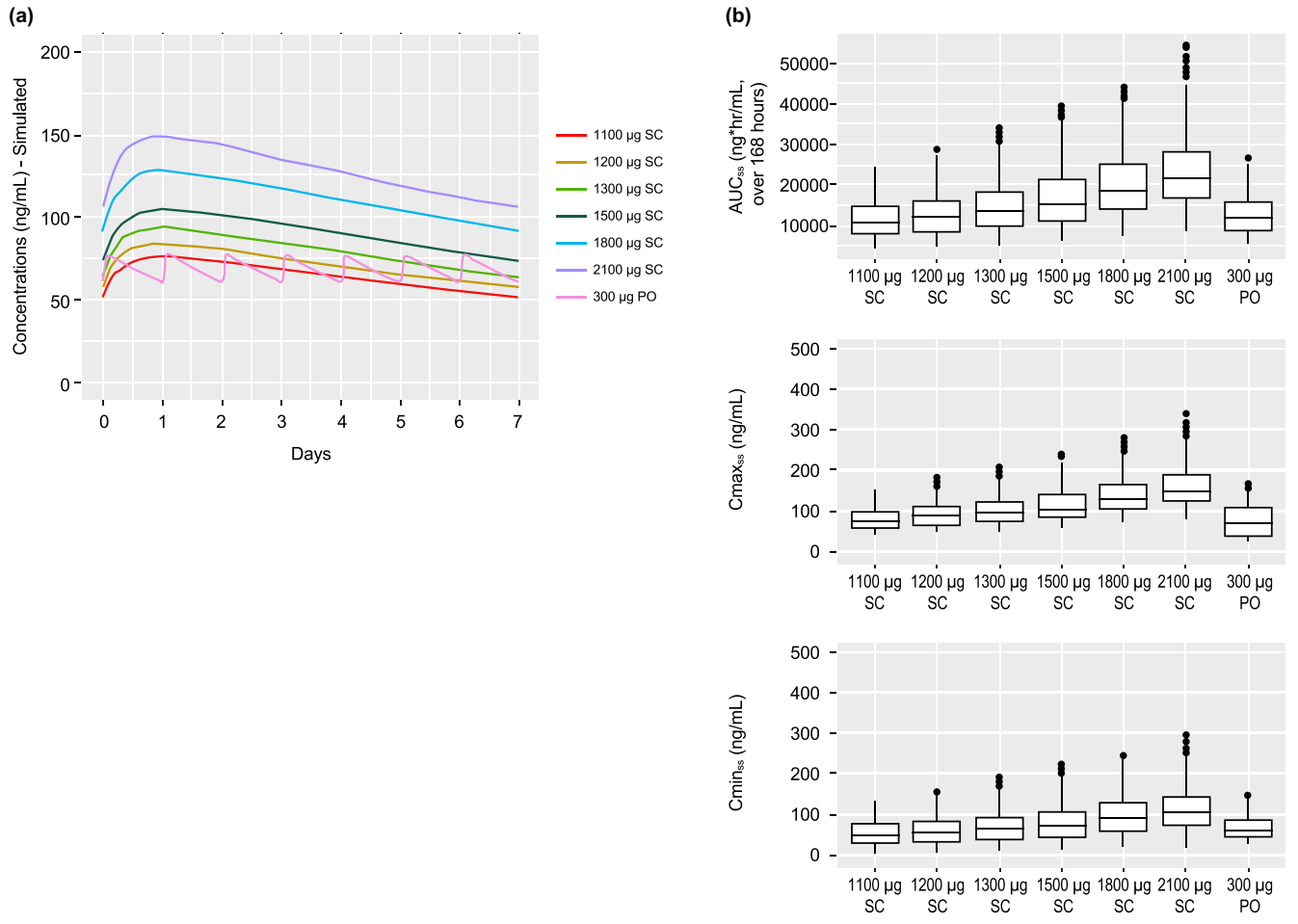

FIGURE 5 | (a) Simulated median concentration-time curve of levothyroxine at steady-state. (b) Simulated levothyroxine AUC, C_{max}, and C_{min} at steady state.

disease (34%), irritable bowel syndrome (10%), lactose intolerance (8%), or a history of gastric bypass surgery or bowel resection (3%) [19].

Currently, there are no approved injectable T4 formulations for the treatment of hypothyroidism. XP-8121 is a novel, ready-to-use, weekly SC injection formulation of T4 in development that bypasses the GI tract, mitigating the limitations of oral therapy. The safety and exposure profiles of XP-8121 have been evaluated through preclinical and clinical studies, including a Phase 1, randomized, open-label, PK trial, FDA-approved product labels for oral and intravenous (IV) T4, and published literature.

In a Phase 1 crossover study in healthy participants, a single 300 μg dose of XP-8121 SC was compared to 300 μg IV and oral T4. XP-8121 was well tolerated with no SAEs or significant safety signals across treatment arms. While this study characterized absorption kinetics (C_{max} and T_{max}), the fixed 300 μg dose was insufficient to determine the elimination rate constant (K_{el}) or half-life ($t_{½}$), necessitating further evaluation of XP-8121's PK profile at higher doses.

The present Phase 1 study expanded on these findings by examining the bioavailability, dose proportionality, and pharmacodynamic effects of XP-8121. Baseline-adjusted plasma T4 concentrations demonstrated a slower absorption rate (prolonged T_{max}), lower C_{max}, and extended exposure with XP-8121 SC compared to 600 μg oral T4. Dose proportionality was confirmed across the XP-8121 SC dose range of 600 to 1500 μg, with baseline-adjusted AUC_{0-last} exposure increasing proportionally with dose. Exploratory efficacy analyses demonstrated a decrease in TSH concentrations for all treatment groups (600 μg oral T4, 600 μg XP-8121 SC, 1200 μg XP-8121 SC, and 1500 μg XP-8121 SC), with the magnitude and duration of TSH suppression correlating to T4 plasma levels. The study's PPK modeling suggested that weekly doses of XP-8121 SC equivalent to four times the oral daily dose could achieve comparable steady-state exposure (AUC_{ss}). However, the preliminary PPK models, derived from a relatively small participant pool ($N = 60$), underestimated C_{max} for oral T4. Despite this, simulated versus observed data showed substantial overlap, supporting the model's predicted value. Future studies with larger datasets will be needed to refine the PPK model.

In conclusion, XP-8121 SC demonstrated a favorable safety profile, consistent tolerability between doses, and dose-dependent PK properties, including slower absorption and extended exposure compared to oral T4 as well as dose proportionality. Baseline-adjusted T4 exposure (AUC_{last}) for XP-8121 SC doses of 600, 1200, and 1500 μg exceeded that of 600 μg oral T4. The exploratory efficacy analysis indicated robust TSH suppression, consistent with sustained T4 levels in the plasma. These results, along with predictive PPK modeling, provide strong rationale for advancing XP-8121 into Phase 2 trials. A Phase 2, nonrandomized, open-label, single-arm study of XP-8121 (NCT05823012) as replacement therapy for hypothyroidism was completed in early 2024, with results forthcoming. XP-8121 has the potential to address key limitations of T4 oral therapy, offering a promising alternative for patients with hypothyroidism.

Author Contributions

R.F., D.R.M., V.C., R.H., D.H. wrote the manuscript. R.F., D.R.M., V.C., R.H., D.H. designed the research. R.F., D.R.M. performed the research. R.F., D.R.M., V.C., R.H., D.H. analyzed the data.

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Conflicts of Interest

The following authors are employees of the study sponsor: R.F., V.C., R.H., D.H., and D.R.M. is a consultant for the study sponsor.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.