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First-In-Human Safety, Tolerability, and Pharmacokinetics of PPI-1011, a Synthetic Plasmalogen Precursor

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ABSTRACT

PPI-1011 is a synthetic plasmalogen precursor designed to augment plasmalogen levels in patients with Rhizomelic chondrodysplasia punctata (RCDP), an ultra-rare genetic disorder caused by a plasmalogen deficiency that results in significant physical and mental delays. We report here a Phase I, randomized, double-blind, placebo-controlled study that evaluated the safety, tolerability, and pharmacokinetics (PK) of single (10–100 mg/kg) and multiple (75 and 100 mg/kg/day) ascending doses of PPI-1011 in healthy adults. All treatment-emergent adverse events (TEAEs) were mild, monitorable, and resolved without intervention, suggesting no significant safety concerns. The most common TEAEs were gastrointestinal in both the placebo and PPI-1011 groups, suggesting they were likely related to the oil-based nature of the formulation. PK analysis confirmed that both single (25, 50, 75 and 100 mg/kg) and multiple-dose (75 and 100 mg/kg, once daily) administration of PPI-1011 significantly increased serum levels of the target plasmalogen (PlsEtn 16:0/22:6). With a once-daily regimen, PPI-1011 administration resulted in a sustained increase of PlsEtn 16:0/22:6 serum concentrations in healthy participants over a duration of 14 days and beyond.

1 | Introduction

Rhizomelic chondrodysplasia punctata (RCDP) is an ultra-rare genetic disease with an estimated prevalence of 1 per 100,000 [1, 2] that is caused by an inability to synthesize vinyl-ether lipids called plasmalogens. Mutations can exist in any one of five genes directly involved in the peroxisomal portion of the plasmalogen biosynthetic pathway, which all lead to an inability of the body to produce plasmalogens (see Figure 1). RCDP1 is the most prevalent type and is caused by mutations in peroxisomal biogenesis factor 7 (*PEX7*), which is responsible for importing alkylglycerone phosphate synthase (AGPS) into the peroxisome [3–5]. AGPS is one of two peroxisomal enzymes in the plasmalogen biosynthetic pathway. Mutations in *AGPS* itself result in RCDP3 [6], while mutations in dihydroxyacetone phosphate acyltransferase (*DHAPAT*) result in RCDP2 [7]. There have been reports of RCDP4 and RCDP5, resulting from mutations in fatty alcohol reductase (*FAR1*) and *PEX5*, respectively, but these are less common [8, 9]. Clinically, RCDP is characterized by skeletal dysplasia, congenital cataracts, seizures, growth impairments, frequent respiratory infections, muscle contractures, cognitive impairments, and drastically shortened life expectancy. Notably, disease severity has been shown to correlate with circulating plasmalogen levels, confirming that the disease presentation is driven by the metabolic deficiency [10–13].

RCDP is part of a larger group of related disorders known as peroxisome biogenesis disorders (PBDs), which are caused by mutations in any of numerous other genes involved in the formation and function of the peroxisome. Given the importance of the peroxisome in plasmalogen synthesis, a significant proportion of PBD patients have been shown to be plasmalogen deficient

Summary

- What is the current knowledge on the topic?
  - Plasmalogen deficiency is the underlying cause of the ultra-rare pediatric disorder Rhizomelic chondrodysplasia punctata (RCDP) and has also been associated with other neurodegenerative diseases, including Alzheimer's disease. Pharmacological plasmalogen augmentation using PPI-1011, a first-in-class synthetic plasmalogen precursor designed to augment plasmalogen levels following oral administration, represents a novel treatment option for individuals with RCDP.
- What question did this study address?
  - This study examined the safety, tolerability, and pharmacokinetic response of PPI-1011 in healthy adult subjects.
- What does this study add to our knowledge?
  - PPI-1011 was well tolerated with no severe or serious treatment-emergent adverse events in either the single-or multi-dose portions of the study. Single oral administrations of PPI-1011 between 10 and 100 mg/kg resulted in dose-dependent increases in the target ethanolamine plasmalogen. Repeat daily oral administration of PPI-1011 at 75 or 100 mg/kg/day resulted in sustained elevation of the target ethanolamine plasmalogen, confirming the ability of PPI-1011 to augment plasmalogen levels in vivo.
- How might this change clinical pharmacology or translational science?
  - The Phase I data presented support the overall safety and tolerability of oral PPI-1011 administered daily at clinically meaningful doses. The ability of daily dosing to significantly increase serum plasmalogen levels indicates a high probability that PPI-1011 treatment will augment deficient plasmalogen levels in RCDP patients. Overall, the results provide strong scientific and clinical evidence for the continued development of PPI-1011 as a treatment for plasmalogen deficiency.

[14]. In addition, plasmalogen deficiency has been reported in Alzheimer's disease [15], Parkinson's disease [16], Schizophrenia [17], Down's syndrome [18], and Gaucher's disease [19].

Plasmalogens are vinyl-ether-containing phospholipids critical for maintaining the structure and function of the cellular membrane. They comprise 15%–20% of the phospholipid content of the membrane, with increased levels in neuronal tissue [20] and myelin [21]. The vinyl-ether bond imparts a conformational change in the molecule that affects the physical characteristics of the cell membrane and microdomain architecture, impacting processes such as vesicular fusion and neurotransmission [22, 23], and the activity of membrane-bound proteins such as enzymes, receptors, and transporters [24–26].

PPI-1011 is a first-in-class synthetic plasmalogen precursor designed to bypass the peroxisomal portion of the endogenous plasmalogen biosynthetic pathway impaired in RCDP (see Figure 1). The molecule consists of a glycerol backbone with an ether-linked 16-carbon saturated fatty alcohol at the *sn*1 position, an acyl-linked docosahexaenoic acid (DHA) at the *sn*2 position, and a lipoic acid moiety at the *sn*3 position. Following oral administration, the lipoic acid is cleaved, and the resulting alkylacyl glycerol, which is synonymous with naturally-occurring alkylacyl glycerols, is absorbed. This alkylacyl glycerol is then converted into an ethanolamine plasmalogen by enzymes in the endoplasmic reticulum. Previous in vitro and in vivo studies have confirmed the ability of PPI-1011 to augment plasmalogen levels [27–31].

Clinically, RCDP is poorly managed with a high unmet medical need, as treatment remains exclusively symptomatic. Plasmalogen augmentation represents the most promising disease-modifying treatment for RCDP. Dietary sources of plasmalogens or current alkylglycerol supplements are not available at concentrations sufficient to normalize plasmalogen levels in RCDP patients [32]. PPI-1011 represents a novel approach to increasing plasmalogen levels in patients, with the hypothesis that correcting the underlying metabolic deficiency in RCDP will lead to clinical improvements. Herein, we report the findings of a Phase I clinical trial evaluating the safety, tolerability, and pharmacokinetics of PPI-1011 in healthy adults when administered orally as single and multiple ascending doses.

2 | Methods

2.1 | Study Design

This Phase I, randomized, double-blind, placebo-controlled study (NCT05969977) was conducted at a single clinical trial site in Ontario, Canada (BioPharma Services Inc). The first phase of the study included five single-ascending dose (SAD) cohorts. Within each cohort, eight subjects were randomized to receive a single oral dose of PPI-1011 at 10, 25, 50, 75, or 100 mg/kg, or matching placebo at a 6:2 ratio (Figure 2). Each cohort enrolled a minimum of three subjects of each sex, with at least two males and two females randomized to receive PPI-1011 treatment. All subjects remained confined to the clinic from Day −1 until Day 2 (at least 36 h after dosing). Subjects then returned for scheduled outpatient visits on Days 3, 4, 5, and 6. A sentinel approach was employed in all five SAD cohorts, where one subject was dosed with the study drug and one subject was dosed with placebo. After 24 h, a blinded review of the accumulated safety data was used by the Principal Investigator (PI) to authorize enrollment of the remaining six participants into the cohort. The range of doses was selected based on the human equivalent dose of the no-observed-adverse-effect level in rodent and primate nonclinical studies and the minimal adverse effects anticipated with this type of treatment. Following each cohort, a Safety Review Committee (SRC) met and performed a blinded review of the safety data to determine if it was reasonable to escalate to the next dosage level. The SRC consisted of the PI, an independent medical monitor, and a Sponsor representative.

The second part of the study included two multiple ascending dose (MAD) cohorts at 75 and 100 mg/kg/day. Within each cohort, eight subjects were randomized to receive 14 daily oral doses of PPI-1011 or matching placebo at a 6:2 ratio (Figure 2). Each cohort enrolled a minimum of three subjects of each sex,

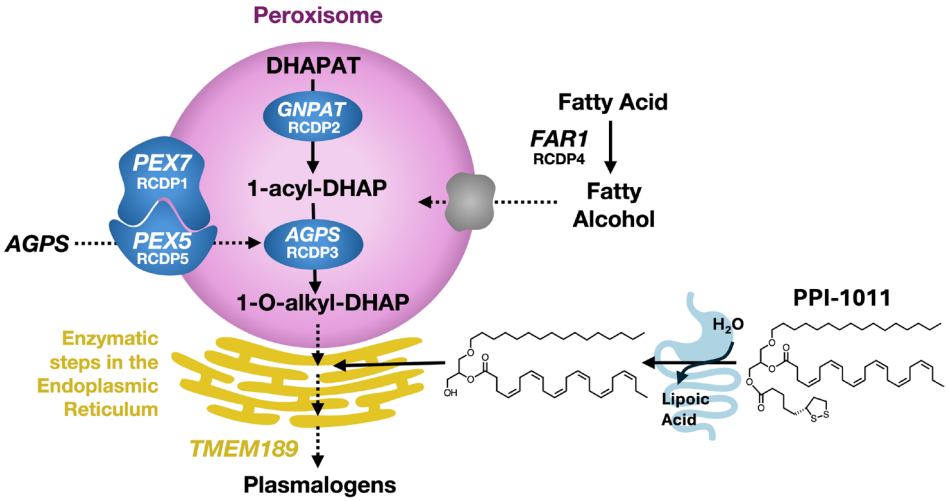

FIGURE 1 | Biosynthetic pathway of plasmalogens and RCDP types based on gene mutation. Plasmalogen biosynthesis primarily occurs in the peroxisome. The type of RCDP is defined by which gene is mutated. Approximately 80% of RCDP is RCDP1, containing mutations in the peroxisomal biogenesis factor 7 (*PEX7*) gene that is responsible for importing alkylglycerone phosphate synthase (AGPS) into the peroxisome in complex with PEX5. Mutations in *PEX5* are rare, but result in RCDP5. Mutations in the fatty alcohol reductase 1 (*FAR1*) gene, involved in the conversion of fatty acids to fatty alcohols needed for ether synthesis, result in RCDP4 which is also rare. Mutations in the genes dihydroxyacetone phosphate acyltransferase (*DHAPAT*) or *AGPS* result in RCDP types 2 and 3, respectively. Once the 1-O-alkyl-DHAP plasmalogen precursor is synthesized in the peroxisome, it is exported to the endoplasmic reticulum where a series of enzymes, including TMEM189, complete the remaining enzymatic steps resulting in vinyl-ether plasmalogens. PPI-1011 was engineered to be an orally bioavailable plasmalogen precursor that bypasses the peroxisomal portion of the biosynthetic pathway, entering downstream of all known RCDP mutations where it can be converted to target plasmalogens by the endoplasmic reticulum.

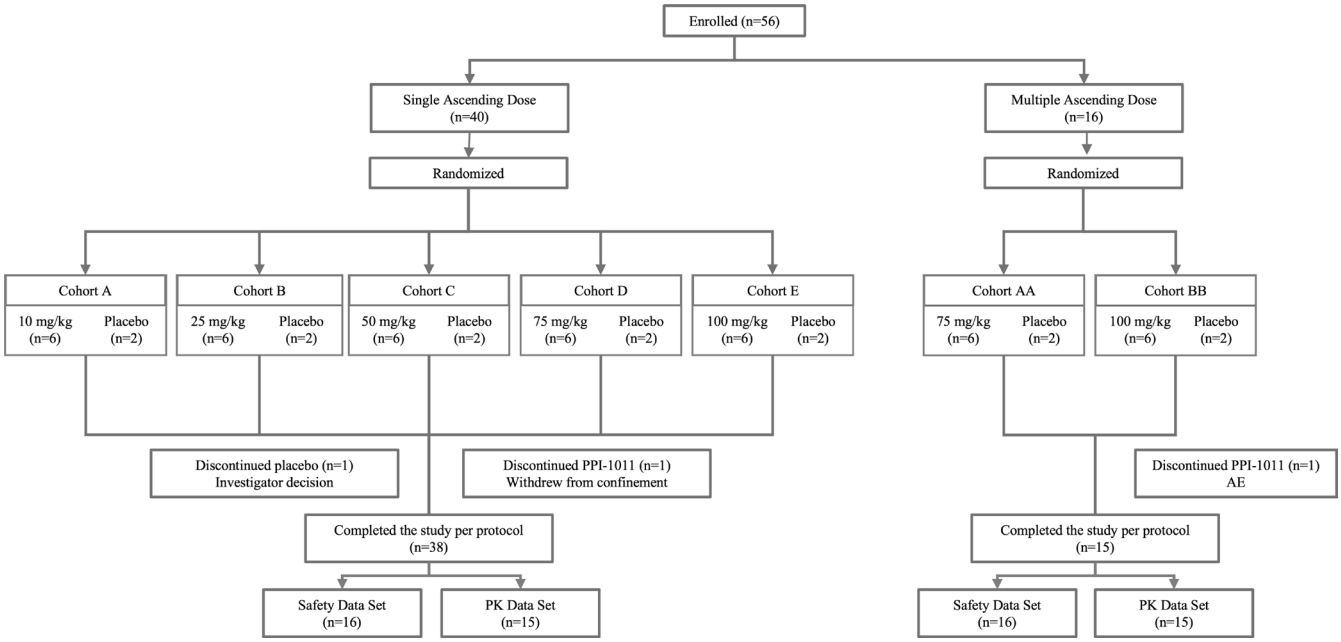

FIGURE 2 | Schematic of the study design for the single ascending dose (SAD) and multiple ascending dose (MAD) phases of the Phase I trial.

with at least two males and two females randomized to receive PPI-1011 treatment. The doses for the MAD cohorts were selected by the SRC based on the cumulative blinded safety review of all data from the SAD study. All subjects remained confined to the clinic from Day −1 through Day 15 (at least 36 h after the last dose). Subjects then returned to the clinic for outpatient assessments on Days 16, 17, 18, 19, and 21.

This study was approved by Health Canada Therapeutic Products Directorate and by Advarra Institutional Review Board (IRB). Clinical conduct and study design were in accordance with the recommendations of the current Food and Drug Administration (FDA) guidance documents and International Council for Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP) and in accordance with the ethical principles

that have their origin in the World Medical Association (WMA) Declaration of Helsinki, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and subsequent amendments. Written informed consent was provided by all participants prior to any study-related procedures.

2.2 | Participants

Eligible participants were healthy non-smoking males and non-pregnant, non-lactating females between 18 and 65 years of age, with a body mass index (BMI) between 18.5–30.0 kg/m [2], and weighing no more than 91.0 kg. The health status of each participant was determined by the PI or their designee at a screening visit and again on Day −1. This assessment was based on a full physical exam, medical history including medication and supplement usage, vital signs, and a 12-lead electrocardiogram (ECG). A full list of the inclusion and exclusion criteria can be found in Table S1.

2.3 | Study Treatment

PPI-1011 was provided in a liquid coconut oil formulation containing 0.1% 1-thioglycerol at a concentration of 421 mg/mL. The matching placebo was liquid coconut oil with 0.1% 1-thioglycerol. Dosing volumes were standardized across all participants within a cohort to allow for a better understanding of any drug-related adverse effects, compared to those associated with oil intake. For all cohorts with a dose of ≤ 85 mg/kg, the dosing volume was 20 mL, while the cohorts above this limit were dosed with 25 mL. All subjects were dosed within 1 h after the start of their breakfast meal. To control for the impact of the diet on study endpoints, all meals and snacks were standardized, with subjects instructed to complete the meal within 30 min. In addition, the breakfast meals on the days when the majority of the PK blood draws took place (SAD Day 1; MAD Day 1 and 14) were further standardized to have similar nutritional content and higher fat levels (25–30 g). A clinical staff member administered the oral solution to each subject from an amber syringe, followed by a mouth check. Subjects were then asked to drink 50 mL of water to rinse any remaining material from their mouth and were additionally offered the ability to swish and spit with apple juice to mitigate any potential bad taste from the treatment.

2.4 | Study Objectives and Assessments

The primary objective was to evaluate the safety and tolerability of single and multiple ascending doses of orally administered PPI-1011 in healthy subjects. The secondary objective was to evaluate the serum pharmacokinetic (PK) profile of PPI-1011 and its primary metabolite ethanolamine plasmalogen 16:0/22:6 (PlsEtn 16:0/22:6), following single and multiple ascending oral doses of PPI-1011 in healthy subjects.

Safety and tolerability were assessed by evaluating the incidence, severity, and dose relationship of treatment-emergent adverse events (TEAEs) along with vital signs, clinical laboratory values (including lipid and coagulation assessments), ECGs, and physical exams. The concentrations of PPI-1011 and PlsEtn 16:0/22:6 were measured using separate fit-for-purpose validated liquid chromatography–tandem mass spectrometry methods (BioPharma Services Inc). The analytical calibration range for the PPI-1011 method was 50 to 2000 ng/mL, while for the PlsEtn 16:0/22:6 method, the range was 400 to 25,000 ng/mL.

2.5 | Statistical Analysis

There was no formal statistical rationale for the sample size selected for this study. Rather, the size was based on industry standards for first-in-human studies to ensure a reliable assessment of safety, tolerability, and PK while minimizing unnecessary subject exposure.

All data were summarized using descriptive statistics and summaries provided in either tabular or graphical format. Descriptive statistics (min, max, median, mean, standard deviation (SD) and coefficient of variation) for PlsEtn 16:0/22:6 concentrations and PK parameters were provided by cohort if applicable. PK analysis was performed using Phoenix WinNonlin version 8.4 (Certara) and statistical analyses were performed using SAS version 9.4 or JMP version 18.01. PK analysis was performed on all subjects who received at least one dose of the study drug and had sufficient data to obtain at least one reliable key PK parameter calculated using non-compartmental analysis (NCA). The following PK parameters were estimated (where possible) for the primary metabolite PlsEtn 16:0/22:6: AUC_t (area under the concentration-time curve from time zero until the last measurable concentration, or whichever occurred first, estimated using the trapezoidal method); $AUC_{0\text{-inf}}$ (area under the concentration-time curve from time zero to infinity, calculated as $AUC_t + Clast/\lambda$, where Clast was the last measurable concentration); $AUC_{0\text{-}24}$ (area under the concentration-time curve from time zero to 24-h); AUC_{tau} (area under the concentration-time curve during the dosing interval at steady state); T_{max} (the time maximal serum concentration observed); $T_{1/2}$ (terminal elimination half-life, estimated as $\ln(2)/\lambda$ where λ was the terminal elimination rate constant). Dose proportionality was assessed graphically and statistically using the power model approach with the natural logarithm (ln) of PK parameters AUC_t as the dependent variables and the ln of the dose as the independent variable. An estimate of the slope with a corresponding 90% CI was obtained from the power model to assess the degree of dose proportionality, using the criterion limit of 0.50–2.00 proposed by J. Hummel [33].

3 | Results

3.1 | Subject Disposition and Demographics

The study was initiated on May 30, 2023, and completed on February 14, 2024. A total of 56 subjects, 40 in the SAD study and 16 in the MAD study, were enrolled and received study treatment. Of the enrolled subjects, 42 received active PPI-1011 treatment, 30 in the SAD study and 12 in the MAD. All 56 subjects were included in the safety data set (see Figure 2).

Of the 56 enrolled subjects, 53 (94.6%) completed the study per protocol, and 3 (5.4%) discontinued early. The early discontinuations included one subject in SAD Cohort A who was withdrawn by the physician due to pregnancy, one subject in SAD Cohort E who withdrew for personal reasons, and one subject in MAD Cohort AA who was discontinued from treatment on Day 8 due to an adverse event (AE) but remained enrolled in the study.

Overall, 28 (50%) females and 28 (50%) males aged 26–65, with BMIs between 19.7 and 30.4 kg/m^2 participated in the study. One subject was included with a BMI of 30.4 kg/m^2 at Day 1 but who had a BMI below 30.0 kg/m^2 at screening. It was determined by the medical monitor and Sponsor that their inclusion was acceptable. There were no significant demographic differences between the placebo and treatment groups. A summary of the demographics by cohort is provided in Table 1.

3.2 | Safety

All subjects were dosed as planned in the SAD study. In the MAD study, one subject in Cohort AA (75 mg/kg) was discontinued from dosing on Day 8 due to mildly elevated liver enzyme (ALT and AST) levels (grade 1) which were considered by the PI to be probably related to treatment. The subject showed no clinical signs throughout the study and remained enrolled through Day 21, although did not resume dosing. All enzyme levels normalized without intervention by Day 37. A list of all TEAEs from the SAD and MAD cohorts is provided in Table S2.

In the SAD portion of the study, 13 subjects (43.3%) reported 22 TEAEs in the PPI-1011 groups (Cohorts A-E), and 4 subjects (40%) reported 6 TEAEs in the placebo-treated group (Table 2) for a total of 28 TEAEs in 17 subjects. All TEAEs were considered grade 1 (mild) and resolved except for one subject in the placebo group who tested positive for pregnancy on Day 3. Two of the TEAEs in the PPI-1011 and two of the TEAEs in the placebo group were considered unrelated or likely unrelated to the treatment by the PI. Half of all reported TEAEs (14/28, 50%) were gastrointestinal-related (Table 2). Additionally, five headache TEAEs were reported (5/28, 17.9%), which was the only non-gastrointestinal AE reported more than twice. One subject in Cohort E had a clinically significant ECG abnormal finding of T wave inversion after receiving 100 mg/kg PPI-1011, which was judged mild and possibly related but resolved without intervention.

In the MAD portion of the study (Table 3), 7 subjects (58.3%) reported 25 TEAEs in the PPI-1011 groups (Cohort AA and BB), and 2 of the subjects (50%) reported 13 TEAEs in the placebo-treated group for a total of 38 TEAEs in 9 subjects. All TEAEs were considered grade 1 (mild) and resolved. Four of the TEAEs in the PPI-1011 and four of the TEAEs in the placebo-group were considered unrelated or likely unrelated to the treatment by the PI. Similar to the SAD study, the majority of TEAEs in the MAD (21/38 or 55.3%) were gastrointestinal-related, with no other AEs reported more than twice throughout the study (Table 3).

Overall, PPI-1011 was safe and well tolerated in all cohorts. There were no deaths or serious TEAEs in either the SAD or MAD portions of the study.

3.3 | Pharmacokinetics

Intact PPI-1011 was not detected above quantifiable levels in the serum of any participants within the SAD or MAD cohorts, confirming that the molecule does not get absorbed fully intact (data not shown). The primary target metabolite that PPI-1011 is converted to in the body is an ethanolamine plasmalogen containing a 16-carbon saturated fatty alcohol at *sn*1 and DHA at *sn*2, denoted as PlsEtn 16:0/22:6. PK calculations were based on serum levels of PlsEtn 16:0/22:6.

The mean serum concentration-time curves of each SAD cohort following a single oral dose of PPI-1011 are shown in Figure 3A. There was a dose-dependent increase in PlsEtn 16:0/22:6 levels following single oral doses of between 10 and 100 mg/kg, with the mean C_{max} increasing from 3891.5 for Cohort A to 9509.3 mg/mL for Cohort E (Table 4). However, the increases in C_{max} for the first two cohorts (10 mg/kg and 25 mg/kg) were only slightly higher than baseline levels, subsequently resulting in high variability of the other PK characteristics and limiting their interpretability. For the cohorts that received 50, 75, and 100 mg/kg, several of the PK characteristics showed consistency. For example, C_{max} for each dose was reached within a T_{max} of between 48 and 53 h, with a $T_{1/2}$ ranging between 63.2 and 86.3 h after dosing. These dynamics indicated a prolonged uptake and conversion period for the compound followed by a slow decline.

Dose proportionality for the SAD was assessed using the power model and linear regression of ln-transformed AUC_t and C_{max}, as shown in Figure 3B,C. The results showed that both AUC_t and C_{max} increased in a linear dose-dependent manner, where for every 10-fold increase in the dose, there was a 2.29-fold increase in the AUC_t (F-Stat 54.2, $p < 0.0001$), and a 2.44-fold increase in the C_{max} (F-Stat 68.3, $p < 0.0001$). A summary of all PK parameters for PlsEtn 16:0/22:6 in the SAD study is shown in Table 4.

Within the MAD study, both the 75 mg/kg/day and 100 mg/kg/day cohorts displayed similar PK profiles after the first dose, closely resembling the SAD (Figure 3D). PlsEtn 16:0/22:6 levels increased over the 24-h period, with C_{max} reaching 4511.3 ng/mL in the 75 mg/kg/day group and 5171.9 ng/mL in the 100 mg/kg/day cohort (Table 4). The T_{max} values in the two cohorts were 24.0 and 23.3 h, respectively, suggesting that overall levels were still increasing when the Day 2 dose was administered. By Day 14, the C_{max} in the 100 mg/kg/day cohort (23689.9 ng/mL) was marginally higher than the 75 mg/kg/day cohort (18877.1 mg/mL), suggesting only a modest dose response, if any (Table 4). In Cohorts AA and BB, the $T_{1/2}$ values were 76.6 and 85.6 h, respectively, suggesting the washout period was similar even after repeat dosing. A summary of all PK parameters for PlsEtn 16:0/22:6 in the MAD study is shown in Table 4.

In addition to the standard PK assessments on Day 1 and Day 14 of the MAD study, PK samples were collected and analyzed each day approximately 1 h prior to dosing to investigate saturation of exposure over the 14 days. In both the 75 mg/kg/day and 100 mg/kg/day cohorts, levels of PlsEtn 16:0/22:6 increased day over day for the first 7–10 days before reaching near steady-state levels in the 75 mg/kg/day group (Figure 3E). The 100 mg/kg/day cohort continued to increase gradually day by day up to the last day of

TABLE 1 | Demographic Summary by Cohort.

	Single ascending dose						Multiple ascending dose		
	Cohort A (10 mg/kg)	**Cohort B (25 mg/kg)**	**Cohort C (50 mg/kg)**	**Cohort D (75 mg/kg)**	**Cohort E (100 mg/kg)**	**Placebo[a]**	**Cohort AA (75 mg/kg)**	**Cohort BB (100 mg/kg)**	**Placebo[a]**
Age (years)									
Mean (min, max)	46.5 (30, 62)	48.3 (29, 62)	57.2 (54, 62)	56.7 (50, 64)	52.3 (26, 62)	50.7 (33, 62)	59.0 (52, 64)	50.7 (33, 65)	48.0 (30, 63)
Sex									
Male	3 (50%)	3 (50%)	3 (50%)	3 (50%)	3 (50%)	5 (50%)	4 (66%)	3 (50%)	3 (75%)
Female	3 (50%)	3 (50%)	3 (50%)	3 (50%)	3 (50%)	5 (50%)	2 (33%)	3 (50%)	1 (25%)
Race									
Asian	0 (0%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	1 (17%)	1 (17%)	0 (0%)
Black/African American	3 (50%)	2 (33%)	2 (33%)	0 (0%)	1 (17%)	3 (30%)	1 (17%)	1 (17%)	1 (25%)
White	3 (50%)	3 (50%)	4 (67%)	6 (100%)	5 (83%)	6 (60%)	4 (67%)	4 (67%)	3 (75%)
BMI (kg/m^2)									
Mean (SD)	26.7 (2.2)	24.1 (1.2)	26.9 (2.6)	26.0 (3.3)	24.5 (2.8)	25.2 (3.7)	26.2 (1.7)	24.8 (2.8)	23.0 (3.3)

Abbreviations: BMI, body mass index; SD, standard deviation.
[a]Data from placebo subjects was combined for the single ascending dose phase (Cohorts A–E) and multiple ascending dose phase (Cohorts AA and BB).

TABLE 2 | Treatment-emergent adverse events reported within the single ascending dose.

	Cohort A (10 mg/kg) (*n* = 6)	Cohort B (25 mg/kg) (*n* = 6)	Cohort C (50 mg/kg) (*n* = 6)	Cohort D (75 mg/kg) (*n* = 6)	Cohort E (100 mg/kg) (*n* = 6)	Placebo[a] (*n* = 10)	Total (*n* = 40)
Count (percent) of subjects with at least one TEAE/No. of TEAEs	3 (50.0%)/5	2 (33.3%)/4	0 (0.0%)/0	2 (33.3%)/5	6 (100%)/8	4 (40.0%)/6	17 (42.5%)/28
Count (percent) of subjects with at least one SAE/No. of SAEs	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0
Count (percent) of subjects with at least one TEAE by relationship/No. of TEAEs by relationship							
Probable	2 (33.3%)/3	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	5 (83.3%)/5	2 (20.0%)/3	9 (22.5%)/11
Possible	1 (16.7%)/1	2 (33.3%)/4	0 (0.0%)/0	2 (33.3%)/5	2 (33.3%)/2	1 (10.0%)/1	8 (20.0%)/13
Unlikely	1 (16.7%)/1	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	1 (16.7%)/1	0 (0.0%)/0	2 (5.0%)/2
Unrelated	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	2 (20.0%)/2	2 (5.0%)/2
Count (percent) of subjects with at least one TEAE by severity/No. of TEAEs by severity							
Mild	3 (50.0%)/5	2 (33.3%)/4	0 (0.0%)/0	2 (33.3%)/5	6 (100%)/8	4 (40.0%)/5	17 (42.5%)/27
Moderate	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	1 (10.0%)/1	1 (2.5%)/1
Severe	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0
Count (percent) of subjects by primary organ system and preferred term/No. of TEAEs by primary organ system and preferred term							
Gastrointestinal disorders	3 (50.0%)/4	1 (16.7%)/1	0 (0.0%)/0	2 (33.3%)/2	4 (66.7%)/5	2 (20.0%)/2	12 (30.0%)/14
Abdominal discomfort	2 (33.3%)/2	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	1 (16.7%)/1	0 (0.0%)/0	3 (7.5%)/3
Abdominal pain	1 (16.7%)/2	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	1 (16.7%)/1	0 (0.0%)/0	2 (5.0%)/3
Diarrhea	0 (0.0%)/0	1 (16.7%)/1	0 (0.0%)/0	2 (33.3%)/2	2 (33.3%)/2	0 (0.0%)/0	5 (12.5%)/5
Nausea	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	1 (16.7%)/1	2 (20.0%)/2	3 (7.5%)/3
General disorders and administration site conditions	1 (16.7%)/1	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	1 (2.5%)/1
Fatigue	1 (16.7%)/1	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	1 (2.5%)/1
Investigations	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	1 (16.7%)/1	1 (10.0%)/1	2 (5.0%)/2
Electrocardiogram abnormal	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	1 (16.7%)/1	0 (0.0%)/0	1 (2.5%)/1
Pregnancy test positive	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	1 (10.0%)/1	1 (2.5%)/1

(Continues)

TABLE 2 | (Continued)

	Cohort A (10 mg/kg) ($n=6$)	Cohort B (25 mg/kg) ($n=6$)	Cohort C (50 mg/kg) ($n=6$)	Cohort D (75 mg/kg) ($n=6$)	Cohort E (100 mg/kg) ($n=6$)	Placebo[a] ($n=10$)	Total ($n=40$)
Musculoskeletal and connective tissue disorders	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	1 (16.7%)/1	1 (10.0%)/1	2 (5.0%)/2
Back pain	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	1 (16.7%)/1	1 (10.0%)/1	2 (5.0%)/2
Nervous system disorders	0 (0.0%)/0	1 (16.7%)/3	0 (0.0%)/0	1 (16.7%)/3	1 (16.7%)/1	2 (20.0%)/2	5 (12.5%)/9
Dizziness	0 (0.0%)/0	1 (16.7%)/1	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	1 (2.5%)/1
Headache	0 (0.0%)/0	1 (16.7%)/1	0 (0.0%)/0	1 (16.7%)/2	1 (16.7%)/1	1 (10.0%)/1	4 (10.0%)/5
Somnolence	0 (0.0%)/0	1 (16.7%)/1	0 (0.0%)/0	1 (16.7%)/1	0 (0.0%)/0	0 (0.0%)/0	2 (5.0%)/2
Taste disorder	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	1 (10.0%)/1	1 (2.5%)/1

Abbreviations: No, number of events; SAE, serious adverse events; SD, standard deviation; TEAE, treatment-emergent adverse events.
[a]Data from all placebo subjects was combined (Cohorts A–E).

dosing, after which both dose cohorts began to decline, as seen by Days 15–19 following withdrawal of treatment.

4 | Discussion

We report here for the first time that high doses of orally administered plasmalogen precursor PPI-1011 are well-tolerated in healthy adults following single and multiple ascending doses. There were no serious AEs reported in either the SAD or MAD trial, and all TEAEs possibly or probably related to PPI-1011 were mild, monitorable, and resolved without intervention.

As anticipated due to the oil-based nature of the compound, gastrointestinal TEAEs were the most common TEAEs in both the PPI-1011 and placebo groups. While gastrointestinal TEAEs were relatively common and accounted for approximately half of all the TEAEs in the study, they were all considered mild and did not require intervention or discontinuation of the treatment, nor did they increase over time in the MAD cohort. A single subject had TEAEs related to elevated liver function tests in the 75 mg/kg MAD cohort, which resulted in discontinuation of treatment. While the subject had no clinical signs throughout the study, the PI determined that the enzyme levels were sufficiently elevated to discontinue treatment on Day 8 of the study, after which liver enzyme function returned to normal without intervention by Day 37. Given the known correlation between fat intake and liver changes, and mild to moderate AEs being reported in chronic nonclinical animal studies, the liver findings were not completely unexpected. To further understand the impact of PPI-1011 on blood markers of liver function, we graphed the daily levels of four liver function blood levels in all MAD subjects. Other than the two subjects (one in the 75 mg/kg and one subject in the 100 mg/kg group) which had documented TEAEs related to liver function tests, all other subjects showed no changes in levels over the MAD study period (Figure S1). Future clinical studies should limit the volume of PPI-1011 administered to decrease the likelihood of liver-related TEAEs and include regular monitoring of liver enzyme levels.

Most patients with RCDP are fed by a gastrointestinal tube or nasogastric tube and require a strict feeding schedule to maintain their body weight and overall health. As such, RCDP patients are rarely, if ever, in a fasted state. Therefore, we ensured in the Phase I that the drug was administered to non-fasted subjects as the neat formulated oil (not encapsulated). While uncommon in a first-in-human healthy subject trial, it was required to understand the PK and tolerability of PPI-1011 as it is intended to be administered within the RCDP population. While diet can impact the absorption of a drug, we controlled for this by providing a standardized meal plan to study subjects to ensure they were in a similar fed-state throughout the confinement period.

PPI-1011 is a non-naturally occurring synthetic compound designed for rapid conversion to its target plasmalogen species PlsEtn 16:0/22:6, which is indistinguishable from the natural endogenous form in the body. Although we had previously confirmed this metabolic fate in preclinical data by failing to detect intact PPI-1011 in the circulation of treated animals [31], the same observations in this study confirmed that this rapid

TABLE 3 | Treatment-emergent adverse events reported within the multiple ascending dose cohort.

	Cohort AA 75 mg/kg ($n=6$)	Cohort BB 100 mg/kg ($n=6$)	Placebo[a] ($n=4$)	Total ($n=16$)
Count (percent) of subjects with at least one TEAE/No. of TEAEs	3 (50.0%)/14	4 (66.7%)/11	2 (50.0%)/13	9 (56.3%)/38
Count (percent) of subjects with at least one SAE/No. of SAEs	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0
Count (percent) of subjects with at least one TEAE by relationship/No. of TEAEs by relationship				
Probable	2 (33.3%)/8	3 (50.0%)/9	1 (25.0%)/6	6 (37.5%)/23
Possible	2 (33.3%)/3	1 (16.7%)/1	2 (50.0%)/3	5 (31.3%)/7
Unlikely	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0
Unrelated	1 (16.7%)/3	1 (16.7%)/1	2 (50.0%)/4	4 (25.0%)/8
Count (percent) of subjects with at least one TEAE by severity/No. of TEAEs by severity				
Mild	3 (50.0%)/14	4 (66.7%)/11	2 (50.0%)/13	9 (56.3%)/38
Moderate	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0
Severe	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0	0 (0.0%)/0
Count (percent) of subjects by primary organ system and preferred term/No. of TEAEs by primary organ system and preferred term				
Gastrointestinal disorders	1 (16.7%)/4	3 (50.0%)/9	2 (50.0%)/8	6 (37.5%)/21
Abdominal distension	1 (16.7%)/2	1 (16.7%)/1	1 (25.0%)/1	3 (18.8%)/4
Abdominal pain	0 (0.0%)/0	0 (0.0%)/0	1 (25.0%)/1	1 (6.3%)/1
Abdominal pain upper	0 (0.0%)/0	1 (16.7%)/1	0 (0.0%)/0	1 (6.3%)/1
Constipation	1 (16.7%)/1	0 (0.0%)/0	1 (25.0%)/1	2 (12.5%)/2
Diarrhea	0 (0.0%)/0	2 (33.3%)/2	1 (25.0%)/3	3 (18.8%)/5
Flatulence	1 (16.7%)/1	0 (0.0%)/0	0 (0.0%)/0	1 (6.3%)/1
Nausea	0 (0.0%)/0	1 (16.7%)/5	2 (50.0%)/2	3 (18.8%)/7
General disorders and administration site conditions	1 (16.7%)/2	1 (16.7%)/1	1 (25.0%)/2	3 (18.8%)/5
Application Site erythema	0 (0.0%)/0	0 (0.0%)/0	1 (25.0%)/1	1 (6.3%)/1
Application site pruritus	1 (16.7%)/1	0 (0.0%)/0	1 (25.0%)/1	2 (12.5%)/2
Application site rash	1 (16.7%)/1	0 (0.0%)/0	0 (0.0%)/0	1 (6.3%)/1
Vessel puncture site bruise	0 (0.0%)/0	1 (16.7%)/1	0 (0.0%)/0	1 (6.3%)/1
Injury, poisoning, and procedural complications	0 (0.0%)/0	0 (0.0%)/0	1 (25.0%)/1	1 (6.3%)/1
Limb injury	0 (0.0%)/0	0 (0.0%)/0	1 (25.0%)/1	1 (6.3%)/1
Investigations	2 (33.3%)/5	1 (16.7%)/1	1 (25.0%)/1	4 (25.0%)/7
Alanine aminotransferase increased	1 (16.7%)/1	1 (16.7%)/1	0 (0.0%)/0	2 (12.5%)/2
Aspartate aminotransferase increased	1 (16.7%)/1	0 (0.0%)/0	0 (0.0%)/0	1 (6.3%)/1
Blood alkaline phosphatase increased	1 (16.7%)/1	0 (0.0%)/0	0 (0.0%)/0	1 (6.3%)/1
Gamma-glutamyltransferase increased	1 (16.7%)/1	0 (0.0%)/0	0 (0.0%)/0	1 (6.3%)/1

(Continues)

TABLE 3 | (Continued)

	Cohort AA 75 mg/kg ($n=6$)	Cohort BB 100 mg/kg ($n=6$)	Placebo[a] ($n=4$)	Total ($n=16$)
Glomerular filtration rate decreased	1 (16.7%)/1	0 (0.0%)/0	1 (25.0%)/1	2 (12.5%)/2
Metabolism and nutrition disorders	2 (33.3%)/2	0 (0.0%)/0	0 (0.0%)/0	2 (12.5%)/2
Decreased appetite	2 (33.3%)/2	0 (0.0%)/0	0 (0.0%)/0	2 (12.5%)/2
Musculoskeletal and connective tissue disorders	0 (0.0%)/0	0 (0.0%)/0	1 (25.0%)/1	1 (6.3%)/1
Pain in extremity	0 (0.0%)/0	0 (0.0%)/0	1 (25.0%)/1	1 (6.3%)/1
Psychiatric disorders	1 (16.7%)/1	0 (0.0%)/0	0 (0.0%)/0	1 (6.3%)/1
Anxiety	1 (16.7%)/1	0 (0.0%)/0	0 (0.0%)/0	1 (6.3%)/1

Abbreviations: No, number of events; SAE, serious adverse events; SD, standard deviation; TEAE, treatment-emergent adverse events.
[a]Data from all placebo subjects was combined (Cohorts AA and BB).

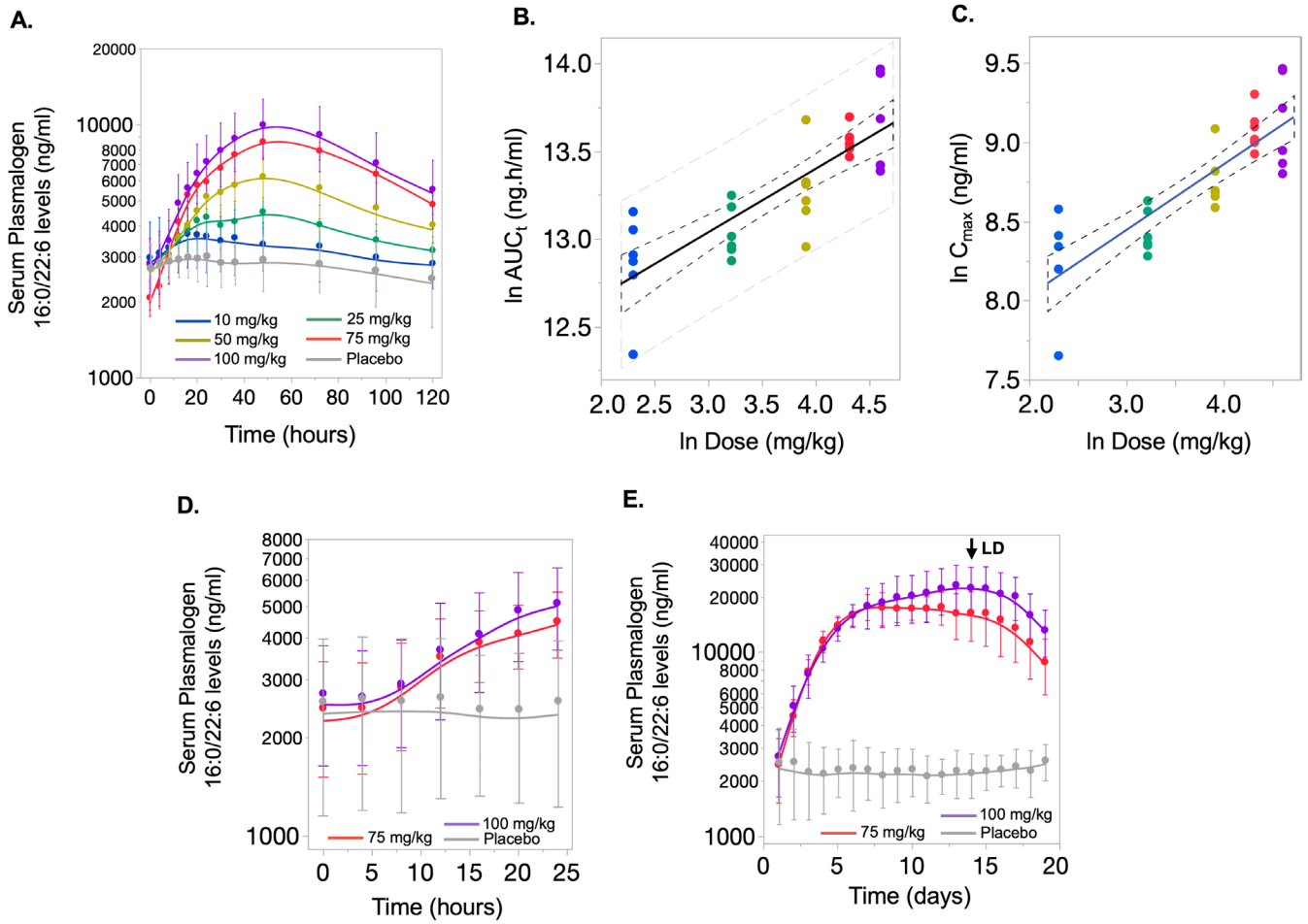

FIGURE 3 | Pharmacokinetic (PK) plots. (A) Mean serum levels (±SD) of target plasmalogen metabolite 16:0/22:6 versus time following a single administration of increasing doses (SAD phase); (B). Dose proportionality plot of the ln of dose versus the ln of AUC_t (SAD phase, $p<0.0001$, F-Stat 54.2); (C). Dose proportionality plot of the ln of dose versus ln of C_{max} (SAD phase, $p<0.0001$, F-Stat 68.3); (D). Mean serum levels (±SD) of target plasmalogen metabolite 16:0/22:6 versus time over the first 24 h following the first administration of PPI-1011 in the MAD phase; E). Mean serum levels (±SD) of target plasmalogen metabolite 16:0/22:6 versus time by day over the entire MAD phase. Note that the last dose (LD) was on Day 14 indicated by the arrow.

metabolism also occurs in humans. One limitation of this analysis is that we only assayed for intact PPI-1011 containing lipoic acid and not the alkylacyl glycerol intermediate, which would also be indistinguishable from the endogenous form. Given that it is the creation of the ether-bond that is compromised in RCDP and we previously demonstrated in preclinical studies that PPI-1011 results in vinyl-ether plasmalogen augmentation [27–31], it was not necessary to assay this intermediate.

TABLE 4 | Serum pharmacokinetic parameters of PlsEtn 16:0/22:6 following PPI-1011 oral administration.

	SAD					MAD Day 1		MAD Day 14	
Parameter	**Cohort A 10 mg/kg**	**Cohort B 25 mg/kg**	**Cohort C 50 mg/kg**	**Cohort D 75 mg/kg**	**Cohort E 100 mg/kg**	**Cohort AA 75 mg/kg**	**Cohort BB 100 mg/kg**	**Cohort AA 75 mg/kg**	**Cohort BB 100 mg/kg**
C_{max} (ng/mL), mean ± SD	3891.5 ± 1074.4	4618.0 ± 646.8	6420.40 ± 1254.0	8823.9 ± 1209.3	9509.3 ± 2814.3	4511.35 ± 1144.05	5171.9 ± 1486.8	18877.1 ± 3291.9	23689.9 ± 7005.9
T_{max} (h), mean ± SD Median (range)	24.7 ± 15.3 20.1 (4.0–48.2)	38.1 ± 13.6 42.1 (20.0–50.7)	52.1 ± 16.4 48.2 (36.0–72.4)	53.9 ± 14.6 48.1 (36.0–72.0)	48.1 ± 15.3 48.0 (24.0–72.4)	24.0 ± 0.0 24.0 (24.0–24.0)	23.34 ± 1.63 24.0 (20.02–24.00)	14.4 ± 11.5 20.0 (0.0–24.0)	11.3 ± 12.5 10.0 (0.0–24.0)
AUC_t (h ng/mL) Mean ± SD	393715.5 ± 98676.6	462780.7 ± 70032.1	596466.0 ± 151392.8	777996.4 ± 61458.3	900793.1 ± 245066.0			419106.8 ± 79543.5	534289.0 ± 163915.0
$AUC_{0\text{-}inf}$ (h ng/ml) Mean ± SD	1389597.7 ± 600930.1	1267992.8 ± 311752.9	931031.5 ± 141282.4	1220109.0 ± 82510.3	1419915.9 ± 459297.4	—	—	—	—
$T_{1/2}$ (h), mean (SD)	271.8 ± 228.4	177.0 ± 78.0	86.3 ± 6.0	63.2 ± 5.2	76.0 ± 28.7	—	—	76.64 ± 17.36	85.56 ± 28.74
$AUC_{0\text{-}24}$ (h ng/mL) Mean ± SD	—	—	—	—	—	82855.00 ± 25141.06	88701.1 ± 29675.22	1823113.0 ± 392267.3	2325806.0 ± 682733.5
AUC_{tau} (h ng/mL) Mean ± SD	—	—	—	—	—	—	—	76.6 ± 17.36	85.6 ± 28.7

Note: Data are geometric means ± standard deviation.

Abbreviations: AUC, area under the curve; AUC_{0-24}, area under the concentration-time curve from time 0 to 24 h; AUC_{0-inf}, area under the concentration-time curve from time 0 to infinity; AUC_t, area under the concentration-time curve from time zero until the last measurable concentration or last sampling time; AUC_{tau}, area under the concentration-time curve from time 0 to tau (the length of the dosing interval) at steady state; C_{max}, the maximal observed serum concentration; h, hours; MAD, multiple ascending dose; SAD, single ascending dose; SD, standard deviation; $T_{1/2}$, terminal elimination half-life; T_{max}, time when the maximal serum concentration is observed.

Prior to the study, it was unknown whether levels of PlsEtn 16:0/22:6 could be adequately increased with PPI-1011 treatment, particularly in the SAD cohorts, given the relatively high endogenous levels seen in healthy adults. A clear dose–response above baseline levels was observed in the SAD study with levels in all cohorts, but particularly those above 50 mg/kg (Figure 3). The uptake and conversion of PPI-1011 occurred over a period of 48 h or more in the highest three cohorts. This prolonged uptake period was anticipated and is in general agreement with PK characteristics observed in preclinical rat studies [27]. These findings confirmed the ability of the compound to augment the PlsEtn 16:0/22:6 pool. Based on this prolonged uptake, a once-daily administration was chosen for the MAD study to evaluate the ability of PPI-1011 to gradually augment plasmalogen levels over time. The MAD study demonstrated that with repeated dosing, significantly elevated serum levels of PlsEtn 16:0/22:6 could be achieved to a level approaching 10 times baseline levels. There was no difference in exposure between 75 and 100 mg/kg/day for the first 7–8 days with levels rising equivalently in both cohorts. After this time, the 75 mg/kg/day cohort plateaued while the 100 mg/kg/day group continued to increase gradually. Given that the drug is intended for chronic administration and conversion to an endogenous metabolite, and that what is not absorbed is primarily excreted [27], it is likely that with extended time both doses would reach a similar steady state. Furthermore, there is currently no anticipated clinical benefit of increasing plasmalogen levels above what is considered normal, and therefore augmentation of plasmalogen levels within the serum was the only proof of target engagement measure that was feasible in healthy adults. Longer-exposure pharmacodynamic and pharmacokinetic endpoints will be tested in a future Phase II study in RCDP patients. These future studies could also lead to changes in the administration schedule, to less frequent dosing if indicated. Ultimately, the goal of PPI-1011 treatment in RCDP patients is to restore deficient plasmalogen levels, which our PK findings suggest is achievable within a relatively short period of time. Given that RCDP is due solely to the inability of the body to synthesize plasmalogens, the greatest likelihood of clinical improvement is dependent upon the ability of treatment to adequately replace the deficiency within the body.

Plasmalogen extracts, primarily from marine sources, are commercially available and have been evaluated in a few small open-label studies. These studies evaluated doses up to 1 mg/day (on par with the levels of marketed products) for as long as 24 weeks in patients with Alzheimer's disease and failed to demonstrate increases in circulating plasmalogen levels [34, 35]. Given the low dose of the extracts used, these results are unsurprising. A synthetic alkyl diacyl plasmalogen precursor has also been reported in a small open-label human study where subjects were dosed with 900 mg/day for 1 month, then 1800 mg/day for months two and three, and finally 3600 mg/day for the fourth month. Assuming an average body weight of approximately 75 kg, this correlates with daily dosing between 12 and 48 mg/kg/day. Relative to baseline levels, the study reported a 1.2 (900 mg), 1.4 (1800 mg), and 1.7 (3600 mg) fold increase in serum plasmalogen levels with treatment [36]. Despite 4 months of dosing, less augmentation was observed than we report after a single dose of 50 mg/kg of PPI-1011, suggesting the synthetic alkyl diacyl precursor was either less concentrated or less pure than labeled, or that PPI-1011 as designed is truly pharmacokinetically superior to generic alkylacyl glycerols. Together, the data on supplements to date indicate that they are clinically unviable due to limited concentration and potency.

In summary, the results of this Phase I study show that the administration of PPI-1011 results in the safe and effective augmentation of plasmalogens in humans. Our findings support the continued clinical development of PPI-1011 as a treatment for RCDP, as well as other diseases associated with plasmalogen deficiency, including PBDs, Alzheimer's disease, and Parkinson's disease.

Author Contributions

T.S. and S.A.R. wrote the manuscript; T.S., K.J.K., and S.A.R. designed the research; T.S. performed the research. T.S. and S.A.R. analyzed the data.

Conflicts of Interest

T.S., K.J.K., and S.A.R. are full-time paid employees of Med-Life Discoveries LP.

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Supporting Information

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