Clementia Pharmaceuticals Inc.

Clinical Study Protocol

A Phase 2, Open-Label Extension, Efficacy and Safety Study of a RARγ-Specific Agonist (Palovarotene) in the Treatment of Preosseous Flare-ups in Subjects with Fibrodysplasia Ossificans Progressiva (FOP)

Study Number: PVO-1A-202

Original Protocol: 04 June 2014
Amendment 1: 30 September 2014
Amendment 2: 22 June 2015
Amendment 3: 10 March 2016
Amendment 4: 01 September 2017
Amendment 5: 06 June 2018
Amendment 6: 08 March 2019
Amendment 7: 01 November 2019
Amendment 8: 30 November 2020

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PROTOCOL SIGNATURE PAGE

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Protocol Number: PVO-1A-202

Signature of Approval for Protocol PVO-1A-202 (Amendment 8: 30 November 2020)

CLEMENTIA PHARMACEUTICALS INC.
PI , **MD**
PI

NAME: PI

SIGNATURE: _____ **DATE:** _____

PROTOCOL AMENDMENT 8 SUMMARY OF CHANGES

This eighth amendment to the protocol for Study PVO-1A-202 was finalized on 30 November 2020.

Location/Section Number	Change	Rationale
Major changes that affected the clinical conduct of the study:		
Protocol Synopsis Tables 1 and 4 Section 1.1.3.2 Clinical Data Section 3.1 Overview of Study Design Section 3.2 Study Rationale Section 7 Study Procedures and Assessments Section 2.3 Secondary Objectives Section 5.7 Subject Withdrawal or Early Termination Section 9.1.10 Follow-up of Adverse Events and Serious Adverse Events	Part D was added for skeletally immature subjects who stopped taking study drug for any reason before completion of Part A/B/C. Part D includes yearly visits for up to a 2-year follow-up period following last dose. No dosing will occur during Part D. Assessments obtained in Part D include yearly linear height, knee height, weight, physical exam, vital signs, radiographic assessments of the knee and hand/wrist, low-dose WBCT imaging excluding head, adverse events, and concomitant medications. Participation in Part D will continue as long as subjects remain skeletally immature. The up to 2-year period would begin the last day the subject stopped receiving study drug in Part A/B/C. The total duration of participation in Part C and Part D, is a maximum of 4 years. Secondary objective added for Part D to monitor off treatment longer-term safety in skeletally immature subjects off treatment. Safety will be summarized for Part D.	To implement safety measures based on DMC recommendations given the serious identified risk of premature physeal closure. Part D is being implemented to ensure that assessments of safety are offered for up to 2 years to subjects who were skeletally immature at the time they stopped taking study drug for any reason before completion of Part A/B/C. A 2-year follow up is an adequate timeframe to assess growth and physeal changes off palovarotene treatment. Preliminary data suggest that the risk of premature epiphyseal fusion is higher in subjects with open epiphyseal growth plates who have received the flare-up dosing regimen. A 2-year follow up is an adequate timeframe to assess growth and epiphyseal changes off palovarotene treatment. To allow for provision of study medication until commercial availability.
Protocol Synopsis Section 3.1 Overview of Study Design Section 3.2 Study Rationale Section 5.1 Study Population (Adult and Pediatric Cohorts – Part B) Section 7.7 Temporary Measures (Procedures Related to COVID-19 Pandemic)	As of 04Dec2019 all subjects < 14 years of age were required to interrupt study drug due to a partial clinical hold placed on the palovarotene clinical development program by the US FDA. Treatment will subsequently not be restarted in children <14 years of age.	As a consequence of FDA Partial Clinical Hold subjects remained off treatment for a prolonged period of time. As such a significant gap in dosing occurred which would render any further data to inform additional benefit/risk uninterpretable in this patient population. Part D was added to ensure continued collection of safety data off treatment.

Protocol Synopsis Tables 1 and 2 Sections 2.3 and 4.2 Secondary Endpoints Section 3.1 Overview of Study Design Section 7 Study Procedures & Assessments Section 7.2.2 Physical Examination Section 7.2.3 Body Weight and Linear Growth Section 7.2.4 Vital Signs Section 7.2.5 Electrocardiogram Section 7.2.6 Clinical Laboratory Test Section 7.3.1 Columbia-Suicide Severity Rating Scale Section 7.3.2 Knee and Hand/Wrist Radiographs Section 7.4 Efficacy Assessments Section 7.4.1 Low-dose Whole Body Computed Tomography Section 7.4.2 FOP-Physical Function Questionnaire Section 7.4.3 PROMIS Global Health Scale Section 7.4.4 Cumulative Analogue Joint Involvement Scale	In Part C, subjects may continue on the study for up to an additional 12 months.	To allow for provision of study medication until commercial availability.
Section 7.3.3 Bone Safety Management Plan	Added assessments for spinal health carried out on low dose WBCT scans collected in the study.	Emerging data from PVO-2A-201 trial in the multiple osteochondroma indication has suggested a potential effect of PVO on bone mineral accrual. As such, assessments were added to further characterize this risk in subjects with FOP.
Section 7.1 Screening, Recruitment, and Informed Consent Section 7.7 Temporary Measures (Procedures Related to the COVID Pandemic)	Integrated protocol amendment 7 addendum previously created to describe temporary measures applied during the COVID pandemic. Additional update to these temporary measures to clarify that radiographic assessments are required for subjects ≥14 years (who were skeletally immature at their last assessment) as part of the minimal safety procedures	To integrate protocol amendment 7 for addendum. To assess skeletal maturity in subjects ≥14 years re-initiating treatment in order to ensure appropriate safety follow up as well as determine if weight-based dosing is required.

	prior to re-initiation of palovarotene.	
Changes that did not affect the clinical conduct of the study:		
Table 3	Removed ECG row that was included in error; correcting table and footnotes.	Integration of administrative change from protocol amendment 7 addendum.
Section 7.6	Added DMC language.	Clarifying DMC oversight
Section 9.1.10 Follow up of Adverse Events and Serious Adverse Events	Collection of SAE reports, including deaths, will continue until 30 days past end of study.	Clarification of end date of collection of SAE, including death reports.
General	Corrected minor errors and formatting irregularities.	To provide a consistent presentation.

GROUPS RESPONSIBLE FOR STUDY CONTACT

Task	Vendor or Responsible Group
Trial Oversight and Management **Medical Writing**	Clementia Pharmaceuticals Inc. 1000, De La Gauchetière, Suite 1200 Montreal, Quebec, Canada H3B 4W5 Tel: 1.514.940.3600 Fax: 1.888.966.0135
Data Management **Clinical Monitoring** **Biostatistics** **Statistical Programming** **Electronic Data Capture System**	Medpace, Inc. 5375 Medpace Way Cincinnati, Ohio 45227 USA Tel: 1.800.730.5779 Fax: 1.513.579.0444
Medical Monitoring	PI , MD Medical Monitor Medpace PI PI Tel: PI ext. PI Fax: PI Email: PI
Central Laboratory	Medpace Reference Laboratories LLC 5365 Medpace Way Cincinnati, Ohio 45227 USA Tel: 1.800.749.1737 Fax: 1.800.705.2177
Central Electrocardiogram Laboratory	Medpace Cardiovascular Core Laboratory 5365 Medpace Way Cincinnati, Ohio 45227 USA Tel: 1.513.366.3234 or 1.513.579.9911 ext. 2126 Fax: 1.513.366.3237
Imaging Core Laboratory	PAREXEL Informatics 195 West Street Waltham, MA 02451 Tel: 1.866.289.4464 Fax: 1.781.768.5512

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Title	A Phase 2, Open-Label Extension, Efficacy and Safety Study of a RARγ-Specific Agonist (Palovarotene) in the Treatment of Preosseous Flare-ups in Subjects with Fibrodysplasia Ossificans Progressiva (FOP).
Sponsor	Clementia Pharmaceuticals Inc.
Objectives	Primary Objective • To evaluate the safety and efficacy of different palovarotene dosing regimens in subjects with FOP. Efficacy will be based on the ability of palovarotene to prevent the formation of new heterotopic ossification (HO) as assessed by low-dose whole body computed tomography (WBCT) scan, excluding head. Secondary Objectives • To evaluate the effect of palovarotene on range of motion (ROM) as assessed by the Cumulative Analogue Joint Involvement Scale (CAJIS) for FOP. • To evaluate the effect of palovarotene on physical function using age-appropriate forms of the FOP-Physical Function Questionnaire (PFQ). • To evaluate the effect of palovarotene on physical and mental health using age-appropriate forms of the Patient Reported Outcomes Measurement Information System (PROMIS) Global Health Scale. • To evaluate the pharmacokinetics of palovarotene. Secondary Objective (Part D) • To implement safety measures based on DMC recommendations in order to ensure that assessments of safety continue for up to 2 years post last dose of study treatment for skeletally immature subjects.
Study Design	A Phase 2, multicenter, open-label study that will explore different dosing regimens of palovarotene in adult and pediatric subjects with FOP. **Part A** includes all data obtained prior to Amendment 3 (dated 10 March 2016) during which pediatric and adult subjects successfully completing Study PVO-1A-201 were enrolled and followed for up to 36 months. Any subject experiencing an eligible flare-up under Part A received treatment with open-label palovarotene at a dose of 10 mg once daily for 14 days followed by 5 mg once daily for 28 days (or weight-based equivalent) and underwent all study procedures as specified in the original protocol, Amendment 1, and Amendment 2. **Part B** includes all data obtained under Amendment 3 (dated 10 March 2016) during which subjects successfully completing Study PVO-1A-201 (including any subject who participated in Part A of Study PVO-1A-202) as well as up to 20 new adult subjects were followed for up to 24 months. **Part C** includes all data obtained under Amendment 4 (dated 01 September 2017) and subsequent amendments during which subjects who participated in Part B will be followed for up to an additional 48 months. There will be no new subjects in Part C. Part C plus Part D total duration will not exceed 48 months. **Part D** annual post last dose of study treatment assessments for up to 2 years will be obtained in subjects who were skeletally immature at the time of study treatment discontinuation in order to obtain longer-term safety data. No new subjects will be enrolled into Part D. Subjects will follow assessments as outlined in Table 4 for as long as they are not 100% skeletally mature. Part C plus Part D total duration will not exceed 48 months. **Non-Flare-up-based Treatment**

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All subjects will receive non-flare-up-based treatment of 5 mg palovarotene once daily (weight-adjusted doses for skeletally immature subjects). Note: all weight-based dosing, both chronic and flare-up, will cease when subjects achieve ≥90% skeletal maturity based on hand/wrist radiography, but radiographic assessment of the growth plate (performed every 6 months) will continue until these subjects achieve 100% skeletal maturity defined as growth plate closure at both knee and hand/wrist locations. Additional radiographic assessments will be performed every 3 months in those subjects who (1) received the flare-up dosing regimen in the period of time since their last radiographic assessment; and (2) had not achieved 100% skeletal maturity on their last radiographic assessment.

Subjects will follow all assessments as outlined in Table 1 and Table 2. Subjects who cannot receive non-flare-up-based treatment will only undergo annual assessments (clinical laboratory tests will not be performed). In the event of a flare-up or traumatic event, these subjects will receive flare-up-based treatment and undergo all flare-up-based assessments, including clinical laboratory tests and radiographs if they have not reached 100% skeletal maturity.

Subjects from Part B Continuing Non-Flare-up-based Treatment into Part C

Subjects who began non-flare-up-based treatment during Part B will continue the same visit schedule into Part C (includes Protocol Amendment 4 and subsequent amendments), and will receive non-flare-up-based treatment for up to an additional 48 months. Therefore, these subjects may undergo non-flare-up-based treatment for up to 72 months over the entire study.

Subjects continuing into Part C will follow all procedures and undergo all assessments as specified in the Schedule of Assessments in Table 1. Site visits will occur at Months 12, 24, 36, 48, 60 and 72. Non-flare-up Day 1 is the first day that non-flare-up-based treatment was initiated during Part B, and total duration of treatment will continue into Part C.

Remote visits (eg, at home or at a local medical facility; and via telephone contact from clinical site personnel) will occur every 3 months unless the Investigator deems that a site visit is necessary; urine pregnancy tests will be performed each month for females of childbearing potential (FOCBP).

Subjects from Part B Starting Non-Flare-up-based Treatment During Part C

Subjects who will start non-flare-up-based treatment during Part C will receive non-flare-up-based treatment for up to 48 months. These subjects will follow all procedures and undergo all assessments as specified in the Schedule of Assessments in Table 2. Site visits will occur at Part C Screening and/or Non-flare-up Day 1, and at Months 6, 12, 24, 36 and 48. Non-flare-up Day 1 is the first day that non-flare-up-based treatment is initiated during Part C for these subjects.

Remote visits (eg, at home or at a local medical facility; and via telephone contact from clinical site personnel) will occur every 3 months unless the Investigator deems that a site visit is necessary; urine pregnancy tests will be performed each month for FOCBP.

Flare-up-based Treatment

Subjects will report potential flare-up symptoms to site personnel; such symptoms include, but are not limited to, pain, swelling, redness, decreased range of motion, stiffness, and warmth. Only one symptom is required to define a flare-up. If these symptoms are consistent with previous flare-ups, include a subject-reported onset date, and are confirmed by the Investigator as associated with a flare-up, subjects will immediately receive open-label palovarotene treatment as follows:

- 20 mg for 4 weeks (28 days) once daily. The first dose will be taken upon flare-up confirmation by the Investigator. To be followed by:

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- 10 mg for 8 weeks (56 days) once daily, for a total flare-up treatment duration of 12 weeks (84 days); 10 mg treatment may be extended if the flare-up is ongoing and continue until the flare-up resolves. Dosing will be extended in 4-week intervals and be based on clinical signs and symptoms as assessed by the Investigator.

Flare-up dosing will be weight-adjusted in subjects under the age of 18 years with less than 90% skeletal maturity on hand/wrist radiography at Screening. Note: all weight-based flare-up dosing will cease when subjects achieve ≥90% skeletal maturity based on hand/wrist radiography, but radiographic assessment of the growth plate will continue until these subjects achieve 100% skeletal maturity (defined as growth plate closure) at both knee and hand/wrist locations.

Flare-up-based dosing should also be initiated if the Investigator confirms the presence of a substantial high-risk traumatic event likely to lead to a flare-up.

Should a subject experience an intercurrent flare-up, or other substantial traumatic event likely to lead to a flare-up, at any time during flare-up-based treatment, the 12- week dosing regimen will restart upon new intercurrent flare-up or traumatic event confirmation by the Investigator (ie, 4 weeks of 20 mg palovarotene followed by 8 weeks of 10 mg palovarotene [or weight-based equivalent]). A Flare-up Cycle will include the first flare-up or traumatic event and any subsequent intercurrent flare-ups or traumatic events during the same dosing period. Flare-Up Cycle Safety Day 1 is defined as the first day that study drug is administered for the first flare-up or traumatic event during that cycle. Safety assessments will be performed at Flare-up Cycle Safety Day 1 and then every 12 weeks thereafter until treatment of the last flare-up or traumatic event in the cycle is completed. If any flare-up in a cycle has not resolved after 12 weeks, treatment and safety assessments will be extended and 10 mg palovarotene (or the weight-based equivalent) will be administered in 4-week intervals until all the flare-ups or traumatic events resolve and flare-up-based treatment has been completed. It is possible that subjects may experience more than one Flare-up Cycle during the study.

Subjects receiving flare-up-based treatment will follow all procedures and undergo all assessments as specified in the Schedule of Assessments in Table 3. All assessments will occur remotely, unless the Investigator deems it necessary to evaluate subjects at the clinical site.

Once all flare-ups in a cycle have resolved and flare-up-based treatment has been completed, subjects will resume non-flare-up-based treatment with 5 mg palovarotene once daily (weight-adjusted doses for skeletally immature subjects).

The pharmacokinetics (PK) of palovarotene dosing will be assessed at the first 3-month safety assessment during non-flare-up-based treatment; if samples cannot be or were not obtained during the first 3-month safety assessment, or if subjects are on flare-up-based treatment, then PK blood samples for non-flare-up treatment can be obtained during any subsequent 3-month safety visit.

Pharmacokinetics will also be assessed twice during flare-up-based treatment: once during the 20-mg regimen at any time between Study Days 4 to 28, and once during the 10-mg regimen at any time between Study Days 32 to 84, for the first treated flare-up only. If this is not possible for the first treated flare-up, PK blood samples can be obtained during any subsequent flare-up dosing cycle. Pharmacokinetic blood samples will be collected at pre-dose and 3, 6, 10, and 24 hours post-dose. Subjects who underwent a PK assessment for flare-up-based treatment under PVO-1A-202 Protocol Amendment 3 will not have flare-up PK assessed again. However, these subjects will require a non-flare-up treatment PK assessed at a 3-month safety visit

As of 04 December 2019 all subjects < 14 years of age were required to interrupt study drug due to a partial clinical hold placed on the palovarotene clinical development

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	program by the US FDA. Treatment will subsequently not be restarted in children <14 years of age. Off Treatment Part D: No study drug will be administered in Part D. For skeletally immature subjects in Part D, added Year 1 (Y1) and Year 2 (Y2) post last dose of study treatment assessments that include linear height, knee height, weight, physical exam, vital signs, radiographic assessments of the knee and hand/wrist, low-dose WBCT imaging, adverse events, and concomitant medications. Once subjects reach skeletal maturity their participation in Part D will end. The total duration of participation in Part C and Part D combined is a maximum of 4 years (±1 month).
Number of Subjects	A total of approximately 60 subjects will be enrolled: • Up to 40 subjects enrolled from Study PVO-1A-201. • Up to 20 new adult subjects enrolled during Part B.
Total Number of Sites	A total of approximately eight international investigational sites
Study Population (Adult and Pediatric Cohorts – Part B)	Inclusion Criteria 1. Completion of Study PVO-1A-201 (through Study Day 84); or Adult Cohort subjects not enrolled in Study PVO-1A-201, have the confirmed R206H genetic mutation consistent with FOP, have had at least two acute symptomatic flare-ups in the past 2 years but no flare-up symptoms within the past 4 weeks, including at the time of enrollment, have a CAJIS score of 6 to 16, inclusive, and must be able to receive non-flare-up-based dosing. 2. For the Adult Cohort, subjects under the age of 18 must have knee and hand/wrist radiographs confirming ≥ 90% skeletal maturity. 3. Written, signed, and dated subject/parent informed consent; and, for subjects who are minors, age-appropriate assent (this must be performed according to local regulations). Exclusion Criteria 1. Simultaneous participation in another clinical research study (except for Studies PVO-1A-201, PVO-1A-203, or PVO-1A-001) within 4 weeks prior to Part B Screening. 2. Any reason that, in the opinion of the Investigator, would lead to the inability of the subject and/or family to comply with the protocol.
Study Population for Non-Flare-up-based Treatment **(Adult Cohort – Part B)**	Inclusion Criteria 1. Females of child-bearing potential (FOCBP) must have a negative blood or urine pregnancy test (with sensitivity of at least 50 mIU/mL) prior to administration of palovarotene. Male and FOCBP subjects must agree to remain abstinent during treatment and for 1 month after treatment or, if sexually active, to use two highly effective methods of birth control during and for 1 month after treatment. Additionally, sexually active FOCBP subjects must already be using two highly effective methods of birth control 1 month before treatment is to start. Specific risks of the use of retinoids during pregnancy, and the agreement to remain abstinent or use two highly effective methods of birth control will be clearly defined in the informed consent and the subject or legally authorized representatives (eg, parents, caregivers, or legal guardians) must specifically sign this section. 2. Subjects must be accessible for treatment with palovarotene and follow-up. Subjects living at distant locations from the investigational site must be able and willing to travel to a site for the initial and all on-site follow-up visits.

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	Exclusion Criteria 1. Weight <20 kg. 2. Intercurrent known or suspected non-healed fracture at any location. 3. Currently using vitamin A or beta carotene, multivitamins containing vitamin A or beta carotene, or herbal preparations, fish oil, and unable or unwilling to discontinue use of these products during palovarotene treatment. 4. Exposure to synthetic oral retinoids other than palovarotene in the past 30 days prior to Part B Screening (signature of the informed consent). 5. Concurrent treatment with tetracycline or any tetracycline derivatives due to the potential increased risk of pseudotumor cerebri 6. History of allergy or hypersensitivity to retinoids or lactose. 7. Concomitant medications that are inhibitors or inducers of cytochrome P450 (CYP450) 3A4 activity (see Section 5.6). 8. Amylase or lipase >2x above the upper limit of normal (ULN) or with a history of chronic pancreatitis. 9. Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5x ULN. 10. Fasting triglycerides >400 mg/dL with or without therapy. 11. Female subjects who are breastfeeding. 12. Subjects with uncontrolled cardiovascular, hepatic, pulmonary, gastrointestinal, endocrine, metabolic, ophthalmologic, immunologic, psychiatric, or other significant disease. 13. Subjects experiencing suicidal ideation (type 4 or 5) or any suicidal behavior within the past month as defined by the C-SSRS.
Study Population for Flare-up-based Treatment **(Adult and Pediatric Cohorts – Part B)**	Inclusion Criteria 1. Symptomatic onset of a flare-up within 7 days before the first dose of study drug and defined by the presence of at least two of the following symptoms: pain, soft tissue swelling, decreased ROM, stiffness, redness, and warmth. Symptoms must be reported by the subject, be consistent with their previous flare-ups, and include a subject-reported onset date, and flare-up must be confirmed by the Investigator. 2. Flare-up is at an appendicular area (upper or lower extremity), abdomen, chest, neck, or lower back; and subject has received, is receiving, or is willing to receive treatment per standard of care, which may or may not include prednisone (2 mg/kg PO to a maximum dose of 100 mg daily) for 4 days. 3. Females of child-bearing potential (FOCBP) must have a negative blood or urine pregnancy test (with sensitivity of at least 50 mIU/mL) prior to administration of palovarotene. Male and FOCBP subjects must agree to remain abstinent during treatment and for 1 month after treatment or, if sexually active, to use two highly effective methods of birth control during and for 1 month after treatment. Additionally, sexually active FOCBP subjects must already be using two highly effective methods of birth control 1 month before treatment is to start. Specific risks of the use of retinoids during pregnancy, and the agreement to remain abstinent or use two highly effective methods of birth control will be clearly defined in the informed consent and the subject or legally authorized representatives (eg, parents, caregivers, or legal guardians) must specifically sign this section. 4. Subjects must be accessible for treatment with palovarotene and follow-up. Subjects living at distant locations from the investigational site must be able and willing to travel to a site for the initial and all on-site follow-up visits. Exclusion Criteria 1. Weight <20 kg.

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	2. Intercurrent known or suspected non-healed fracture at any location. 3. Complete immobilization of joint at site of flare-up. 4. Inability of the subject to undergo imaging assessments using plain radiographs. 5. Currently using vitamin A or beta carotene, multivitamins containing vitamin A or beta carotene, or herbal preparations, fish oil, and unable or unwilling to discontinue use of these products during palovarotene treatment. 6. Exposure to synthetic oral retinoids other than palovarotene in the past 30 days prior to Flare-up Screening (signature of the informed consent). 7. Concurrent treatment with tetracycline or any tetracycline derivatives due to the potential increased risk of pseudotumor cerebri. 8. History of allergy or hypersensitivity to retinoids or lactose. 9. Concomitant medications that are inhibitors or inducers of CYP450 3A4 activity (see Section 5.6.1). 10. Any subject with clinically significant elevations in amylase, lipase, AST, ALT, or fasting triglycerides during the most recent clinical laboratory assessment will require re-test prior to immediate flare-up-based dosing with palovarotene per the Investigator. If upon re-test, the laboratory value in question remains clinically significant abnormal, then the subject will not receive flare-up-based treatment for this flare-up. 11. Female subjects who are breastfeeding. 12. Subjects with uncontrolled cardiovascular, hepatic, pulmonary, gastrointestinal, endocrine, metabolic, ophthalmologic, immunologic, psychiatric, or other significant disease. 13. Subjects experiencing suicidal ideation (type 4 or 5) or any suicidal behavior within the past month as defined by the C-SSRS. 14. Any reason that, in the opinion of the Investigator, would lead to the inability of the subject and/or family to comply with the protocol.
Study Population (All Subjects – Part C)	Inclusion Criteria 1. Prior participation in Part B of the current study (PVO-1A-202). 2. Written, signed, and dated subject/parent informed consent; and, for subjects who are minors, age-appropriate assent (this must be performed according to local regulations). 3. Females of child-bearing potential must have a negative blood or urine pregnancy test (with sensitivity of at least 50 mIU/mL) prior to administration of palovarotene. Male and FOCBP subjects must agree to remain abstinent from heterosexual sex during treatment and for 1 month after treatment or, if sexually active, to use two effective methods of birth control during and for 1 month after treatment. Additionally, sexually active FOCBP subjects must already be using two effective methods of birth control 1 month before treatment is to start. Specific risks of the use of retinoids during pregnancy, and the agreement to remain abstinent or use two effective methods of birth control will be clearly defined in the informed consent and the subject or legally authorized representatives (eg, parents, caregivers, or legal guardians) must specifically sign this section. Exclusion Criteria 1. Any reason that, in the opinion of the Investigator, would lead to the inability of the subject and/or family to comply with the protocol. 2. Currently using vitamin A or beta carotene, multivitamins containing vitamin A or beta carotene, herbal preparations containing vitamin A or beta carotene, or fish oil, and unable or unwilling to discontinue use of these products during palovarotene treatment.

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Study Population of Subjects Starting Non-Flare-up-based Treatment During Part C

Inclusion Criteria

1. Subjects must be accessible for treatment with palovarotene and follow-up. Subjects living at distant locations from the investigational site must be able and willing to travel to a site for the initial and all on-site follow-up visits.
2. Subjects must be able to undergo low-dose WBCT scan, excluding head.

Exclusion Criteria

1. Amylase or lipase >2x above the upper limit of normal (ULN) or with a history of chronic pancreatitis.
2. Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5x ULN.
3. Fasting triglycerides >400 mg/dL with or without therapy.
4. Subjects experiencing suicidal ideation (type 4 or 5) or any suicidal behavior within the past month as defined by the Columbia Suicide Severity Rating Scale (C-SSRS).

Investigational Product

Palovarotene supplied as powder-filled hard gelatin capsules. The capsules may be swallowed whole or opened and the contents added onto specific food: apple sauce, pudding, or yogurt.

Dose/Route/Regimen for Non-Flare-up-based Treatment

Palovarotene: 5 mg daily or weight-based equivalent for skeletally immature subjects (<90%, upon entry into the study) / taken orally with food / at approximately the same time each day. For 5 mg palovarotene, weight equivalent doses for 20 to <40 kg, 40 to <60 kg, and ≥60 kg will be 3 mg, 4 mg, and 5 mg, respectively.

Dose/Route/Regimen for Flare-up-based Treatment

Palovarotene initiated at the start of a flare-up: 20 mg for 4 weeks (28 days) once daily, 10 mg for 8 weeks (56 days) once daily for a total of 12 weeks (84 days) (may be extended in 4-week intervals if flare-up is ongoing and continue until flare-up resolves) / weight-adjusted for skeletally immature subjects (<90%) / taken orally with food / at approximately the same time each day.

The weight-adjusted palovarotene doses and dose de-escalation for flare-up and non-flare-up-based dosing are:

Weight Range Category	20-mg Equiv-alent	15-mg Equiv-alent*	10-mg Equiv-alent	7.5-mg Equiv-alent*	5-mg Equiv-alent*	2.5-mg Equiv-alent*
20 to <40 kg	12.5 mg	10 mg	6 mg	4 mg	3 mg	1.5 mg
40 to <60 kg	15 mg	12.5 mg	7.5 mg	5 mg	4 mg	2 mg
≥60 kg	20 mg	15 mg	10 mg	7.5 mg	5 mg	2.5 mg

* In the event of dose de-escalation from 20-mg, 10-mg, or 5-mg equivalent, respectively.

Comparator Product Dose/Route/Regimen

Not Applicable – this is an open-label extension study.

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Assessments of Efficacy	Primary Efficacy Endpoint 1. Annualized change in new HO volume as assessed by low-dose WBCT scan, excluding head. The annualized change from Parts B and C will be compared to data collected from the NHS. Secondary Endpoints (Note: baseline is Non-flare-up Day 1.) Some subjects may be assessed for up to 72 months. 1. Percent of subjects with new HO at Months 12, 24, 36, 48, 60, 72 and overall. 2. Change from baseline in ROM as assessed by CAJIS at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72. 3. Change from baseline in physical function using age appropriate forms of the FOP-PFQ at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72. 4. Change from baseline in physical and mental function for subjects ≥15 years old and mental function for subjects <15 years old using age appropriate forms of the PROMIS Global Health Scale at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72.
Assessments of Safety	Safety evaluations will include AE and serious AE (SAE) reporting, electrocardiograms (for subjects receiving treatment), vital signs (temperature, respiratory rate, blood pressure, and heart rate), physical examination, body weight and height, laboratory parameters (hematology, biochemistry, and urinalysis), urine pregnancy tests for FOCBP, and concomitant medication reporting. Concomitant medications will include treatment per standard of care, which may or may not include corticosteroids (eg, prednisone at 2 mg/kg PO to a maximum dose of 100 mg daily) for 4 days. Evaluation of subjects under the age of 18 years with open epiphyses at the last assessment will include knee (anterior/posterior [AP] view) and hand/wrist (posterior/anterior [PA] view) radiographs for assessment of epiphyseal growth plate; and standardized stadiometry and knee height for assessments of linear growth (in triplicate). If there is evidence of premature growth plate closure (with or without linear growth deceleration) the Investigator may require that study drug be continued, interrupted, de-escalated, or discontinued. Dose modification decisions will be made by the Investigator upon review of the subject's clinical and radiographic information, and following discussion of the risk/benefit with the subject/parent. The Investigator may consult with the sponsor and the DMC. In addition, bilateral hand/wrist and knee growth plate morphology will be assessed by WBCT scan safety reads. Bilateral hip growth plate morphology will also be assessed for avascular necrosis (AVN) in all subjects. Limb/joint AEs in these subjects will be evaluated by clinical and radiographic assessments as deemed appropriate by the Investigator. Adverse event severity will be assessed and reported according to criteria defined in the protocol (mild, moderate, severe). Adverse events known to be associated with retinoids (eg, mucocutaneous events) will be further graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03, 14 June 2010. Subjects 8 years of age and older will be assessed for suicidal ideation and behavior every 3 months using the age-appropriate C-SSRS and at all visits during a Flare-up Cycle. The Data Monitoring Committee (DMC) will assess the safety of the subjects during the course of the study. The DMC can recommend temporary or permanent stopping of the study at any time if there are significant safety concerns. The DMC can also make recommendations for potential dose modifications for individual subjects in the event of

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	treatment-related adverse bone effects. The DMC Charter includes recommended safety stopping rules (see Section 7.6).
Statistical Analysis Part C	The primary efficacy endpoint for Part C is the annualized change in new HO volume (as assessed by low-dose WBCT scan, excluding head). The annualized change in Part C will be compared to data collected from a natural history study using a weighted linear mixed effects model with baseline HO volume divided by age as the only covariate and weights used to account for the different lengths of observed subject follow-up. A subject-specific random effect will be included to account for within-subject correlation.

Table 1. Schedule of Assessments During Non-Flare-up-based Treatment (Subjects from Part B Continuing Non-Flare-up-based Treatment into Part C)

Assessment/Procedure	Part C Consent/Assent[1] Remote Visit	Every Month Remote Visit[1,2] (±1 week)	Every 3 Months Remote Visit[1,2,3] (±2 weeks)	Months 6, 18, 30, 42, 54, 66 Remote Visit[1,2,4] (±1 month)	Months 12, 24, 36, 48, 60, 72/EOT/EOS[1,4,5] Site Visit (±1 month)
Informed consent/assent[1]	X				
Inclusion/ exclusion	X				
Knee and hand/wrist radiographs[6]			X[7]	X	X
Linear growth assessment (stadiometry, knee height; subjects <18 years of age)[6]				X	X
Physical examination					X
Body weight			X	X	X
Electrocardiogram					X
Study drug dispensing	As needed from Non-flare-up Day 1 through Month 72				
Study drug treatment	Continuous from Non-flare-up Day 1 through Month 72[8]				
Dispense/review subject diary	Dispense diary as needed and review at every subject contact				
Vital signs			X	X	X
C-SSRS (age-appropriate)			X	X	X
Reassess for child bearing status (females only) and pregnancy prevention measures (females and males)			X	X	X
Hematology[9]				X	X
Biochemistry (includes lipids, serum pregnancy test)[9]				X	X
Urinalysis[10]				X	X
Pregnancy test[11]		X			
FOP-PFQ[12]				X	X
PROMIS Global Health Scale[12]				X	X
CAJIS				X[13]	X
Low-dose WBCT scan, excluding head[14]					X
Prior/concomitant medications	At every subject contact				
Adverse events	At every subject contact				
Pharmacokinetic blood sample[15]			Month 3 or later[15]		
Telephone contact[3]			X		

1 Consent may be obtained remotely via email or faxed. Visits can be combined with flare-up visits when appropriate. Subjects who began non-flare-up-based treatment during Part B will continue the same visit schedule into Part C (includes Protocol Amendment 4 and subsequent amendments).

2 Remote visits, except for knee and hand/wrist radiographs, will be performed at the subject's home by qualified study personnel, at a local medical facility, or via video-conferencing or telephone contact, unless the Investigator deems that a site visit is necessary. Remote visits that occur every 3 months should align with the remote visits at Months 6, 18, 30, 42, 54 and 66. Monthly remote visits will only be conducted for FOCBP subjects.

3 At the time of a remote visit, subjects will be contacted by telephone every 3 months from the time of informed consent until study completion to assess AEs and concomitant medications. Every effort should be made to conduct the telephone contact on the same day as the remote visit completed every 3 months. However, the visit window of ±2 weeks will allow for flexibility in scheduling if needed.

[4] Non-flare-up Day 1 is the first day that non-flare-up-based treatment was initiated during Part B, and total duration of treatment will continue into Part C. Subjects who began non-flare-up-based treatment during Part B will continue the same visit schedule into Part C, and will receive non-flare-up-based treatment for up to an additional 48 months. Therefore, these subjects may undergo non-flare-up-based treatment for up to 72 months over the entire study. Subjects who decide to stop treatment more than 1 month after an annual visit but who remain in the study will undergo all assessments included in an annual visit as part of their EOT assessments. If the next annual visit is in less than 6 months, the EOT will serve as their EOS assessments and will conclude their participation in the study if subjects decide not to participate in Part D. If the next annual visit is in more than 6 months, these subjects will be assessed again at the next annual visit and undergo all assessments included in an annual visit. This will serve as their EOS assessment and will conclude their participation in the study if subjects decide not to participate in Part D. If the Part C EOS visit (at completion of the trial) is > 6 months from the last annual visit, this visit will serve as the EOT/EOS site visit, will include all annual assessments and will end their participation in the study.

[5] Adult subjects who cannot receive non-flare-up-based treatment will only undergo annual assessments (clinical laboratory tests will not be performed).

[6] Subjects with open epiphyseal growth plates at the most recent assessment will be evaluated at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72. As the linear growth assessments cannot be performed remotely, all assessments scheduled at these time points will be performed at the clinical site. Limb/joint AEs in these subjects will be evaluated by clinical and radiographic assessments deemed appropriate by the Investigator. Once a subject has achieved 100% skeletal maturity (confirmed by radiography as complete closure of the growth plate), knee and hand/wrist radiographs will no longer be required. If 100% skeletal maturity is not achieved at both locations, then only the location that is still maturing would need to be monitored. In addition, once a subject is 18 years old, linear growth assessments in triplicate and knee height will no longer be required.

[7] These additional knee and hand/wrist radiograph assessments will be performed every 3 months (±2 weeks) in those subjects who (1) received flare-up dosing in the period of time since their last assessment; and (2) had not achieved 100% skeletal maturity on their last assessment. Radiographic assessments required because of flare-up status at the time of a remote visit will instead be conducted at the clinical site unless the Investigator determines they can be performed at a local medical facility. All remote assessments will be performed at the clinical site if the radiographs cannot be performed locally.

[8] Continuous non-flare-up-based treatment unless flare-up-based treatment is initiated.

[9] Analysis of samples can be completed at a local, qualified laboratory. The investigative site should notify the study team if the local laboratory cannot test all the analytes listed in Table 5. If the total thyroxine (Total T4), free T4, uric acid, gamma glutamyl transferase, inorganic phosphorous, very low-density lipoprotein, or globulin parameters are not available through the local laboratory, and alternative arrangements cannot be made, testing of these analytes may be omitted provided other subject-assessments of thyroid function (ie, thyroid-stimulating hormone), lipid metabolism (ie, triglycerides, low-density lipoprotein, high-density lipoprotein, and total cholesterol), and protein metabolism (ie, total protein and albumin) are available and confirmed to be stable as per the Investigator. Alternative arrangements to test the listed analytes are to be made if the Investigator, Medical Monitor, or sponsor determines that they have the potential to impact subject safety. In the event the local laboratory is unable to test any other analytes, they may be omitted in exceptional circumstances after consultation with the sponsor. Such exceptions will not be applied to any of the key safety analytes (see Section 7.2.6).

[10] If urinalysis results are abnormal, then a microscopic evaluation will be completed.

[11] Pregnancy testing will be performed monthly for females of child-bearing potential. A urine pregnancy test will be performed only when a serum pregnancy test is not obtained.

[12] Age-appropriate versions of the FOP-PFQ and PROMIS Global Health Scale will be used.

[13] CAJIS assessment may be performed remotely or by videoconferencing.

[14] Baseline for low-dose WBCT scan, excluding head, was performed prior to the initiation of non-flare-up-based dosing during Part B.

[15] Blood samples for PK assessment of non-flare-up dosing will be collected at the first 3-month safety assessment at pre-dose and 3, 6, 10, and 24 hours post-dose; if samples cannot be or were not obtained at the 3-month safety assessment, or if a subject is on flare-up-based treatment, then the PK blood sample for non-flare-up-based treatment can be obtained during any subsequent 3-month safety visit.

AE = adverse event(s), CAJIS = Cumulative Analogue Joint Involvement Scale for FOP, C-SSRS = Columbia Suicide Severity Rating Scale, EOS = end of study, EOT = end of treatment, FOCBP = female of child-bearing potential, FOP-PFQ = Fibrodysplasia Ossificans Progressiva physical function questionnaire, PK = pharmacokinetic(s), PROMIS = Patient Reported Outcomes Measurement Information System, WBCT = whole body computed tomography.

Table 2. Schedule of Assessments During Non-Flare-up-based Treatment (Subjects Starting Non-Flare-up-based Treatment During Part C)

Assessment/Procedure	Part C Screening/ Non-Flare-up Day 1[1]/Site Visit (-1 month)	Every Month Remote Visit[1,2] (±1 week)	Every 3 Months Remote Visit[1,2,3] (±2 weeks)	Months 18, 30, 42 Remote Visit[1,2] (±1 month)	Months 6, 12, 24, 36, 48/EOT/EOS[1,4,5] Site Visit (±1 month)
Informed consent/assent[1]	X				
Inclusion/exclusion	X				
Knee and hand/wrist radiographs for assessment of epiphyseal growth plate[6]	X		X[7]	X	X
Linear and knee height growth assessments (<18 years of age)[6]	X			X	X
Physical examination	X				X
Body weight	X		X	X	X
Electrocardiogram	X				X
Study drug dispensing	As needed from Non-flare-up Day 1 through Month 48				
Study drug treatment	Continuous from Non-flare-up Day 1 through Month 48[8]				
Dispense/review subject diary	Dispense diary as needed and review at every subject contact				
Vital signs	X		X	X	X
C-SSRS (age-appropriate)	X		X	X	X
Reassess for child bearing status (females only) and pregnancy prevention measures (females and males)			X	X	X
Hematology[9]	X			X	X
Biochemistry (includes lipids, serum pregnancy test)[10]	X			X	X
Urinalysis[10]	X			X	X
Pregnancy test[11]		X			
FOP-PFQ[12]	X			X	X
PROMIS Global Health Scale[12]	X			X	X
CAJIS	X			X[13]	X
Low-dose WBCT scan, excluding head[14]	X				X[14]
Prior/concomitant medications	At every subject contact				
Adverse events	At every subject contact				
Pharmacokinetic blood sample[15]			Month 3 or later[15]		
Telephone contact[3]			X		

1 Consent may be obtained remotely via email or faxed. A visit will be scheduled as soon as possible after Protocol Amendment 5 is approved at the clinical site and non-flare-up-based treatment will be started during that visit (Non-flare-up Day 1). Part C includes Protocol Amendment 4 and subsequent amendments. Visits can be combined with flare-up visits when appropriate.

2 Remote visits, except for knee and hand/wrist radiographs, will be performed at the subject's home by qualified study personnel, at a local medical facility, or via video-conferencing or telephone contact unless the Investigator deems that a site visit is necessary. Remote visits that occur every 3 months should align with the remote visits at Months 18, 30 and 42. Monthly remote visits will only be conducted for FOCBP subjects.

3 At the time of a remote visit, subjects will be contacted by telephone every 3 months from the time of informed consent until study completion to assess AEs and concomitant medications. Every effort should be made to conduct the telephone contact on the same day as the remote visit completed every 3 months. However, the visit window of ±2 weeks will allow for flexibility in scheduling if needed.

[4] Subjects who decide to stop treatment more than 1 month after an annual visit but who remain in the study will undergo all assessments included in an annual visit as part of their EOT assessments. If the next annual visit is in less than 6 months, the EOT will serve as their EOS assessments and will conclude their participation in the study. If the next annual visit is in more than 6 months, these subjects will be assessed again at the next annual visit and undergo all assessments included in an annual visit. This will serve as their EOS assessment and will conclude their participation in the study. If the Part C EOS visit (at completion of the trial) is > 6 months from the last annual visit, this visit will serve as the EOT/EOS site visit, will include all annual assessments and will end their participation in the study.

[5] Adult subjects who cannot receive non-flare-up-based treatment will only undergo annual assessments (clinical laboratory tests will not be performed).

[6] Subjects with open epiphyseal growth plates at the most recent assessment will undergo knee (AP view) and hand/wrist (PA view) radiographs and measurements of linear and knee height (in triplicate) at Part C Screening and/or Non-flare-up Day 1. As the linear growth assessments cannot be performed remotely, all assessments scheduled at these time points will be performed at the clinical site. Subjects for whom radiographs were performed within the last 3 months will not need to repeat radiographs at Screening. Subjects with open epiphyseal growth plates at this assessment will also be evaluated at Months 6, 12, 18, 24, 30, 36, 42 and 48. Limb/joint AEs in these subjects will be evaluated by clinical and radiographic assessments deemed appropriate by the Investigator. Once a subject has achieved 100% skeletal maturity (confirmed by radiography), knee and hand/wrist radiographs will no longer be required. If 100% skeletal maturity is not achieved at both locations, then only the location that is still maturing would need to be monitored. In addition, once a subject is 18 years old, linear growth assessments in triplicate and knee height will no longer be required.

[7] These additional knee and hand/wrist radiograph assessments will be performed every 3 months (±2 weeks) in those subjects who (1) received flare-up dosing in the period of time since their last assessment; and (2) had not achieved 100% skeletal maturity on their last assessment. These radiographic assessments required because of flare-up status at the time of a remote visit will instead be conducted at the clinical site unless the Investigator determines they can be performed at a local medical facility. All remote assessments will be performed at the clinical site if the radiographs cannot be performed locally.

[8] Continuous non-flare-up-based treatment unless flare-up-based treatment is initiated.

[9] Analysis of samples can be completed at a local, qualified laboratory. The investigative site should notify the study team if the local laboratory cannot test all the analytes listed in Table 5. If the total thyroxine (Total T4), free T4, uric acid, gamma glutamyl transferase, inorganic phosphorous, very low-density lipoprotein, or globulin parameters are not available through the local laboratory, and alternative arrangements cannot be made, testing of these analytes may be omitted provided other subject-assessments of thyroid function (ie, thyroid-stimulating hormone), lipid metabolism (ie, triglycerides, low-density lipoprotein, high-density lipoprotein, and total cholesterol), and protein metabolism (ie, total protein and albumin) are available and confirmed to be stable as per the Investigator. Alternative arrangements to test the listed analytes are to be made if the Investigator, Medical Monitor, or sponsor determines that they have the potential to impact subject safety. In the event the local laboratory is unable to test any other analytes, they may be omitted in exceptional circumstances after consultation with the sponsor. Such exceptions will not be applied to any of the key safety analytes (see Section 7.2.6).

[10] If urinalysis results are abnormal, then a microscopic evaluation will be completed.

[11] Pregnancy testing will be performed monthly for females of child-bearing potential. A urine pregnancy test will be performed only when a serum pregnancy test is not obtained.

[12] Age-appropriate versions of the FOP-PFQ and PROMIS Global Health Scale will be used.

[13] CAJIS assessment may be performed remotely or by videoconferencing.

[14] Baseline for low-dose WBCT scan, excluding head, will be at Part C Screening (ie, when the subject provides informed consent/assent for Study PVO-1A-202 Part C). The low-dose WBCT scans, excluding head, will only be performed during annual visits (not at the 6-month visit).

[15] Blood samples for PK assessment of non-flare-up dosing will be collected at the first 3-month safety assessment at pre-dose and 3, 6, 10, and 24 hours post-dose; if samples cannot be or were not obtained at the 3-month safety assessment, or if a subject is on flare-up-based treatment, then the PK blood sample for non-flare-up-based treatment can be obtained during any subsequent 3-month safety visit.

AE = adverse event(s), AP = anterior/posterior, CAJIS = Cumulative Analogue Joint Involvement Scale for FOP, C-SSRS = Columbia Suicide Severity Rating Scale, EOS = end of study, EOT = end of treatment, FOP-PFQ = Fibrodysplasia Ossificans Progressiva physical function questionnaire, P/A = posterior/anterior, PK = pharmacokinetic, PROMIS = Patient Reported Outcomes Measurement Information System, WBCT = whole body computed tomography.

Table 3. Schedule of Assessments for Flare-up-based Treatment (Subjects with a Flare-Up)

Assessment/Procedure	Flare-Up Cycle Safety Day 1[3]	FLARE-UP CYCLE SAFETY ASSESSMENTS Remote Visits[1,2] (±5 days) Every 12 Weeks[3]
Vital signs and body weight	X	X
Hematology[4,5]	X	X
Biochemistry (includes lipids)[4,5]	X	X
Urinalysis[4,5,6]	X	X
C-SSRS (age appropriate)	X	X
Pregnancy testing[7]	X	Every 4 weeks
Study drug dispensing		As needed from Cycle Day 1 to end of treatment of last flare-up cycle[8,9]
Study drug treatment		Continuous from Cycle Day 1 to end of treatment of last flare-up cycle[3,8,9]
Dispense/review subject diary		Dispense diary as needed and review at every subject contact
Flare-up(s) status and end date confirmation[10]	X	At every subject contact
Prior/concomitant medications		At every subject contact
Adverse events		At every subject contact

Treatment/Assessment	FLARE-UP TREATMENT[8] AND PHARMACOKINETICS			
	Flare-Up Day 1[5,12,14]	High Dose Treatment	Low Dose Treatment	
Flare-up (first flare-up or restart for intercurrent flare-up)[10,11]	X	Week 1 to 4 (4 weeks)	Week 4 to 12 (8 weeks)	4-Week Extension (if applicable)
Pharmacokinetic blood sample		X[12]	X[12]	
Telephone contact[13]			End of Week 12	End of each 4-week extension

1 All visit windows are ±5 days, except the End of Flare-Up Cycle Safety Assessments of the first flare-up, which is -5 days because a blood draw is required for pharmacokinetic analysis.

2 Remote visits will be performed at the subject's home by qualified study personnel or at a local medical facility, unless the Investigator deems that a site visit is necessary. Remote visits during treatment extension, if applicable, will occur every 12 weeks until all the flare-ups within a cycle have resolved and treatment has been completed.

3 A Flare-up Cycle will include the first flare-up and any subsequent intercurrent flare-ups or traumatic events during the same dosing period. Flare-Up Cycle Safety Day 1 is defined as the first day that study drug is administered for the first flare-up or traumatic event upon confirmation by the Investigator. Flare-up cycle safety assessments will be performed on Flare-up Cycle Safety Day 1 and then every 12 weeks thereafter until treatment of the last flare-up or traumatic event within a Flare-up Cycle is completed. If treatment of the last flare-up or traumatic event in a cycle resolves within 4 weeks of the last flare-up cycle safety assessment, then another flare- up cycle safety visit does not need to be performed. Once all flare-ups in a cycle have resolved and flare-up-based treatment has been completed, subjects will resume non-flare-up-based treatment with 5 mg palovarotene once daily (weight-adjusted doses for skeletally immature subjects). It is possible that

subjects may experience more than one Flare-up Cycle during Part C of the study. Note that the Flare-up Cycle assessments will also be applicable to any treated high-risk traumatic event likely to lead to a flare-up.

[4] Flare-up-based treatment can begin immediately after the Investigator confirms the presence of a flare-up and prior to availability of safety laboratory results, unless the Investigator determines that the results are required prior to treatment initiation (eg, clinically significant abnormal laboratory test results requiring follow-up). Analysis of samples can be completed at a local, qualified laboratory. The investigative site should notify the study team if the local laboratory cannot test all the analytes listed in Table 5. If the total thyroxine (Total T4), free T4, uric acid, gamma glutamyl transferase, inorganic phosphorous, very low-density lipoprotein, or globulin parameters are not available through the local laboratory, and alternative arrangements cannot be made, testing of these analytes may be omitted provided other subject- assessments of thyroid function (ie, thyroid-stimulating hormone), lipid metabolism (ie, triglycerides, low-density lipoprotein, high-density lipoprotein, and total cholesterol), and protein metabolism (ie, total protein and albumin) are available and confirmed to be stable as per the Investigator. Alternative arrangements to test the listed analytes are to be made if the Investigator, Medical Monitor, or sponsor determines that they have the potential to impact subject safety. In the event the local laboratory is unable to test any other analytes, they may be omitted in exceptional circumstances after consultation with the sponsor. Such exceptions will not be applied to any of the key safety analytes (see Section 7.2.6).

[5] Subjects with normal or non-clinically significant abnormal safety laboratory results observed within 1 month of flare-up-based treatment will not need to have laboratory tests performed at Flare-up Cycle Safety Day 1. The Investigator will determine whether subjects with clinically significant abnormal laboratory results in the most recent assessment will need to be re-assessed prior to beginning flare-up-based treatment. The only exception is for pregnancy testing, which must be performed at the start of each Flare-up Cycle and every 4 weeks thereafter until the end of the cycle. However, if a pregnancy test was performed within 4 weeks prior to the start of treatment for a flare-up or traumatic event, treatment will not be delayed pending repeat pregnancy testing.

[6] If urinalysis results are abnormal, then a microscopic evaluation should be completed.

[7] Pregnancy testing will be performed for females of child-bearing potential. A urine pregnancy test will be performed only when a serum pregnancy test is not obtained.

[8] A flare-up, or substantial high-risk traumatic event likely to lead to a flare-up, will be treated with a minimum of 4 weeks (28 days) of 20 mg palovarotene once daily followed by 8 weeks (56 days) of 10 mg palovarotene once daily (or weight-based equivalent) for a total of 12 weeks (84 days). If the flare-up has not resolved after 12 weeks, treatment will be extended in 4-week intervals until the flare-up resolves.

[9] Should a subject experience an intercurrent flare-up, or other substantial high-risk traumatic event likely to lead to a flare-up, at any time during flare-up-based treatment, the 12-week (84 day) dosing regimen will restart upon confirmation by the Investigator (ie, 4 weeks of 20 mg palovarotene followed by 8 weeks of 10 mg palovarotene [or weight-based equivalent]). This may occur more than once during a Flare-up Cycle.

[10] At each contact, flare-up status will be assessed for every flare-up and flare-up end date will be recorded when a flare-up resolves. Flare-up status will also be assessed at Week 12 of the initial flare-up (if only one flare-up) or the last ongoing intercurrent flare-up (if more than one flare-up); if any flare-up is still ongoing, the on-going flare-up(s) will be assessed every 4 weeks until the last flare-up has resolved.

[11] Flare-up Day 1 is the first day of treatment for a flare-up/substantial high-risk traumatic event (upon confirmation by the Investigator).

[12] Pharmacokinetics of palovarotene dosing will be assessed twice: once during the 20-mg regimen at any time between Study Days 4 to 28, and once during the 10-mg regimen at any time during Study Days 32 to 84, for the first treated flare-up only. If not possible for the first treated flare-up, PK blood samples can be obtained during any subsequent flare-up dosing cycle. Blood samples will be collected at pre-dose and 3, 6, 10, and 24 hours post-dose. Subjects who underwent a PK assessment for flare-up-based treatment under PVO-1A-202 Protocol Amendment 3 will not have flare-up PK assessed again. However, these subjects will require a non-flare-up treatment PK assessed at a 3-month safety visit.

[13] Flare-up will be evaluated remotely, or by telephone or video-conferencing, unless the Investigator deems that a site visit is necessary. This will include subject-reported current flare-up location, symptoms, and probable causes.

Note: study procedures that require sedation will not be performed.

C-SSRS = Columbia Suicide Severity Rating Scale, PK = pharmacokinetic(s)

Table 4. Schedule of Assessments for Part D

Assessment/Procedure	Y1 and Y2 Post Treatment Site Visit[1]
Informed consent[2,3]	X
Knee and hand/wrist radiographs[4,5]	X
Linear and knee height growth assessments (<18 years of age)[4]	X
Physical examination	X
Body weight[2]	X
Vital signs[2]	X
Low-dose, WBCT scan (excluding head)	X
Prior/concomitant medications[2]	At every subject contact
Adverse events[2,6]	At every subject contact

[1] Year 1 (Y1) and Year 2 (Y2) visits following the last dose of study drug will be done within the total study duration from enrolment from Part A. Y1 to be completed in the window of ≥ 6 to < 18 months post last dose of study drug. If Part A, B or C EOS date is within the Y1 window then the EOS will serve as the Y1 visit.
If Part A, B or C EOS date is prior to Y1 window then Y1 should be scheduled ≥ 6 months from Part A, B or C EOS date but still within the Y1 window. Y2 to be completed ≥18 – 24 months post last dose of study drug. If Part A, B or C EOS date is within the Y2 window then the EOS will serve as the Y2 visit.
If Part A, B or C EOS date or Y1 date (if applicable) is prior to Y2 window then Y2 should be scheduled ≥ 6 months from the Part A, B or C EOS date or the Y1 date, whichever is later, but still within the Y2 window.
If subjects had their last dose of study medication and completed Part A, B or C EOS more than 2 years prior to their consent for Part D, then these subjects will only complete Y2 following their consent for Part D.

[2] Assessments may be performed remotely (eg, at the subject's home by qualified study personnel, at a local medical facility, or via videoconference or telephone contact from clinical site personnel) unless the Investigator deems that a site visit is necessary.

[3] Part D informed consent is required prior to conducting Part D assessments/procedures.

[4] Subjects found to be skeletally immature will continue knee and hand/wrist radiographs, and linear and knee height measurements (all in triplicate) at Year 1 (Y1) and Year 2 (Y2). Limb/joint AEs in these subjects will be evaluated by any clinical and radiographic assessments deemed appropriate by the Investigator. Once a subject has achieved 100% skeletal maturity (confirmed by radiography and defined by growth plate closures), knee and hand/wrist radiographs will no longer be required, and this will serve as their Part D study completion. In addition, once a subject is 18 years old, linear and knee height growth assessments will no longer be required. If 100% skeletal maturity is not achieved at both locations, then only the location that is still maturing would need to be monitored.

[5] Knee and hand/wrist radiograph assessments will be conducted at the clinical site unless the Investigator determines they can be performed at a local medical facility. All assessments will be performed at the clinical site if the radiographs cannot be performed locally.

[6] At each AE assessment, the Investigator must ask the subject about any joint-related complaints.

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Abbreviation	Definition
ACVR1/ALK2	activin receptor type IA/activin-like kinase 2
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AP	anterior/posterior view
AST	aspartate aminotransferase
AUC	area under the curve
AVN	avascular necrosis
BMP	bone morphogenetic protein
CAJIS	Cumulative Analogue Joint Involvement Scale for FOP
CI	confidence interval
C_{max}	maximum or peak measured plasma concentration
COPD	chronic obstructive pulmonary disease
COVID	Corona virus disease
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P
DDI	drug-drug interaction
DMC	Data Monitoring Committee
EAP	early access program
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	end of study
EOT	end of treatment
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FOCBP	female of child-bearing potential
FOP	Fibrodysplasia Ossificans Progressiva
FOP-PFQ	FOP-Physical Function Questionnaire
FOP-PFQ-P	Pediatric FOP-PFQ
GCP	Good Clinical Practices
GGT	gamma glutamyl transferase
HDL	high-density lipoprotein
HED	human equivalent dose
HO	heterotopic ossification
IC_{50}	concentration of drug producing 50% inhibition
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

IRB	Institutional Review Board
LC-MS/MS	Liquid chromatography–mass spectrometry
LDL	low-density lipoprotein
LME	linear mixed effects
LOQ	limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSC	mesenchymal stem cell
NHS	Natural History Study
OMIM	Online Mendelian Inheritance in Man
PA	posterior/anterior view
PAS	Pharmacokinetic Analysis Set
PCS	potentially clinically significant
PK	pharmacokinetic(s)
PO	per os
PPS	Per-Protocol Set
PROMIS	Patient Reported Outcomes Measurement Information System
RAR	retinoic acid receptor
RARγ	retinoic acid receptor gamma
ROM	range of motion
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SD	standard deviation
$t_{½}$	apparent terminal elimination half-life
T_{max}	time of maximum or peak measured plasma concentration at steady-state
ULN	upper limit of normal
US	United States
VLDL	very low-density lipoprotein
WBCT	whole body computed tomography
wLME	weighted linear mixed effects

1. INTRODUCTION

1.1 Background

1.1.1 Fibrodysplasia Ossificans Progressiva

Fibrodysplasia Ossificans Progressiva (FOP) (OMIM #135100) is a rare, severely disabling disease characterized by heterotopic ossification (HO) in muscles, tendons, and ligaments often associated with painful, recurrent episodes of soft tissue swelling (flare-ups). Lesions begin in early childhood and lead to progressive ankyloses of major joints with resultant loss of movement. Prognosis is poor and life expectancy is reduced. FOP is caused by an activating mutation in the bone morphogenetic protein (BMP) type I receptor, or activin receptor type IA (ACVR1), also known as activin-like-kinase 2 (ALK2) type I receptor. Most patients with FOP (approximately 97%) have the same point mutation, R206H. The International FOP Association, a US-based patient group organization, reports approximately 800 confirmed cases of FOP globally.[1] The prevalence is estimated at approximately 1.36 per million individuals, with no geographic, ethnic, racial, or gender preference.[2] FOP is misdiagnosed approximately 80% of the time resulting in great harm to patients.[3] The preosseous flare-ups that characterize the disease have been misinterpreted as lymphedema, soft tissue sarcoma, or juvenile fibromatosis, often resulting in harmful diagnostic biopsies that exacerbate the progression of the disease, and/or unnecessary chemotherapeutic interventions. Individuals with FOP appear normal at birth except for the pathognomonic malformation of the great toes, which are typically short (lack a phalange) and deviated in hallux valgus.[4]

Heterotopic ossification is episodic and cumulative throughout life, resulting in segments, sheets, and ribbons of extra bone developing throughout the body and across joints, progressively restricting movement. Rapidly growing bony spurs have been known to protrude through the skin causing pain and a risk of infections.[5] Only the tongue, heart, and diaphragm muscle are spared for reasons that have yet to be elucidated. Asymmetric HO in the rib cage and subsequent contralateral growth can lead to a rapid progression in spinal deformity and cause respiratory insufficiency. Ankyloses of the temporomandibular joints results in severe tooth decay and malnutrition. Periods of flare-up activity are interspersed with variable-length intervals of apparently quiescent disease in the absence of obvious clinical symptoms. In some subjects, the presence of substantial soft tissue edema and muscle necrosis observed in imaging performed within 7 days of flare-up symptom-onset suggests that the process that ultimately leads to new HO formation starts before clinical symptoms are reported. Fibrodysplasia Ossificans Progressiva might be similar to other chronic diseases that are characterized by acute exacerbations/relapses, followed by variable-length periods of apparent disease quiescence (eg, relapsing/remitting multiple sclerosis) without clinical symptoms.

The majority of FOP patients are confined to a wheelchair by the third decade of life, and require caregiver assistance to perform daily living activities. The median age of survival is approximately 56 years with mortality often resulting from complications of respiratory insufficiency.[6,7]

1.1.2 Current Therapeutic Options for Fibrodysplasia Ossificans Progressiva

Currently there are no effective medical treatment options to prevent the formation of

heterotopic bone in FOP, nor have there been well-controlled trials of other therapeutics in this disease.

Treatments are aimed at the symptomatic management of the disease. Removal of heterotopic bone and other trauma are avoided. Surgical trauma to tissues is likely to induce additional bone formation;[3,8] and intramuscular immunizations; blocks for dental work; muscle fatigue; blunt muscle trauma from bumps, bruises, or falls; or influenza-like viral illnesses can trigger flare-ups leading to HO formation.[9] Falls are a severe form of trauma; in one survey of FOP patients, flare-ups were induced in two-thirds of falls and resulted in permanent loss of movement in 93% of patients.[10] Glucocorticoids are used to manage symptoms of flare-ups affecting major joints of the appendicular skeleton and jaw, especially when used immediately after the onset of a flare-up. Non-steroidal anti-inflammatory agents, cyclooxygenase-2 inhibitors, mast cell stabilizers, and leukotriene inhibitors are reported by patients to manage chronic pain and ongoing disease progression.

The identification of the recurrent point mutation that causes FOP in all classically affected individuals provides a specific target for drug development.[11] An innovative therapeutic approach that can be evaluated in FOP includes diverting the responding mesenchymal stromal cells to a soft tissue fate.[12,13,14] This pathway is the mechanism by which palovarotene is believed to prevent HO in animal models of FOP.

1.1.3 Overview of Palovarotene

Palovarotene is 4-[(E)-2-(5,5,8,8-tetramethyl-3-pyrazol-1-ylmethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-benzoic acid. Palovarotene is an orally bioavailable retinoic acid receptor gamma (RARγ) selective agonist licensed from Roche following the completion of Phase 2 studies in COPD patients (program discontinued due to lack of efficacy), and is being developed by Clementia Pharmaceuticals Inc. as a re-purposed drug for the treatment of FOP.

RARγ agonists potently impair heterotopic endochondral ossification by redirecting prechondrogenic mesenchymal stem cells (MSCs) to a nonosseous soft tissue fate. The rationale for testing retinoids as inhibitors of HO was based on the observation that retinoid signaling is a strong inhibitor of chondrogenesis[15] and that unliganded RAR transcriptional repressor activity is needed for chondrogenic differentiation.[16,17] Inhibition of HO with non-selective retinoids or RARα receptor agonists has also been achieved but to a lesser degree.[13]

RARγ is expressed in chondrogenic cells and chondrocytes[18] where it also operates as an unliganded transcriptional repressor.[19] Hence, an RARγ agonist-based anti-HO therapy could be very effective because it would target both chondrogenic cells and chondrocytes. It has been shown that RARγ agonists exert their action on bone formation through post-translational regulation of BMP signaling by inhibiting Smad phosphorylation and promoting proteasome-regulated degradation of Smads specific to the BMP signaling pathway. Thus, RARγ agonists could directly prevent the activating (R206H) mutation in the BMP type I receptor of FOP patients. Inhibition of both prechondrogenic and chondrogenic cells is also thought to occur through possible stimulation of Wnt-β-catenin signaling.[20,21]

The process of HO consists of two major phases: a catabolic phase of inflammation and tissue destruction followed by an anabolic phase of tissue neogenesis involving the formation of a

transient cartilaginous scaffold and its replacement with mature heterotopic bone. A key feature of all HO is the formation of a bridging cartilaginous scaffold that is under control of the BMP and possibly the Wnt–β-catenin signaling pathways. RARγ agonists affect both BMP and Wnt-β-catenin signaling and interfere with the building of the cartilaginous scaffold, thereby disrupting the bridge and derailing HO.[12]

Palovarotene has been evaluated in various animal models of HO including a BMP-implant model, a constitutively-active receptor model (Q207D), and a highly physiological human mutation knock-in model (R206H). Following injury, the results consistently demonstrate dose-dependent reductions in HO with palovarotene across the models, and significant reduction in spontaneous (non-injury) HO with chronic treatment. The data from the injury-based Q207D mouse model of FOP demonstrated that a human equivalent dose (HED) of 20 mg palovarotene may be required for the greatest inhibition of HO across all injury conditions.

In addition to the injury-based model, palovarotene has also been effective in preventing HO formation in a spontaneous HO model (*Prrx1-R206H* model) that recapitulates many of the phenotypic features of FOP seen in patients including malformed great toes. An average HED of approximately 5 mg palovarotene administered daily by oral gavage to young *Prrx1-R206H* mice markedly reduced the formation of spontaneous HO, suggesting that daily dosing with palovarotene may be an important component of the treatment regimen in humans.

1.1.3.1 Nonclinical Data

The toxicology of palovarotene has been extensively characterized in rodent and non-rodent studies, including single-dose, repeat-dose (sub-chronic and chronic), reproductive toxicity, genotoxicity, and phototoxicity studies in support of clinical studies in humans. Toxicity studies of four metabolites of palovarotene were also performed. A detailed summary of these studies and the observed effects is provided in the Investigator's Brochure.

The toxicology profile of palovarotene in animals is similar to that which is expected for a retinoid based on the extensive data available for compounds in this class of agents.[22] The toxic potential of this molecule was evaluated in rats dosed daily for up to 6 months and in dogs dosed daily for up to 9 months. Initial chronic toxicity studies at dose levels up to 0.15 mg/kg/day in rats (6-month study) and 0.006 mg/kg/day in dogs (9-month study) did not induce any observed palovarotene-related changes. These studies identified these top doses as the no-observed-effect-level for chronic exposure. Further studies at higher dose levels characterized the toxic potential of this molecule after similar chronic administration periods in these two species. The maximum tolerated dose following chronic exposure was 0.6 mg/kg/day in rats and 0.04 mg/kg/day in dogs. Moreover, in order to evaluate the toxicity profile of metabolites at high exposure levels, 6-month studies were conducted in rats and 9-month studies were conducted in dogs with a mixture of metabolites M2, M3, M4a, and M4b given orally. The toxicity profile of these metabolites was similar to that of parent drug in rats and dogs.

The dose limiting toxicities in adult animals were primarily mucocutaneous effects, with mild/moderate and reversible chondrodystrophy observed at the clinically relevant dose of 1 mg/kg/day in 7 to 8-week old rats. The toxicity of palovarotene has also been evaluated in a 6-week repeat-dose oral toxicity study in juvenile rats (3 weeks old at the start of dosing). These results did not reveal any toxicities not observed in older animals, with the primary toxicologic

effects related to bone. At a dose level that produced systemic exposures similar to those predicted in patients, skeletal effects were relatively limited and mild and showed evidence of reversing when dosing stopped, even though juvenile rats were exposed to palovarotene over a period of skeletal development that would be similar to chronic daily dosing from age 2 to 12 years in humans.

In rat and dog mass balance studies, recovery of the administered [^{14}C]-palovarotene dose was complete within 7 days, and elimination of the dose, which was mostly complete within the first 24 hours after dosing, was exclusively biliary/fecal. At least 68% and 50% of the administered dose was absorbed in rats and dogs, respectively.

After the once-daily [^{14}C]-palovarotene oral dose administration for 5 days in rats, radioactivity was slowly, but extensively distributed into tissues, with the highest exposures seen in the adrenal cortex, adrenal medulla, liver, and the walls of the small intestine and caecum. Radioactivity in all tissues decreased 8 hours after the last dose, except for the radioactivity in the adrenal cortex.

Inhibition of the six human CYP450 isoforms by palovarotene was moderate, suggesting a low probability that palovarotene would inhibit the clearance of concomitantly administered drugs. The IC_{50} values for all metabolites against human CYP450 3A4 were very high (>100 μM). The oxidative metabolism of the parent drug was primarily by CYP450 3A4.

1.1.3.2 Clinical Data

Palovarotene Pharmacokinetics

The data describing the clinical pharmacokinetics (PK) of palovarotene are based on 12 completed Phase 1 clinical pharmacology studies in healthy subjects, including a single ascending dose study; a multiple ascending dose study; five drug-drug interaction (DDI) studies with ketoconazole (a strong cytochrome P450 [CYP] 3A4 inhibitor), rifampicin (a strong CYP3A4 inducer), inhibition and induction potential with midazolam (a CYP3A4 substrate), and prednisone (a weak CYP3A4 inhibitor); a bioequivalence study; a [^{14}C]-radiolabeled single-dose mass balance study; a single-dose age and sex study; a single-dose bridging study in Japanese and non-Asian subjects; a definitive food-effect/mode of administration study (as part of the midazolam induction potential study mentioned above); and a thorough QT study and a study evaluating the concentration of palovarotene in seminal fluid.

Pharmacokinetic data were also collected in two multiple-dose studies in subjects with COPD, and three multiple-dose studies in subjects with FOP (one completed Phase 2 study, one ongoing Phase 2 study, and one ongoing Phase 3 study). A population PK model was developed for palovarotene using data obtained after single- and multiple-dose oral administration to healthy volunteers and subjects with COPD and FOP.

To date, over 1200 subjects have received at least one dose of palovarotene across the following indications:

- 309 healthy volunteers received single or multiple doses between 0.02 and 50 mg for up to 4 weeks

- 611 subjects with COPD received multiple doses between 0.2 and 5 mg daily for up to 24 months

- 164 subjects with FOP received multiple doses between 2.5 and 20 mg once daily for up to 4 years, and

- approximately 129 subjects with MO received multiple doses of 2.5 or 5.0 mg once daily for up to 18 months. In addition, seven FOP subjects received palovarotene in an early access program (EAP)

In healthy subjects, the palovarotene pharmacokinetics were linear and dose-proportional up to a single dose of 50 mg or a multiple dose of 10 mg under a fed condition. The plasma palovarotene T_{max} was approximately 4 hours and its $T_{½}$ was approximately 8 hours. The calculated effective half-life was between 5 to 10 hours. With repeated administration, steady-state palovarotene plasma concentrations were attained by day 3.

In a study of Japanese versus non-Asian healthy volunteers, mean plasma concentrations after 5 and 10 mg palovarotene peaked at 4 hours post-dose for both subject populations; the mean terminal half-life ranged from 9.7 to 13 hours. Palovarotene was absorbed and eliminated in a similar manner for both populations, and pharmacokinetic parameters were similar at both dose levels based on geometric mean ratios and CIs for C_{max}, $AUC_{(0-\infty)}$, and $AUC_{(0-t)}$.

Palovarotene was primarily metabolized by CYP3A4. Five metabolites, 6,7-dihydroxy (M1), 6-hydroxy (M2), 7-hydroxy (M3), 6-oxo (M4a), and 7-oxo (M4b) were observed for palovarotene in the clinical pharmacology studies. M1 was present in very low concentrations, usually below the limit of quantification (LOQ). Following administration of ^{14}C-radiolabeled palovarotene, 97% of the dose was recovered in the feces and 3.2% in the urine. Overall, the metabolite profile was qualitatively similar to that reported in all the animal species.

In healthy subjects, palovarotene exposure at steady-state increased approximately three-fold with ketoconazole (a strong CYP3A4 inhibitor), decreased approximately 10-fold with rifampicin (a strong CYP3A4 inducer), increased slightly by 14% with prednisone (a weak CYP3A4 inhibitor), and did not change consistently with midazolam (a CYP3A4 substrate). Palovarotene did not impact the pharmacokinetics of concomitantly administered drugs, including oral prednisone and midazolam.

Co-administration of palovarotene with food resulted in a 40% increase in $AUC_{0-\infty}$ and a 16% increase in C_{max} compared with administration under fasted conditions. Additionally, T_{max} appeared to be slightly shorter for fasted subjects dosed with palovarotene. Opening the capsule and sprinkling the contents onto soft food did not affect the PK of palovarotene. No clinically relevant differences in palovarotene pharmacokinetics were found between young males and elderly males and between elderly males and elderly females.

A population PK model was used to simulate palovarotene administration in pediatric patients in order to assess the appropriateness of weight-based dosing in skeletally immature children. The simulations identified weight-adjusted doses that provide derived steady-state exposures ($AUC_{0-\tau}$, $C_{max,ss}$, and $C_{min,ss}$) within the range of those for adults after receiving the 10- and 20-mg doses.

Palovarotene Phase 2 Interventional Studies

The Phase 2 interventional studies for which subjects with FOP have received treatment include:

- Study PVO-1A-201 provided a preliminary assessment of palovarotene efficacy across two different dosing regimens following 6 weeks of treatment for a flare-up relative to placebo (ie, flare-up only regimen). Forty subjects were randomized (3:3:2) within 1 week of a flare-up to receive either 10 mg palovarotene daily for 2 weeks followed by 5 mg daily for 4 weeks (10/5 mg); 5 mg palovarotene for 2 weeks followed by 2.5 mg for 4 weeks (5/2.5 mg); or placebo for 6 weeks. After the 6-week treatment period, subjects began a 6-week follow-up period during which no study drug was administered.

- Study PVO-1A-202/Part A, an open-label extension of Study PVO-1A-201, evaluated the long-term safety and efficacy of prior palovarotene treatment after an additional 12 months of follow-up. Open-label palovarotene was administered to all subjects, including any randomized to placebo during Study PVO-1A-201, experiencing additional eligible flare-ups (ie, flare-up only regimens). Subjects were treated with high dose palovarotene (10 mg palovarotene for 2 weeks followed by 5 mg for 4 weeks) regimen for 6 weeks, followed by a 6-week period in which no study drug was administered.

- Study PVO-1A-202/Part B (corresponds to Study PVO-1A-204 in France) included chronic daily doses (5 mg) of palovarotene in subjects with at least 90% skeletal maturity. During a flare-up, all subjects received higher dose/longer duration treatment with palovarotene (20 mg for 4 weeks followed by 10 mg for 8 weeks). This "chronic/flare-up" regimen is the dosing regimen employed in the current study, PVO-1A-202/Part C, that will include chronic or non-flare-up dosing for skeletally mature as well as skeletally immature subjects. This corresponds to Study PVO-1A-204 Amendment 3 in France.

- Study PVO-1A-202/Part C (corresponds to Study PVO-1A-204 in France, ongoing) extends the chronic/flare-up palovarotene regimen to all subjects, including skeletally immature children. Part D was added for skeletally immature subjects who stopped taking study drug for any reason before completion of Part A/B/C. Part D includes yearly visits for up to a 2-year follow-up period following last dose. No dosing is to occur during Part D.

Palovarotene Safety

Consistent with other retinoids, the most commonly reported adverse events across all palovarotene dosing regimens in the FOP interventional studies were mucocutaneous and dermatologic events such as dry skin and lips, erythema, and pruritus. In general, the incidence, total number, duration and severity of mucocutaneous and dermatologic events increased with increasing palovarotene dose. These AEs generally resolved without sequelae after completion of palovarotene treatment. Musculoskeletal events such as arthralgia, pain in extremity, and condition aggravated (the Medical Dictionary for Regulatory Activities [MedDRA] preferred term used to capture reports of FOP flare-ups) were also commonly reported.

The majority of AEs in the palovarotene Phase 2 studies in FOP were mild or moderate in severity.

In the current study, and in the ongoing FOP Phase 2 study, subjects enrolled with open epiphyses undergo knee (anterior/posterior [AP] view) and hand/wrist radiographs (posterior/anterior [PA] view) for assessment of epiphyseal growth plate; and linear and knee height measurements for assessment of growth. The most common epiphyseal growth plate abnormality is growth recovery lines (dense metaphyseal lines) at both baseline and post-baseline time points. Potential premature closure of the epiphysis is closely monitored, and data are reviewed quarterly by an independent Data Monitoring Committee (DMC). Premature epiphyseal closure has been observed in subjects in the interventional FOP studies that have been reported as serious adverse events. Analysis of the SAEs suggests that the risk of premature epiphyseal fusion is higher in subjects with open epiphyseal growth plates who have received the flare-up dosing regimen. The finding of premature epiphyseal closure has been seen across all ages although the potential impact on growth is likely to be greater in the youngest, most skeletally immature subjects, given limitations in time to attain a greater percent of their final adult height.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is:

- To evaluate the safety and efficacy of different palovarotene dosing regimens in subjects with FOP. Efficacy will be assessed based on the ability of palovarotene to prevent the formation of new heterotopic ossification (HO) as assessed by low-dose whole body computed tomography (WBCT) scan, excluding head.

2.2 Secondary Objectives

- To evaluate the effect of palovarotene on range of motion (ROM) as assessed by the Cumulative Analogue Joint Involvement Scale (CAJIS) for FOP.
- To evaluate the effect of palovarotene on physical function using age-appropriate forms of the FOP-Physical Function Questionnaire (PFQ).
- To evaluate the effect of palovarotene on physical and mental health using age-appropriate forms of the Patient Reported Outcomes Measurement Information System (PROMIS) Global Health Scale.
- To evaluate the pharmacokinetics of palovarotene.

2.3 Secondary Objective (Part D)

- To implement safety measures based on DMC recommendations in order to ensure that assessments of safety continue for up to 2 years post last dose of study treatment for skeletally immature subjects.

3. STUDY DESIGN

3.1 Overview of the Study Design

This is a Phase 2, multicenter, open-label extension study that will explore different dosing regimens of palovarotene in adult and pediatric subjects with FOP.

Part A includes all data obtained prior to Amendment 3 (dated 10 March 2016) during which pediatric and adult subjects successfully completing Study PVO-1A-201 were enrolled and followed for up to 36 months. Any subject experiencing an eligible flare-up under Part A received treatment with open-label palovarotene at a dose of 10 mg once daily for 14 days followed by 5 mg once daily for 28 days (or weight-based equivalent) and underwent all study procedures as specified in the original protocol, Amendment 1, and Amendment 2.

Part B includes all data obtained under Amendment 3 (dated 10 March 2016) during which subjects successfully completing Study PVO-1A-201 (including any subject who previously participated in Part A of Study PVO-1A-202) as well as up to 20 new adult subjects were followed for up to 24 months.

Part C includes all data obtained under Amendment 4 (dated 01 September 2017) and subsequent amendments during which subjects who participated in Part B will be followed for up to an additional 48 months. There will be no new subjects in Part C. Part C plus Part D total duration will not exceed 48 months.

Part D annual post last dose of study treatment assessments for up to 2 years will be obtained in subjects who were skeletally immature at the time of study treatment discontinuation in order to obtain longer-term safety data. No new subjects will be enrolled into Part D. Subjects will follow assessments as outlined in Table 4 for as long as they are not 100% skeletally mature. Part C plus Part D total duration will not exceed 48 months.

All subjects will receive non-flare-up-based treatment of 5 mg palovarotene once daily (weight-adjusted doses for skeletally immature subjects [ie, subjects under the age of 18 years with less than 90% skeletal maturity on hand/wrist radiography at Screening]). Note: all weight-based dosing will cease when subjects achieve ≥90% skeletal maturity based on hand/wrist radiography, but radiographic assessment of the growth plate (performed every 6 months) will continue until these subjects achieve 100% skeletal maturity (defined as growth plate closure) at both knee and hand/wrist locations. Additional radiographic assessments will be performed every 3 months in those subjects who (1) received the flare-up dosing regimen in the period of time since their last radiographic assessment; and (2) had not achieved 100% skeletal maturity on their last radiographic assessment.

Subjects will follow all assessments as outlined in Table 1 and Table 2. Adult subjects who cannot receive non-flare-up-based treatment will only undergo annual assessments (clinical laboratory tests will not be performed). In the event of a flare-up or traumatic event, these subjects will receive flare-up-based treatment and undergo all flare-up-based assessments, including clinical laboratory tests and radiographs if they have not reached 100% skeletal maturity.

Adverse events will be assessed at every site and remote visit during both non-flare-up-based and flare-up-based treatment. In case of early termination or withdrawal of a subject, every reasonable effort will be made by the study staff to have the subject return to the site in order to complete all end of treatment (EOT) and end of study (EOS) evaluations.

Travel arrangements to the site for subjects and caregivers will take into consideration subjects' disability in a manner that will minimize any possible injury to subjects. For example, ground travel could utilize an ambulance if deemed necessary; air travel could consist of first class seating or use of a private jet or air ambulance; and hotel accommodations could consist of disability accessible rooms. It should be noted that all travel arrangements are to be made in consultation with the Investigator so that the safety of the subject is always fully considered.

As of 04 December 2019, all subjects < 14 years of age were required to interrupt study drug due to a partial clinical hold placed on the palovarotene clinical development program by the US FDA. Treatment will subsequently not be restarted in children <14 years of age.

Subjects from Part B Continuing Non-Flare-up-based Treatment into Part C

Subjects who began non-flare-up-based treatment during Part B will continue the same visit schedule into Part C (includes Protocol Amendment 4 and subsequent amendments), and will receive non-flare-up-based treatment for up to an additional 48 months. Therefore, these subjects may undergo non-flare-up-based treatment for up to 72 months over the entire study. Subjects continuing into Part C will follow all procedures and undergo all assessments as specified in the Schedule of Assessments in Table 1. Site visits will occur at Months 12, 24, 36, 48, 60 and 72. Non-flare-up Day 1 is the first day that non-flare-up-based treatment was initiated during Part B, and total duration of treatment will continue into Part C. Non-flare-up Day 1 is the first day that non-flare-up-based treatment is initiated during Part B, and total duration of treatment will continue into Part C.

Remote visits (eg, at home or at a local medical facility; and via telephone contact with clinical site personnel) will occur every 3 months unless the Investigator deems that a site visit is necessary; urine pregnancy tests will be performed each month for females of childbearing potential (FOCBP).

Subjects from Part B Starting Non-Flare-up-based Treatment During Part C

Subjects who will start non-flare-up-based treatment during Part C will receive non-flare-up-based treatment for up to 48 months. These subjects will follow all procedures and undergo all assessments as specified in the Schedule of Assessments in Table 2. Site visits will occur at Part C Screening and/or Non-flare-up Day 1, and at Months 6, 12, 24, 36 and 48. Non-flare-up Day 1 is the first day that non-flare-up-based treatment is initiated during Part C for these subjects.

Remote visits (eg, at home or at a local medical facility; and via telephone contact with clinical site personnel) will occur every 3 months unless the Investigator deems that a site visit is necessary; urine pregnancy tests will be performed each month for FOCBP.

Part D:

Annual post last dose of study treatment assessments for up to 2 years will be obtained in subjects who were skeletally immature at the time of study treatment discontinuation in order to obtain longer-term safety data. No new subjects will be enrolled into Part D. Subjects who were enrolled in Parts A, B or C who have discontinued the study and were skeletally immature at their last assessment will be invited back to participate in the off-treatment Part D safety follow-up. These subjects will follow all procedures and undergo all assessments as specified in the Schedule of Assessments in Table 4.

Assessments will include knee and hand/wrist radiographs, linear and knee height growth assessments, physical examination, body weight, vital signs, low-dose WBCT scan (excluding head), prior/concomitant medications, and adverse events.

Flare-up-based Treatment

Subjects and/or their parents/caregivers will report potential flare-up symptoms to site personnel; such symptoms include, but are not limited to, pain, swelling, redness, decreased range of motion, stiffness, and warmth. Only one symptom is required to define a flare-up. If these symptoms are consistent with previous flare-ups, include a subject-reported onset date, and are confirmed by the Investigator as associated with a flare-up, subjects will immediately receive open-label palovarotene treatment as follows:

- 20 mg for 4 weeks (28 days) once daily. The first dose will be taken upon flare-up confirmation by the Investigator.

To be followed by:

- 10 mg for 8 weeks (56 days) once daily, for a total flare-up treatment duration of 12 weeks (84 days); 10 mg treatment may be extended if the flare-up is ongoing and continue until the flare-up resolves. Dosing will be extended in 4-week intervals and be based on clinical signs and symptoms as assessed by the Investigator.

Flare-up-based dosing should also be initiated if the Investigator confirms the presence of a substantial high-risk traumatic event likely to lead to a flare-up.

All dosing, be it non-flare-up or flare-up-based, will be weight-adjusted in subjects under the age of 18 years with less than 90% skeletal maturity on hand/wrist radiography at Screening (Table 5). Note: all weight-based dosing will cease when subjects achieve ≥90% skeletal maturity based on hand/wrist radiography, but radiographic assessment of the growth plate will continue until these subjects achieve 100% skeletal maturity (defined as growth plate closure) at both knee and hand/wrist locations.

The weight-adjusted palovarotene doses and dose de-escalation doses are:

Table 5. Weight-Adjusted Palovarotene Doses and Dose De-Escalation Doses

Weight Range Category	20-mg Equivalent	15-mg Equivalent*	10-mg Equivalent	7.5-mg Equivalent*	5-mg Equivalent*	2.5-mg Equivalent*
20 to <40 kg	12.5 mg	10 mg	6 mg	4 mg	3 mg	1.5 mg

40 to <60 kg	15 mg	12.5 mg	7.5 mg	5 mg	4 mg	2 mg
≥60 kg	20 mg	15 mg	10 mg	7.5 mg	5 mg	2.5 mg

* In the event of dose de-escalation from 20-mg, 10-mg, or 5-mg equivalent, respectively.

If the subject experiences intolerable side effects, the dose may be reduced to the next lower dose as shown in Table 5; if the subject is already receiving the lowest possible dose, then study drug will be discontinued. In the event the subject required dose de-escalation due to an intolerable side effect for a previous flare-up, then the dose the subject will receive for a subsequent flare-up will be determined by the Investigator and the Medical Monitor. If there is evidence of partial or complete premature growth plate closure (with or without growth deceleration) study drug may be continued, interrupted, de-escalated, or discontinued. Dose modification decisions will be made by the Investigator upon review of the subject's clinical and radiographic information, and following discussion of the risk/benefit with the subject/parent. The Investigator may also consult with the sponsor and the DMC.

Should a subject experience an intercurrent flare-up (defined as a new flare-up or marked worsening of the original flare-up), or if the Investigator confirms the presence of a substantial high-risk traumatic event likely to lead to a flare-up, at any time during flare-up-based treatment, the 12-week dosing regimen will restart upon new intercurrent flare-up confirmation by the Investigator (ie, 4 weeks of 20 mg palovarotene followed by 8 weeks of 10 mg palovarotene [or weight-based equivalent]). A Flare-up Cycle will include the first flare-up or traumatic event and any subsequent intercurrent flare-ups or traumatic events during the same dosing period. Flare-Up Cycle Safety Day 1 is defined as the first day that study drug is administered for the first flare-up or traumatic event during that cycle. Safety assessments will be performed on Flare-up Cycle Safety Day 1 and every 12 weeks thereafter until treatment of the last flare-up or traumatic event in the flare-up cycle is completed. If any flare-up in a cycle has not resolved after 12 weeks, treatment and safety assessments will be extended and 10 mg palovarotene (or the weight-based equivalent) will be administered in 4-week intervals until all the flare-ups resolve and flare-up-based treatment has been completed. It is possible that subjects may experience more than one Flare-up Cycle during the study.

Subjects receiving flare-up-based treatment will follow all procedures and undergo all assessments as specified in the Schedule of Assessments in Table 3. All assessments will occur remotely, unless the Investigator deems it necessary to evaluate subjects at the clinical site.

Once all flare-ups or traumatic events in a cycle have resolved and flare-up-based treatment has been completed, subjects will resume non-flare-up-based treatment with 5 mg palovarotene once daily (weight-adjusted doses for skeletally immature subjects).

The PK of palovarotene dosing will be assessed at the first 3-month safety assessment during non-flare-up-based treatment; if samples cannot be or were not obtained during the first 3-month safety assessment, or if subjects are on flare-up-based treatment, then PK blood samples for non-flare-up treatment can be obtained during any subsequent 3-month safety visit.

Pharmacokinetics of palovarotene dosing will also be assessed twice during flare-up-based treatment: once during the 20-mg regimen at any time between Study Days 4 to 28, and once during the 10-mg regimen at any time between Study Days 32 to 84, for the first treated flare-up only. If this is not possible for the first treated flare-up, PK blood samples can be obtained

during any subsequent flare-up dosing cycle. Pharmacokinetic blood samples will be collected at pre-dose and 3, 6, 10, and 24 hours post-dose. Subjects who underwent a PK assessment for flare-up-based treatment under PVO-1A-202 Protocol Amendment 3 will not have flare-up PK assessed again. However, these subjects will require a non-flare-up treatment PK assessed at a 3-month safety visit (Section 7.5).

3.2 Study Rationale

Prior to Protocol Amendment 3, this study followed subjects who rolled over from Study PVO-1A-201 and provided open-label active treatment to any subject who experienced a subsequent flare-up. This allowed for the collection of long-term efficacy and safety data of palovarotene (10 mg for 14 days, followed by 5 mg for 28 days), and provided active treatment to all subjects experiencing eligible flare-ups including those who were randomized to placebo during Study PVO-1A-201. Clinical data obtained from the Phase 2 interventional studies, as well as recent animal pharmacology data, have contributed to the understanding of FOP disease progression, the risk factors leading to HO formation, and the potential utility of palovarotene in preventing HO formation.

Fibrodysplasia Ossificans Progressiva is a disease that is characterized by HO that may develop spontaneously or after soft tissue trauma, vaccinations, or influenza infections. The HO accumulates throughout life, resulting in segments, sheets, and ribbons of extra bone throughout the body and across joints, progressively restricting movement. While HO formation may be preceded by signs and symptoms of a flare-up such as pain, swelling, redness, decreased range of motion, stiffness, and warmth, the biological process that results in the formation of HO may begin before the onset of symptoms. Thus, the optimal treatment for FOP might be similar to other chronic diseases that are characterized by acute exacerbations/relapses, followed by variable-length periods of apparent disease quiescence (eg, relapsing/remitting multiple sclerosis) during which clinical symptoms are not observed.

It is hypothesized that daily treatment in the absence of flare-up symptoms, which will ensure exposure to palovarotene when the endochondral process starts, together with increasing the dose immediately upon symptom onset (the chronic flare-up regimen), may be a better approach than treating only when clinical symptoms are present (the flare-up only regimen). Under Protocol Amendment 3, adult subjects initiated non-flare-up-based daily treatment with palovarotene, which is extended to the Pediatric Cohort subjects under Protocol Amendments 4 and 5. In addition, subjects experiencing an eligible intercurrent flare-up will restart flare-up-based dosing in order to continue exposure to palovarotene and provide an optimal treatment for all flare-ups that may occur during the study.

As of 04 December 2019, all subjects < 14 years of age were required to interrupt study drug due to a partial clinical hold placed on the PVO clinical development program by the US FDA. Treatment will subsequently not be restarted in children < 14 years of age as subjects remained off treatment for such a prolonged period of time as to render any further data to inform additional benefit/risk uninterpretable in this patient population.

Given the serious identified risk of premature physeal closure, Part D was added to implement safety measures based on DMC recommendations in order to ensure that assessments of safety continue for up to 2 years post last dose of study treatment in Part A/B/C for skeletally immature

subjects who stopped treatment for any reason.

3.3 Dose Justification

Fibrodysplasia Ossificans Progressiva is an extremely rare, chronic, severely disabling disease characterized by periods of relative disease quiescence interspersed with episodic flare-ups and the formation of HO that is irreversible and the disability is permanent. Because the risks of under-treatment are very high, FOP should be treated aggressively in order to evaluate the maximal potential treatment benefit, while carefully monitoring for potential safety concerns. The dose regimens selected for the current study address these aspects of the disease and are based on emerging nonclinical and clinical data:

- **Chronic dosing regimen:** In a non-injury-based mouse model of FOP that recapitulates much of the clinical phenotype observed in patients, including spontaneous HO formation, chronic daily treatment with palovarotene at an HED of approximately 5 mg prevented HO formation. Importantly in this R206H FOP-relevant animal model, the dosing regimen did not impair long bone growth but partially normalized the abnormal growth plate histology and shortened long bones that are key phenotypic features of this model. The results raised the possibility that chronic daily palovarotene dosing may be a major component of an optimized clinical dosing strategy.

- **Flare-up dosing regimen:** The rationale for increasing the chronic palovarotene dose at the time of a flare-up comes from both the animal pharmacology and available clinical trial results. The nonclinical data from two different mouse models of FOP demonstrated a dose-related decrease in HO volume; and suggested that flare-up-based treatment using an HED of 20 mg may be necessary to optimally prevent HO following an injury (equivalent to a flare-up in humans). The Phase 2 program has evaluated four different palovarotene dosing regimens, three flare-up-based episodic treatment regimens and one chronic/flare-up regimen. Preliminary clinical data on 103 prospectively assessed flare-ups demonstrated an approximate 45% reduction in the proportion of flare-ups with new HO, and an approximate 75% decrease in new HO volume, in those flare-ups treated with palovarotene 10/5 mg over 6 weeks compared to placebo/untreated flare-ups; and an approximate 65% reduction in proportion of flare-ups with new HO and an approximate 98% reduction in HO volume in those flare-ups treated with the chronic/flare-up regimen 20/10 mg over 12 weeks (the regimen in the current study) compared to placebo/untreated flare-ups. These data provide a strong rationale for the continued evaluation of palovarotene as a potential treatment of FOP, and the selection of chronic daily administration of 5 mg palovarotene, with dose escalation to 20 mg once daily for 4 weeks followed by 10 mg for 8 weeks (with treatment extension possible per Investigator discretion for persistent flare-ups) for all subjects. The flare-up dosage will be adjusted for weight in skeletally immature children.

- While it is recognized that flare-ups can occur in the absence of any apparent causative factor, there is a high risk that substantial traumatic events such as surgery, intramuscular immunizations, mandibular blocks for dental work, muscle fatigue, blunt muscle trauma from bumps, bruises, falls, or influenza-like viral illnesses can induce flare-ups and progressive HO formation.[9] In one survey of FOP patients, flare-ups were induced in

two-thirds of falls and resulted in permanent loss of movement in 93% of patients.[10] Thus, subjects experiencing substantial high-risk traumatic events that the Investigators deem likely to lead to a flare-up will be treated with the flare-up regimen.

It is acknowledged that palovarotene plasma exposure in humans receiving treatment with this regimen will be similar to or greater than the threshold for adverse effects in juvenile rats, adult rats, or adult dogs. The toxicological effects were primarily mucocutaneous (in adult animals) and skeletal (in juvenile animals after chronic exposure). Current safety monitoring in the current Phase 2 and Phase 3 studies has confirmed mucocutaneous adverse effects that are managed with prophylactic treatment or dose reduction. In addition, Phase 2 monitoring of the growth plate revealed that the most common finding was dense metaphyseal lines in approximately 70% of subjects at both baseline and post-baseline time points. Premature epiphyseal closure has also been observed in the current Phase 2 and Phase 3 studies. Therefore, careful safety monitoring and dose modification procedures for intolerable side effects will be employed in the current study.

3.4 Appropriateness of Measurements

3.4.1 Imaging

A number of different imaging modalities have been utilized in patients presenting with soft tissue swelling/masses including plain radiographs, computed tomography (CT) scan,[23] magnetic resonance imaging (MRI),[24] and radionuclide bone scan.[25] Most are performed at the time of the initial flare-up as part of the diagnostic evaluation and prior to the diagnosis of FOP. Following the accurate diagnosis of FOP, imaging is not routinely performed[4] as such imaging does not play a role in the supportive care offered to patients. Although most of the experience with documentation of HO following a flare-up has been with x-ray, it has been noted that CT scans may allow earlier detection of new areas of HO.[26]

Flare-up site, low-dose CT scan was found to be more sensitive to the detection and quantification of new HO following a flare-up in the initial interventional Phase 2 study (PVO-1A-201) compared to plain radiograph. The Natural History Study (PVO-1A-001) demonstrated the utility of WBCT at documenting the presence, location, and quantification of whole body HO, including new HO formation at 12-months. This also assesses HO in areas remote to flare-up symptoms, which more accurately reflects the status of the subject at follow-up. For these reasons, the imaging modality utilized in the current study to assess the primary and secondary endpoints will be low-dose WBCT scan (excluding head).

In order to ensure consistency and standardization, interpretation of the acquired images will be performed by a central imaging laboratory. The clinical trial imaging methodology will be documented (eg, imaging charter and imaging guideline) prior to study initiation.

3.4.2 Measures of Functional Disability and General Health

Two key measures of functional disability include:

- The CAJIS for FOP is an objective measure of joint movement completed by the Investigators to document total joint involvement. This scale, which was developed by the Investigators from the Center for Research in FOP and Related Disorders, assesses

functional disability by categorizing range of motion across 12 joints (shoulder, elbow, wrist, hip, knee, ankle on both right and left), and three body regions (cervical spine [neck], thoracic/lumbar spine and jaw) with each joint/region assessed as: 0=uninvolved; 1=affected; 2=functionally ankylosed. The total score range is 0-30. The CAJIS is provided in Appendix 1.

- The FOP-PFQ is a disease-specific patient-reported outcome measure of physical impairment. The FOP-PFQ was developed by Clementia based on the Food and Drug Administration (FDA) Guidance for Industry, "Patient Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims". This patient-reported outcome instrument was developed to assess the relationship between patient reports of physical impairment due to HO, thereby providing evidence of HO as a clinically meaningful endpoint. Age-appropriate forms provide a measure of functional impairment experienced by subjects and include questions related to activities of daily living and physical performance. These data are analyzed as a percent of the total possible score, with higher percentages representing greater functional impairment. The adult and pediatric versions of the FOP-PFQ are provided in Appendix 2A.

4. STUDY ENDPOINTS

4.1 Primary Endpoints

The primary endpoint is the annualized change in new HO volume as assessed by low-dose WBCT scan, excluding head. The annualized change from Parts B and C will be compared to data collected from the NHS.

4.2 Secondary Endpoints

Note: Baseline is Non-flare-up Day 1. Some subjects may be assessed for up to 72 months.

1 Percent of subjects with new HO at Months 12, 24, 36, 48, 60, 72 and overall.

2 Change from baseline in ROM as assessed by CAJIS at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72.

3 Change from baseline in physical function using age appropriate forms of the FOP-PFQ at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72.

4 Change from baseline in physical and mental function for subjects ≥15 years old and mental function for subjects <15 years old using age appropriate forms of the PROMIS Global Health Scale at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72.

5. SELECTION OF STUDY POPULATION

The target study population consists of up to 40 adult and pediatric subjects with FOP who have completed Study PVO-1A-201 (through Study Day 84), as well as up to 20 new adult subjects who were enrolled during Part B.

5.1 Study Population (Adult and Pediatric Cohorts – Part B)

As of 04 December 2019 all subjects < 14 years of age were required to interrupt study drug due to a partial clinical hold placed on the palovarotene clinical development program by the US FDA. Treatment will subsequently not be restarted in children <14 years of age.

5.1.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1 Completion of Study PVO-1A-201 (through Study Day 84); or Adult Cohort subjects not enrolled in Study PVO-1A-201, have the confirmed R206H genetic mutation consistent with FOP, have had at least two acute symptomatic flare-ups in the past 2 years but no flare-up symptoms within the past 4 weeks, including at the time of enrollment, have a CAJIS score of 6 to 16, inclusive, and must be able to receive non-flare-up-based dosing.

2 For the Adult Cohort, subjects under the age of 18 must have knee and hand/wrist radiographs confirming ≥ 90% skeletal maturity.

3 Written, signed, and dated subject/parent informed consent; and, for subjects who are minors, age-appropriate assent (this must be performed according to local regulations).

5.1.2 Exclusion Criteria

1 Simultaneous participation in another clinical research study (except for Studies PVO-1A-201, PVO-1A-203, or PVO-1A-001) within the 4 weeks prior to Part B Screening.

2 Any reason that, in the opinion of the Investigator, would lead to the inability of the subject and/or family to comply with the protocol.

5.2 Study Population for Non-Flare-up-based Treatment (Adult Cohort – Part B)

5.2.1 Inclusion Criteria

1 Females of child-bearing potential (FOCBP) must have a negative blood or urine pregnancy test (with sensitivity of at least 50 mIU/mL) prior to administration of palovarotene. Male and FOCBP subjects must agree to remain abstinent during treatment and for 1 month after treatment or, if sexually active, to use two highly effective methods of birth control during and for 1 month after treatment. Additionally, sexually active FOCBP subjects must already be using two highly effective methods of birth control 1 month before treatment is to start. Specific risks of the use of retinoids during pregnancy, and the agreement to remain abstinent or use two highly effective methods of birth control will be clearly defined in the informed consent, and the subject or legally authorized representative (eg, parents, caregivers, or legal guardians) must specifically sign this section.

2 Subjects must be accessible for treatment with palovarotene and follow-up. Subjects living at distant locations from the investigational site must be able and willing to travel to a site for the initial and all on-site follow-up visits.

5.2.2 Exclusion Criteria

1 Weight <20 kg.

2 Intercurrent known or suspected non-healed fracture at any location.

3 Currently using vitamin A or beta carotene, multivitamins containing vitamin A or beta carotene, or herbal preparations, fish oil, and unable or unwilling to discontinue use of these products during palovarotene treatment.

4 Exposure to synthetic oral retinoids other than palovarotene in the past 30 days prior to Part B Screening (signature of the informed consent).

5 Concurrent treatment with tetracycline or any tetracycline derivatives due to the potential increased risk of pseudotumor cerebri.

6 History of allergy or hypersensitivity to retinoids or lactose.

7 Concomitant medications that are inhibitors or inducers of cytochrome P450 (CYP450) 3A4 activity (see Section 5.6).

8 Amylase or lipase >2x above the upper limit of normal (ULN) or with a history of chronic pancreatitis.

9 Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5x ULN.

10 Fasting triglycerides >400 mg/dL with or without therapy.

11 Female subjects who are breastfeeding.

12 Subjects with uncontrolled cardiovascular, hepatic, pulmonary, gastrointestinal, endocrine, metabolic, ophthalmologic, immunologic, psychiatric, or other significant disease.

13 Subjects experiencing suicidal ideation (type 4 or 5) or any suicidal behavior within the past month as defined by the Columbia Suicide Severity Rating Scale (C-SSRS).

5.3 Study Population for Flare-up-based Treatment (Adult and Pediatric Cohorts – Part B)

5.3.1 Inclusion Criteria

1 Symptomatic onset of a flare-up within 7 days before the first dose of study drug and defined by the presence of at least two of the following symptoms: pain, soft tissue swelling, decreased ROM, stiffness, redness, and warmth. Symptoms must be

reported by the subject, be consistent with their previous flare-ups, and include a subject-reported onset date, and flare-up must be confirmed by the Investigator.

2 Flare-up is at an appendicular area (upper or lower extremity), abdomen, chest, neck, or lower back; and subject has received, is receiving, or is willing to receive treatment per standard of care, which may or may not include prednisone (2 mg/kg PO to a maximum dose of 100 mg daily) for 4 days.

3 Females of child-bearing potential (FOCBP) must have a negative blood or urine pregnancy test (with sensitivity of at least 50 mIU/mL) prior to administration of palovarotene. Male and FOCBP subjects must agree to remain abstinent during treatment and for 1 month after treatment or, if sexually active, to use two highly effective methods of birth control during and for 1 month after treatment. Additionally, sexually active FOCBP subjects must already be using two highly effective methods of birth control 1 month before treatment is to start. Specific risks of the use of retinoids during pregnancy, and the agreement to remain abstinent or use two highly effective methods of birth control will be clearly defined in the informed consent and the subject or legally authorized representatives (eg, parents, caregivers, or legal guardians) must specifically sign this section.

4 Subjects must be accessible for treatment with palovarotene and follow-up. Subjects living at distant locations from the investigational site must be able and willing to travel to a site for the initial and all on-site follow-up visits.

5.3.2 Exclusion Criteria

1 Weight <20 kg.

2 Intercurrent known or suspected non-healed fracture at any location.

3 Complete immobilization of joint at site of flare-up.

4 The inability of the subject to undergo imaging assessments using plain radiographs.

5 Currently using vitamin A or beta carotene, multivitamins containing vitamin A or beta carotene, or herbal preparations, fish oil, and unable or unwilling to discontinue use of these products during palovarotene treatment.

6 Exposure to synthetic oral retinoids other than palovarotene in the past 30 days prior to Flare-up Screening (signature of the informed consent).

7 Concurrent treatment with tetracycline or any tetracycline derivatives due to the potential increased risk of pseudotumor cerebri.

8 History of allergy or hypersensitivity to retinoids or lactose.

9 Concomitant medications that are inhibitors or inducers of CYP450 3A4 activity (see Section 5.6).

10 Any subject with clinically significant elevations in amylase, lipase, AST, ALT, or fasting triglycerides during the most recent clinical laboratory assessment will require re-test prior to immediate flare-up-based dosing with palovarotene per the Investigator. If upon re-test, the laboratory value in question remains clinically significant abnormal, then the subject will not receive flare-up-based treatment for this flare-up.

11 Female subjects who are breastfeeding.

12 Subjects with uncontrolled cardiovascular, hepatic, pulmonary, gastrointestinal, endocrine, metabolic, ophthalmologic, immunologic, psychiatric, or other significant disease.

13 Subjects experiencing suicidal ideation (type 4 or 5) or any suicidal behavior within the past month as defined by the Columbia Suicide Severity Rating Scale (C-SSRS).

14 Any reason that, in the opinion of the Investigator, would lead to the inability of the subject and/or family to comply with the protocol.

5.4 Study Population (All Subjects – Part C)

5.4.1 Inclusion Criteria

Subjects must meet the following inclusion criterion to be eligible for enrollment:

1 Prior participation in Part B of the current study (PVO-1A-202).

2 Written, signed, and dated subject/parent informed consent; and, for subjects who are minors, age-appropriate assent (this must be performed according to local regulations).

3 Females of child-bearing potential must have a negative blood or urine pregnancy test (with sensitivity of at least 50 mIU/mL) prior to administration of palovarotene. Male and FOCBP subjects must agree to remain abstinent from heterosexual sex during treatment and for 1 month after treatment or, if sexually active, to use two effective methods of birth control during and for 1 month after treatment. Additionally, sexually active FOCBP subjects must already be using two effective methods of birth control 1 month before treatment is to start. Specific risks of the use of retinoids during pregnancy, and the agreement to remain abstinent or use two effective methods of birth control will be clearly defined in the informed consent and the subject or legally authorized representatives (eg, parents, caregivers, or legal guardians) must specifically sign this section.

5.4.2 Exclusion Criteria

Subjects with the following exclusion criterion will not be eligible for enrollment:

1 Any reason that, in the opinion of the Investigator, would lead to the inability of the subject and/or family to comply with the protocol.

2 Currently using vitamin A or beta carotene, multivitamins containing vitamin A or beta carotene, herbal preparations containing vitamin A or beta carotene, or fish oil, and unable or unwilling to discontinue use of these products during palovarotene treatment.

5.5 Study Population of Subjects Starting Non-Flare-up-based Treatment During Part C

5.5.1 Inclusion Criteria

Subjects must meet the following inclusion criterion to be eligible for enrollment:

1 Subjects must be accessible for treatment with palovarotene and follow-up. Subjects living at distant locations from the investigational site must be able and willing to travel to a site for the initial and all on-site follow-up visits.

2 Subjects must be able to undergo low-dose WBCT scan, excluding head.

5.5.2 Exclusion Criteria

Subjects with the following exclusion criterion will not be eligible for enrollment:

1 Amylase or lipase >2x above the upper limit of normal (ULN) or with a history of chronic pancreatitis.

2 Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5x ULN.

3 Fasting triglycerides >400 mg/dL with or without therapy.

4 Subjects experiencing suicidal ideation (type 4 or 5) or any suicidal behavior within the past month as defined by the Columbia Suicide Severity Rating Scale (C-SSRS).

5.6 Prior and Concomitant Medications and Other Study Restrictions

5.6.1 Prior and Concomitant Medications for Subjects Receiving Palovarotene

Subjects must be willing to receive treatment per the standard of care as noted in the FOP Treatment Guidelines 2011 which, for acute flare-ups, may or may not include corticosteroids (eg, prednisone at 2 mg/kg PO to a maximum dose of 100 mg daily) for 4 days.[27] Ideally, corticosteroids will have been initiated within 24 hours after the start of a flare-up. Initiation of corticosteroids after 24 hours will be based on the clinical judgment of the Investigator taking into consideration the subject's flare-up symptoms and location, and in consultation with the subject's primary physician, if necessary. Other standard-of-care medications are also permitted.

The following medications are not allowed during palovarotene treatment (flare-up or non-flare-up-based):

- Vitamin A or beta carotene, multivitamins containing vitamin A or beta carotene, herbal preparations containing vitamin A or beta carotene, or fish oil are not permitted from the day before the start of treatment until the last day of treatment.

- Synthetic oral retinoids other than palovarotene are not permitted in the 30 days prior to treatment until the last day of treatment.

- Concomitant use of tetracyclines and retinoids has been associated with benign intracranial hypertension. Therefore, use of tetracycline or tetracycline derivatives is prohibited during the study. If the subject experiences a medical condition that requires treatment with tetracycline and/or doxycycline, study drug should be discontinued for the duration of tetracycline treatment and the Medical Monitor should be notified. Prior to restarting treatment with palovarotene, an appropriate wash-out period of 3 days must be considered.

- Strong inhibitors of cytochrome CYP450 3A4 are known to alter the metabolism of palovarotene. Thus, concurrent oral medications identified as strong inhibitors of CYP450 3A4 (see Appendix 3) or kinase inhibitors, such as imatinib, are excluded. If during the study, the subject must take a strong inhibitor of CYP450 3A4, the study drug is to be discontinued for the duration of treatment. Prior to restarting treatment with palovarotene, an appropriate wash-out period (five half-lives) must be considered (see Appendix 3).

- Strong inducers of cytochrome CYP450 3A4 are also known to alter the metabolism of palovarotene. Thus, concurrent oral medications identified as strong inducers of CYP450 3A4 (see Appendix 3) are excluded. If during the study, the subject must take a strong inducer of CYP450 3A4, the study drug may continue, but the Medical Monitor should be notified.

Skin and mucous membrane reactions are the most common side effects associated with treatment with retinoids, therefore a subject leaflet describing recommended treatment for the most common mucocutaneous AEs will be distributed to each subject at the initiation of study treatment. These treatments may also be recommended as prophylaxis per Investigator discretion.

5.6.2 Other Restrictions

Male and FOCBP subjects must either commit to true abstinence from heterosexual sex or agree to use two effective methods of birth control during treatment, and for 1 month after treatment has ended. Sexually active FOCBP subjects must already be using two effective methods of birth control 1 month before treatment is to start. Abstinence from heterosexual sex is only acceptable as “true abstinence.” True abstinence occurs when it is in line with the preferred and usual lifestyle of the subject. Periodic abstinence from heterosexual sex (such as calendar, ovulation, symptothermal, post-ovulation methods), the rhythm method, and withdrawal are not acceptable methods of contraception.

Specific risks of the use of retinoids during pregnancy, and the agreement to remain abstinent from heterosexual sex or to use two effective methods of birth control will be clearly defined in the informed consent form. Subjects or legally authorized representatives (eg, parents,

caregivers, or legal guardians) must sign this specific section. Two effective forms of birth control consist of the concurrent use of AT LEAST one highly effective method of birth control as described in Appendix 4.

In the unlikely event of a pregnancy, a female subject must be instructed to stop taking the study drug and immediately inform the Investigator. Pregnancies occurring up to 30 days after the completion of the study drug must also be reported to the Investigator. The Investigator should report all pregnancies within 24 hours to the sponsor. The Investigator should counsel the subject and discuss the risks of continuing with the pregnancy, and the possible effects on the fetus. Monitoring of the subject should continue until conclusion of the pregnancy.

5.7 Subject Withdrawal or Early Termination from Study

Subjects can voluntarily withdraw from the study at any time for any reason. All reasonable effort should be made by the study personnel to determine the reason for withdrawal. Subjects will be considered lost to follow-up if no response is received in spite of repeated attempts to contact them.

Study drug administration for individual subjects can be discontinued by the Investigator if he/she believes the subject's safety is at risk. Additional details regarding study drug dose modification are provided in Section 6.5.

If any subject enrolled in Part D chooses to enroll in another clinical trial, all reasonable efforts should be made by the study personnel to have the subject continue participation in Study PVO-1A-202 until their final EOS visit.

In the event of an early termination or discontinuation of study drug, all reasonable efforts should be made by the study personnel to have the subject complete all study assessments per the Schedule of Assessments for non-flare-up-based treatment (Table 1 and Table 2), and if appropriate, for flare-up-based treatment (Table 3), including those assessments subsequent to early termination or study drug discontinuation.

5.8 Replacement of Subjects

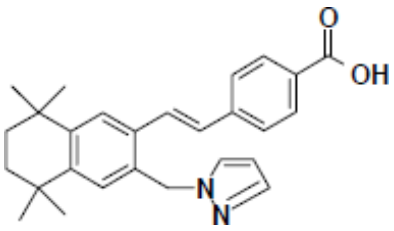
Subjects who drop-out will not be replaced.

6. STUDY DRUG ADMINISTRATION

6.1 Identity of Study Drug

Palovarotene is a white to off-white crystalline powder with the chemical name 4-[(E)-2-(5,5,8,8-tetramethyl-3-pyrazol-1-ylmethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-benzoic acid. Palovarotene is an orally bioavailable RARγ selective agonist. The structure of palovarotene is shown in Figure 1.

Figure 1 Chemical Structure of Palovarotene



6.2 Packaging, Labeling, and Storage

Study drug supplies provided for this study will be manufactured under Good Manufacturing Practices and will be suitable for human use. Palovarotene will be provided in powder-filled opaque hard gelatin capsules using standard USP/EP grade excipients in the following dosage strengths: 10, 5, 4, 3, 2.5, 2, and 1.5 mg (see Section 3.1). Capsules will be packaged in appropriately sized bottles designed for maximum protection.

Study drug will be stored in a secured area at the study site with limited access. All study drug is to be stored at room temperature (not above 30°C/86°F) and protected from light and humidity.

6.3 Randomization and Blinding

This is an open-label study and does not involve randomization or blinding.

6.4 Administration

All subjects will receive non-flare-up-based treatment of 5 mg palovarotene once daily (weight-adjusted doses for skeletally immature subjects). The first day that subjects receive non-flare-up-based treatment will be Non-Flare-Up Day 1. Details for handling, preparing, storing, and discarding study drug will be provided to subjects.

Subjects who began non-flare-up-based treatment during Part B will continue the same visit schedule into Part C, and will receive non-flare-up-based treatment for up to an additional 48 months. Subjects who will start non-flare-up-based treatment during Part C will receive non-flare-up-based treatment for up to 48 months. Subjects who cannot receive non-flare-up-based treatment will only undergo annual assessments (clinical laboratory tests will not be performed). In the event of a flare-up, these subjects will receive flare-up-based treatment and undergo all flare-up-based assessments, including clinical laboratory tests.

Flare-up-based treatment can begin immediately after the Investigator confirms the presence of a flare-up or the presence of a substantial high-risk traumatic event likely to lead to a flare-up. Subjects with normal or non-clinically significant abnormal safety laboratory results observed within 1 month of flare-up-based treatment will not need to have laboratory tests performed at Flare-up Day 1. The Investigator will determine whether subjects with clinically significant abnormal laboratory results in the most recent assessment will need to be re-assessed prior to beginning flare-up-based treatment. The only exception is for pregnancy testing, which must be performed monthly. For subjects receiving flare-up-based treatment, Flare-up Day 1 is defined as the first day that flare-up-based treatment with study drug is administered.

Subjects will report potential flare-up symptoms or traumatic events to site personnel, and if confirmed by the Investigator as associated with a flare-up or, in the case of trauma, likely to lead to a flare-up, subjects will immediately begin flare-up-based treatment with palovarotene 20 mg for 4 weeks (28 days) once daily followed by palovarotene 10 mg for 8 weeks (56 days) once daily (or weight-based equivalent), for a total duration of 12 weeks (84 days). Based on clinical signs and symptoms as determined by the Investigator, treatment may be extended in 4-week intervals while on-treatment with 10 mg palovarotene, and continue until the flare-up resolves and 4-week extension treatment has been completed. Flare-up dosing will be weight-adjusted for skeletally immature (<90%) subjects (Section 3.1). Subjects will be provided with the appropriate dose of study drug to be used to initiate treatment with palovarotene when a flare-up or traumatic event is confirmed by the Investigator. Should a subject experience a new intercurrent flare-up or traumatic event at any time during flare-up-based treatment, the 12-week dosing regimen will restart upon confirmation by the Investigator (ie, 4 weeks of 20 mg palovarotene followed by 8 weeks of 10 mg palovarotene [or weight-based equivalent]).

Once all flare-ups or traumatic events in a cycle have resolved and flare-up-based treatment has been completed, subjects will resume non-flare-up-based treatment with 5 mg palovarotene once daily (weight-adjusted doses for skeletally immature subjects).

The dose of study drug taken each day will be documented in the subject dosing diary.

Many FOP patients experience difficulty swallowing intact capsules or tablets due to ankylosis of the jaw. In order to facilitate drug administration, subjects or caregivers may sprinkle the contents of the capsule onto specific foods as specified in the dosing instructions. Subjects should be instructed to take study drug orally following a full meal at approximately the same time each day and to avoid foods that are known to induce or inhibit the activity of the CYP3A4 enzyme (eg, grapefruit, pomelo, or juices containing these fruits). Due to the potential for dermal absorption of study drug, subjects and caregivers will be instructed to wear protective gloves when handling the study drug capsule.

6.5 Dose Modification

Should a subject experience an AE that is not tolerated, but would not require immediate discontinuation of study drug (eg, skin rash), the subject will be instructed to contact the study site immediately. The Investigator will assess the AE and if appropriate, will instruct the subject to decrease the dose of study drug to the next lower dose as shown in Table 5 (Section 3.1). Dose modification may also be required due to potential bone safety findings as described in the Bone Safety Management Plan (see Section 7.3.3).

If the subject does not have the proper dosage strength in his/her possession, the clinical site will make immediate arrangements to ship the appropriate study drug to the subject. If the subject is already receiving the lowest possible dose, then study drug will be discontinued. The subject should then be followed until resolution or improvement of the AE. Should the AE remain intolerable despite dose reduction, then study drug will be permanently discontinued, and the subject will continue to be followed with all study procedures performed per protocol.

Should a subject experience an AE that requires immediate discontinuation of study drug (eg, acute pancreatitis), then study drug will be discontinued. The Investigator will follow up on all

AEs observed or reported by the subject up to the end of the reporting period or the event stabilizes and follow-up is no longer necessary. In the event the subject required dose de-escalation due to an intolerable side effect for a previous flare-up, then the dose the subject will receive for a subsequent flare-up will be determined by the Investigator and the Medical Monitor.

If there is evidence of partial or complete premature growth plate closure (with or without growth deceleration) study drug may be continued, interrupted, de-escalated, or discontinued. Dose modification decisions will be made by the Investigator upon review of the subject's clinical and radiographic information, and following discussion of the risk/benefit with the subject/parent. The Investigator may also consult with the sponsor and the DMC.

6.6 Study Drug Accountability

The Investigator has the ultimate responsibility for the study drug accountability at the study site. The Investigator or a designated individual (eg, pharmacist or another appropriate person) will maintain records of the study drug's delivery to the study site and to the subject, the inventory at the site (used and unused product containers), the use by each subject, and the return to the sponsor or alternative disposition of unused medication. The study drug must be kept in a locked area that is monitored for temperature at least once per day. Access to study drug will be restricted to authorized study personnel and used only in accordance with the approved protocol. At the conclusion of the study, any remaining study drug supplies will be returned to the sponsor or its designee. The sponsor or its designee will ensure that a final report of study drug accountability is prepared and maintained by the Investigator. The Investigator agrees not to supply or administer study drug to any person except those subjects participating in this study.

6.7 Assessment of Subject Compliance

Compliance will be based on the amount of study drug dispensed to the subject and returned to the site.

7. STUDY PROCEDURES AND ASSESSMENTS

Under Amendment 7 and subsequent amendments, subjects with open epiphyseal growth plates will undergo knee and hand/wrist radiographs (AP view) at the clinical site every 6 months. Additional knee and hand/wrist radiograph assessments will also be performed every 3 months (±2 weeks) in skeletally immature subjects who (1) received flare up dosing in the period of time since their last assessment; and (2) had not achieved 100% skeletal maturity on their last assessment. These radiographic assessments will not be performed remotely unless the Investigator determines they can be performed at a local medical facility. A description of the knee and hand/wrist radiograph assessments is provided in Section 7.3.2.

7.1 Screening, Recruitment, and Informed Consent

Once the PVO-1A-202 Protocol Amendment 8 is approved at the clinical site, subjects currently enrolled in the study will be contacted, informed about the Amendment 8 changes, and given the opportunity to enroll under this amendment.

Subjects who began non-flare-up-based treatment during Part B will continue the same visit schedule into Part C, and will receive non-flare-up-based treatment for up to an additional 48 months. Subjects who started non-flare-up-based treatment during Part C will receive non-flare-up-based treatment for up to 48 months.

Part D was added for skeletally immature subjects who stopped taking study drug for any reason before completion of Part A/B/C. Part D includes yearly visits for up to a 2-year follow-up period following last dose. Maximum length of study is 72 months. No dosing will occur during Part D.

Due to the burden of travel, subjects may undergo an Institutional Review Board (IRB)-approved remote consent/assent process that will include a discussion with the site representative of the study requirements and risks. Signed consents will be emailed or faxed between site and subjects. Potential subjects/parents wishing to participate must sign the informed consent/assent per local requirements prior to undergoing any study-related procedures. Remote consent/assent will allow the screening process to begin prior to the initial site visit, should the Investigator deem it relevant.

As per the global addendum (dated 15Apr2020) to Study PVO-1A-202 Amendment 7, Investigators, in consultation with their site IRB/IEC, are required to inform subjects of the temporary changes (during the COVID-19 global pandemic) to the study conduct and monitoring plans that could impact them and their willingness to continue participation in the trial. The method of communication to subjects (e.g., email, phone call, information letter) and documentation of subject/caregiver acknowledgement is to be performed and documented in accordance with local regulations/EC requests and guidance. All contacts with subjects must be filed in the source records.

7.2 Safety Assessments

Subjects will follow all procedures and undergo all assessments as outlined in the Schedule of Assessments in Table 1, Table 2, Table 3, and Table 4, as appropriate, unless a subject is unable to undergo a procedure due to safety concerns (eg, risk of flare-up) or physical limitation (pain or locked position).

7.2.1 Medical History and Flare-Up Assessment

There will be no new subjects in Part C and a repeat medical history is not necessary.

For subjects receiving flare-up-based treatment, the flare-up assessment will include subject-reported current flare-up location, symptoms, and probable causes, documented on Flare-up Day 1. This will be recorded for each flare-up and intercurrent flare-up within a cycle.

7.2.2 Physical Examination

For subjects from Part B continuing non-flare-up-based treatment into Part C, a physical examination of all body systems is to be documented at Months 12, 24, 36, 48, 60, and 72.

For subjects from Part B starting non-flare-up-based treatment during Part C, a physical examination of all body systems is to be documented at Part C Screening and at Months 6, 12, 24, 36, and 48.

For subjects in Part D, a physical examination of all body systems is to be documented at Year 1 and Year 2 post last dose of study treatment.

The physical examination will monitor for objective changes and for possible adverse reactions associated with therapy. Any post-baseline abnormal physical examination findings assessed as clinically significant will be recorded as AEs.

7.2.3 Body Weight and Linear Growth Assessments

For subjects from Part B continuing non-flare-up-based treatment into Part C, body weight will be documented every 3 months (Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51,
54, 57, 60, 63, 66, 69 and 72).

For subjects from Part B starting non-flare-up-based treatment during Part C, body weight will be documented at Part C Screening and every 3 months (Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33,
36, 39, 42, 45 and 48).

For subjects receiving flare-up-based treatment, body weight will be recorded at Flare-up Cycle Safety Day 1 and every 12 weeks thereafter during safety assessments until treatment of the last flare-up or traumatic event in the flare-up cycle is completed.

Subjects from Part B continuing non-flare-up-based treatment into Part C with open epiphyseal growth plates at the most recent assessment will have linear growth assessments (in triplicate) by stadiometer and knee height measurements (in triplicate) at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72.

Subjects from Part B starting non-flare-up-based treatment during Part C that are under the age of 18 years and who enrolled with open epiphyseal growth plates at the most recent assessment will have linear growth assessments (in triplicate) by stadiometer and knee height measurements (in triplicate) at Screening. Subjects with open epiphyseal growth plates will also be evaluated at Months 6, 12, 18, 24, 30, 36, 42, and 48.

For subjects in Part D, body weight will be documented at Year 1 and Year 2 post last dose of study treatment. Subjects in Part D will have linear growth assessments (in triplicate) by stadiometer and knee height measurements (in triplicate) at Year 1 and Year 2 post last dose of study treatment.

Once a subject is 18 years old, triplicate linear growth and knee height assessments will no longer be required. In Part D subjects will stop participation once they reach 18 years of age.

Linear growth measurements will be performed by trained and qualified study personnel. The stadiometric measurement instructions will include practices that reduce measurement error including calibration of equipment, proper subject positioning, and measurement capture. The same examiner should be used whenever possible to standardize the performance of procedures and minimize the inter-examiner variability. Measurement of knee height will also be standardized.

7.2.4 Vital Signs

Vital signs (temperature, respiratory rate, blood pressure, and heart rate) will be assessed for all subjects.

For subjects from Part B continuing non-flare-up-based treatment into Part C, vital signs (temperature, respiratory rate, blood pressure, and heart rate) will be assessed every 3 months (Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, and 72).

For subjects from Part B starting non-flare-up-based treatment during Part C, vital signs will be assessed at Part C Screening and every 3 months (Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45 and 48).

For subjects receiving flare-up-based treatment, vital signs will be assessed at Flare-up Cycle Safety Day 1 and every 12 weeks thereafter during safety assessments until treatment of the last flare-up or traumatic event in the flare-up cycle is completed.

For subjects in Part D, vital signs will be assessed at Year 1 and Year 2 post last dose of study treatment.

Blood pressure will preferably be measured on the same arm at the same position and with the same instrument at each visit. If a subject is unable to have blood pressure performed on the same arm, the alternate arm or leg will be used. Blood pressure and heart rate will be obtained following a resting period of at least 5 minutes. Automatic blood pressure devices are not allowed due to the risk of over-inflation and potential tissue injury.

7.2.5 Electrocardiogram

For subjects from Part B continuing non-flare-up-based treatment into Part C, a 12-lead electrocardiogram (ECG) will be performed at Months 12, 24, 36, 48, 60, and 72.

For subjects from Part B starting non-flare-up-based treatment during Part C, an ECG will be performed at Part C Screening and at Months 6, 12, 24, 36 and 48.

To ensure consistent generation and interpretation of results, a central ECG laboratory will perform the analysis using standardized procedures. The Investigator will be provided ECG interpretations from the central ECG laboratory, and will review and assess all abnormal results for clinical significance. Any post-baseline ECG abnormalities assessed as clinically significant will be recorded as AEs.

7.2.6 Clinical Laboratory Tests

Blood and urine samples will be collected for hematology, biochemistry (includes lipids), and urinalysis testing.

For subjects from Part B continuing non-flare-up-based treatment into Part C, blood and urine samples will be collected every 6 months (Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72).

For subjects from Part B starting non-flare-up-based treatment during Part C, blood and urine samples will be collected at Part C Screening and every 6 months (Months 6, 12, 18, 24, 30, 36, 42 and 48).

For subjects receiving flare-up-based treatment, blood and urine samples will be collected at Flare-up Cycle Safety Day 1 and every 12 weeks thereafter during safety assessments until treatment of the last flare-up or traumatic event in the flare-up cycle is completed. Subjects with normal or non-clinically significant abnormal safety laboratory results observed within 1 month of flare-up-based treatment will not need to have laboratory tests performed at Flare-up Day 1. The Investigator will determine whether subjects with clinically significant abnormal laboratory results in the most recent assessment will need to be re-assessed prior to beginning flare-up-based treatment. The only exception is for pregnancy testing, which must be performed monthly during non-flare-up-based treatment; and at the start of each flare-up cycle and every 4 weeks thereafter until treatment of the last flare-up or traumatic event in the flare-up cycle is completed. However, if a pregnancy test was performed within 4 weeks prior to the start of a flare-up or traumatic event, treatment of the flare-up or traumatic event will not be delayed pending repeat pregnancy testing.

Blood and urine samples may be collected remotely (eg, at the subject's home) by qualified study personnel or at a local medical facility according to standard operating procedures and applicable regulations. When possible, samples will be collected under fasting conditions. Samples will be packaged and shipped to the designated laboratory for testing. To ensure consistent generation and interpretation of results, a central testing laboratory will perform the analysis of clinical laboratory samples. If urinalysis results are abnormal, a microscopic evaluation will be completed. If results are needed promptly (eg, Screening for eligibility), analysis of samples can be completed at a local, qualified laboratory.

The total blood volume drawn from a subject from Part B continuing non-flare-up-based treatment into Part C over the course of the entire study (up to 72 months) will range from approximately 60 mL (in the case of no flare-ups) to 170 mL (in the case of two expected flare-ups treated per year, or a total of 12 flare-ups treated during the entire study). The total blood volume drawn from a subject from Part B starting non-flare-up-based treatment during Part C over the course of the entire study (up to 48 months) will range from approximately 42 mL (in the case of no flare-ups) to 120 mL (in the case of two expected flare-ups treated per year, or a total of eight flare-ups treated during the entire study). In the event that the total drawn blood volume exceeds the limits established by the clinical site for pediatric subjects, then priority will be given to the key safety laboratory tests, as outlined in the clinical safety laboratory manual. This will ensure that the total blood volume drawn is within the established limits.

The Investigator will be provided all laboratory results and will review and assess out-of-range findings for clinical significance and to determine if any laboratory value meets the safety monitoring/stopping rules outlined in the protocol (Section 7.3, Special Safety Assessments). Any post-baseline abnormal laboratory value assessed as clinically significant will be recorded as an AE. It is recognized that performing phlebotomy in subjects with FOP is very challenging due to their multiple ankyloses and the potential to cause injury resulting in a flare-up following multiple attempts. The Investigator will be notified by the home clinician, the subject/caregiver, the central laboratory, or the local laboratory facility about any protocol-specified safety

laboratory test that could not be obtained despite at least two attempts. Should this occur, or for those samples that were drawn but were not usable (eg, quantity not sufficient, clotted, sample lost, etc.), the Investigator will assess the subject's condition and determine whether repeated attempts should be made to obtain the missing laboratory data for that time point, or reassessed at the next scheduled time point based on the subject's current clinical status (eg, AEs, vital signs) and previous laboratory measures. Every reasonable attempt should be made to adhere to the safety assessments specified in the protocol. The Investigator/designee should discuss with the home nursing team, subject, laboratory, and/or phlebotomy team, as applicable, to determine why assessments were not able to be performed successfully, or are missing, delayed, or unreportable and to identify methods to mitigate recurrence.

If a local laboratory is utilized, the investigative site should notify the study team if the local laboratory cannot test all the analytes listed in Table 6. If the total thyroxine (Total T4), free T4, uric acid, gamma glutamyl transferase, inorganic phosphorous, very low-density lipoprotein, or globulin parameters are not available through the local laboratory, and alternative arrangements cannot be made, testing of these analytes may be omitted provided other subject-assessments of thyroid function (ie, thyroid-stimulating hormone), lipid metabolism (ie, triglycerides, low-density lipoprotein, high-density lipoprotein, and total cholesterol), and protein metabolism (ie, total protein and albumin) are available and confirmed to be stable as per the Investigator. Alternative arrangements to test the listed analytes are to be made if the Investigator, Medical Monitor, or sponsor determines that they have the potential to impact subject safety. In the event the local laboratory is unable to test any other analytes, they may be omitted in exceptional circumstances after consultation with the sponsor. Such exceptions will not be applied to any of the key safety analytes, as outlined below and in the clinical safety laboratory manual.

For subjects with two or more consecutive missing assessments of key safety laboratory analytes, including triglycerides, ALT, AST, bilirubin, lipase, and amylase (as outlined in Section 7.3, Special Safety Assessments), blood collection for evaluation of missing analytes should be performed as soon as possible. If such analytes have not been evaluated over a prolonged period of time (>6 months during chronic treatment or >8 weeks during flare-up treatment), a successful repeat assessment should be performed within 1 month. If key safety laboratory tests cannot be evaluated within 1 month, the subject should be discussed with the Medical Monitor and the EC/IRB, as necessary. If the subject is unable to have venous specimens collected, use of microliter collection techniques and capillary specimens, where available, may be utilized to assess subject safety. Local laboratory results should be promptly documented in the appropriate eCRF.

Table 6 presents the clinical laboratory parameters that will be assessed in this study.

Table 6. Clinical Laboratory Parameters

Biochemistry:	
Sodium	Globulin
Potassium	Alkaline phosphatase (ALP)
Chloride	Aspartate aminotransferase (AST)
Bicarbonate	Alanine aminotransferase (ALT)
Blood urea nitrogen	Gamma glutamyl transferase (GGT)
Creatinine	Uric acid

Calcium	Total thyroxine (T4)
Inorganic phosphorous	Free T4
Glucose	Thyroid-stimulating hormone
Total bilirubin	Amylase
Total proteins	Lipase
Albumin	
Lipid Profile	
Triglycerides	High-density lipoprotein (HDL) Low-density lipoprotein (LDL)
Total cholesterol	Very low-density lipoprotein (VLDL)
Hematology:	
Hemoglobin	Platelets
Hematocrit	White blood cell count (including differentials)
Red blood cell count	Neutrophils
Packed cell volume	Lymphocytes
Mean corpuscular volume	Monocytes
Mean corpuscular hemoglobin	Eosinophils
Mean corpuscular hemoglobin concentration	Basophils
Urinalysis[1]:	
pH	Blood (free hemoglobin)
Protein	Nitrite
Glucose	Urobilinogen
Ketones	Specific gravity
Bilirubin	Color & appearance

[1] If results are abnormal, then a microscopic evaluation will be completed.

7.2.7 Pregnancy Testing

For female subjects of child bearing potential receiving palovarotene, a blood or urine pregnancy test (with sensitivity of at least 50 mIU/mL) will be conducted monthly in Part A, B and C. If the Screening test is positive, the subject will not be eligible for study participation. Any positive pregnancy test during study participation will result in immediate discontinuation of study drug. If a subject becomes pregnant during the study, she will be followed throughout her pregnancy and the health status of the baby will be verified.

Subjects will be reassessed for changes in child bearing status (females only) and pregnancy prevention measures (females and males) every 3 months.

7.2.8 Adverse Events

Adverse event monitoring will be conducted throughout the study for all subjects. Adverse events will be assessed at every site and remote visit during both non-flare-up-based and flare-up-based treatment. The AE reporting period begins at the time of informed consent and continues through study completion. The SAE (including deaths) reporting period begins at the time of informed consent and continues through 30 days after study completion.

The Investigator will follow-up on all AEs observed or reported by the subject up to the end of the reporting period or until the events stabilize and follow-up is no longer necessary. The Investigator will follow-up on SAEs until they are considered resolved or outcome is known. Limb/joint AEs reported by subjects with open epiphyses will be evaluated by clinical and radiographic assessments deemed appropriate by the Investigator.

Definitions, documentation, and reporting of AEs are described in Section 9.1. Serious adverse

events must be reported within 24 hours as described in Section 9.1.8.

7.2.9 Concomitant Medications

Concomitant medications will be assessed at every site and remote visit during both non-flare-up-based, flare-up-based treatment and in Part D.

See Section 5.6 for restrictions for concomitant medications.

7.3 Special Safety Assessments

In light of the established safety profile of the currently marketed oral systemic retinoids and hypothesized potential concerns, clinical and laboratory monitoring of selected AEs and laboratory abnormalities in subjects in this study is indicated. The following potential safety issues will be monitored in the study.

7.3.1 Columbia-Suicide Severity Rating Scale

In accordance with the Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials, 2012, all subjects 8 years of age and older who are receiving palovarotene will be assessed for suicidal ideation and behavior every 3 months using the age-appropriate C-SSRS and at all visits during the Flare-up Cycle Safety Assessments (see Appendix 5A). The adult form will be used for subjects 12 years and older and the pediatric form will be used for subjects 8 to 11 years old. Study personnel administering the questionnaire will receive formal training to ensure accuracy and consistency in application of the instrument.

For subjects from Part B continuing non-flare-up-based treatment into Part C, assessment using the C-SSRS will occur every 3 months (Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45,
48, 51, 54, 57, 60, 63, 66, 69 and 72).

For subjects from Part B starting non-flare-up-based treatment during Part C, assessment using the C-SSRS will occur at Part C Screening and every 3 months (Months 3, 6, 9, 12, 15, 18, 21, 24,
27, 30, 33, 36, 39, 42, 45 and 48). Any subject reporting a type 4 or 5 suicidal ideation or any suicidal behavior within 1 month prior to Part C Screening will not be eligible to receive study drug.

Any subject experiencing a type 4 or 5 suicidal ideation or any suicidal behavior while receiving study drug will have study drug immediately withheld. All such subjects will be referred by the Investigator to a mental health professional for evaluation and counseling as appropriate.

7.3.2 Knee and Hand/Wrist Radiographs

Due to the potential for palovarotene to cause adverse effects on long-bone growth, all subjects at the time of enrollment into Study PVO-1A-202 with open epiphyseal growth plates at Screening had knee (AP view) and hand/wrist (PA view) radiographs.

For subjects from Part B continuing non-flare-up-based treatment into Part C with open

epiphyseal growth plates at the most recent assessment, knee (AP view, preferable on the left side) and hand/wrist (PA view, preferable on the left side) radiographs will be performed at the clinical site at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72.

For subjects from Part B starting non-flare-up-based treatment during Part C with open epiphyseal growth plates at the most recent assessment, knee (AP view, preferable on the left side) and hand/wrist (PA view, preferable on the left side) radiographs will be performed at Part C Screening. Subjects for whom radiographs were performed within the last 3 months will not need to repeat radiographs at Screening. Subjects with open epiphyseal growth plates at this assessment will also be evaluated at Months 6, 12, 18, 24, 30, 36, 42 and 48 at the clinical site.

Subjects who are skeletally immature at the time of study drug discontinuation and entering Part D (Y1 and Y2 post last dose of study treatment) will have follow-up knee (AP view) and hand/wrist radiographs (PA view, preferably on the left side) every year.

Additional knee and hand/wrist radiograph assessments will also be performed every 3 months (±2 weeks) in skeletally immature subjects who (1) received flare-up dosing in the period of time since their last assessment; and (2) had not achieved 100% skeletal maturity on their last assessment. The 3-month radiographic assessments will be performed at the clinical site unless the Investigator determines they can be performed at a local medical facility.

Once a subject has achieved 100% skeletal maturity (defined as closure of all assessed growth plates) as determined by the knee and hand/wrist radiographs, further radiographs will no longer be necessary. If 100% skeletal maturity is not achieved at both locations, then only the location that is still maturing would need to be monitored.

All radiographs will be read by a central imaging laboratory to ensure consistent assessment of the radiographs. The Investigator will be provided all results and will review and assess abnormal results for clinical significance. Any post-baseline abnormal results assessed as clinically significant will be recorded as an AE. Limb/joint AEs in these subjects will be evaluated by clinical and radiographic assessments deemed appropriate by the Investigator.

7.3.3 Bone Safety Management Plan

To enhance subject safety monitoring, a Bone Safety Management Plan has been developed to supplement per-protocol safety monitoring. Of note, in addition to the knee and hand/wrist radiographs described in Section 7.3.2, WBCT scans acquired from subjects under the age of 18 years will be reviewed in a blinded fashion by two independent radiologists to assess the growth plate morphology of bilateral hands/wrists and knees. Reviews of WBCT scans from all subjects regardless of age will also monitor hip morphology for signs of avascular necrosis (AVN), warranted due to the association of corticosteroids with AVN and the presence of AVN of the femoral head in wild-type rats treated with high dose palovarotene. WBCT scans will be reviewed for spinal health including fracture assessment.

The Bone Safety Management Plan will be provided to each clinical site, must be signed by the clinical site Investigator, and will be appended to the Data Monitoring Committee Charter.

Safety findings of these bone images may trigger additional follow-up images and/or dose

modification, as discussed in the Bone Safety Management Plan.

7.3.4 Mucocutaneous Effects (Skin and Mucous Membrane Toxicity Profile)

At every study visit during palovarotene treatment, subjects will be assessed for AEs, including mucocutaneous AEs (eg, dry skin, itching, redness, rash, flaking and peeling of the skin, dry lips, chapped lips, cheilitis, dry eyes, and conjunctivitis). In addition to the severity assessments of mild, moderate, and severe (Section 9.1.4), all mucocutaneous AEs will be rated according to the most recent version of the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03, 14 June 2010 (see Appendix 6). In the event of a subject-report of a mucocutaneous AE, dermatologic photographs may be taken for review by a dermatologist. Permission to obtain dermatologic photographs will be requested in the informed consent/assent document(s).

If any mucocutaneous effects are observed, symptomatic therapy (eg, analgesics, skin emollients, lip moisturizers, artificial tears, or other helpful treatments) may be administered if deemed necessary by the Investigator. In addition, the Investigator may recommend prophylactic use of these therapies at the start of palovarotene treatment. Dose reduction as described in Section 6.5 is recommended for intolerable mucocutaneous effects that would otherwise result in study drug discontinuation. If a subject is already receiving the lowest possible dose, then study drug will be discontinued.

Although palovarotene has not been proven to be phototoxic, precautionary measures for phototoxicity are recommended for subjects who are receiving palovarotene. Excessive exposure to sun should be avoided and protection from sunlight when it cannot be avoided (use of sunscreens, protective clothing, and use of sunglasses).

7.3.5 Serum Lipids

A complete lipid profile will be performed as part of the biochemistry testing (see Section 7.2.6) for all subjects in Part C.

If, during the palovarotene treatment, serum triglyceride levels are ≥800 mg/dL, the study drug should be immediately discontinued, with follow-up assessments performed per protocol.

7.3.6 Liver Enzymes

Liver enzymes will be monitored as part of the biochemistry testing (see Section 7.2.6) for all subjects in Part C.

During palovarotene treatment, drug therapy should be discontinued if any of the following occur:

- AST or ALT ≥5× ULN
- Jaundice is observed
- ALT >3× ULN if accompanied with any bilirubin increase >2× ULN, unexplained abdominal pain, malaise, nausea, and/or vomiting.

Liver toxicity evaluation will follow the Guidance for Industry *Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009)*.

7.3.7 Lipase/Amylase

Amylase and lipase will be monitored as part of the biochemistry testing (see Section 7.2.6) for all subjects in Part C.

Lipase and/or amylase increases during the course of the study should be further evaluated to exclude the occurrence of pancreatitis. With symptoms of pancreatitis or with persistent elevations that cannot be explained, the study drug should be discontinued as per the Investigator's judgment, with follow-up assessments performed per protocol.

7.3.8 Central Nervous System

Retinoid use has been associated with a number of cases of benign intracranial hypertension (also known as pseudotumor cerebri), some of which involved concomitant use of tetracyclines.

The cases of benign intracranial hypertension were manifested with symptoms and signs such as severe headache, nausea and vomiting, and visual disturbances, and may be associated with papilledema. Headache generally occurs within 3 to 4 hours of starting therapy and remits spontaneously.

However, headache of unusual characteristics (eg, severity, location, pattern) to the subject should lead to contacting the Investigator. In case of such headache, it is at the discretion of the Investigator to refer subjects receiving palovarotene treatment for neurological and/or ophthalmological examination to rule out benign intracranial hypertension. Headache will be assessed using the standard AE severity scale (see Section 9.1).

7.3.9 Hearing and Visual Disturbances

Impaired hearing has been reported in subjects taking retinoids. The Investigator should refer subjects receiving palovarotene treatment who experience tinnitus or hearing impairment to specialized care for further evaluation. The subject with a confirmed diagnosis of hearing impairment (felt to be related to the study drug) will be discontinued from treatment.

An ophthalmological examination should be carried out in all subjects receiving palovarotene treatment who are experiencing unexplained visual difficulties.

Corneal opacities have occurred in subjects receiving retinoids and were reversible upon drug discontinuation. Subjects receiving palovarotene treatment with corneal opacities should be assessed by an ophthalmologist.

Decreased night vision has been reported during retinoid therapy. The onset in some subjects can be sudden; therefore, subjects receiving palovarotene treatment should be informed and warned to be cautious when driving or operating vehicles at night.

7.3.10 Teratogenicity

Palovarotene must not be used by female subjects who are or may become pregnant. There is an

extremely high risk that severe birth defects will result if pregnancy occurs while taking palovarotene in any amount, even for short periods of time. Potentially any fetus exposed during pregnancy can be affected. There are no accurate means of determining whether an exposed fetus has been affected.

Birth defects that have been documented following exposure to retinoids include abnormalities of the face, eyes, ears, skull, central nervous system, cardiovascular system, and thymus and parathyroid glands. Cases of IQ scores less than 85 with or without other abnormalities have been reported. There is an increased risk of spontaneous abortion, and premature births have been reported.

Documented external abnormalities with other retinoids include: skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia); facial dysmorphia; and cleft palate. Documented internal abnormalities with other retinoids include: central nervous system abnormalities (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit); cardiovascular abnormalities; thymus gland abnormality; and parathyroid hormone deficiency. In some cases, death has occurred with other retinoids with certain of the abnormalities previously noted.

7.4 Efficacy Assessments

Subjects who began non-flare-up-based treatment during Part B will continue the same visit schedule into Part C, and will receive non-flare-up-based treatment for up to an additional 48 months. Therefore, these subjects may undergo non-flare-up-based treatment for up to 72 months over the entire study. Subjects who will start non-flare-up-based treatment during Part C will receive non-flare-up-based treatment for up to 48 months.

7.4.1 Low-Dose Whole Body Computed Tomography

For subjects from Part B continuing non-flare-up-based treatment into Part C, a low-dose WBCT scan (excluding head) will be performed during annual site visits at Months 12, 24, 36, 48, 60 and 72.

For subjects from Part B starting non-flare-up-based treatment during Part C, a low-dose WBCT scan (excluding head) will be performed at Part C Screening and during annual site visits at Months 12, 24, 36 and 48.

For subjects in Part D, a low-dose WBCT scan (excluding head) will be performed during annual site visits at Y1 and Y2 post last dose of study treatment.

Interpretation of the CT scan will document the absence or presence of HO across various body regions, volume of total body HO, and presence and volume of new HO at follow-up visits. All images will be interpreted by a central imaging core laboratory using standardized procedures detailed in an imaging charter.

7.4.2 FOP-Physical Function Questionnaire

On clinic days when multiple assessments are to be performed, the age-appropriate FOP-PFQ and the age-appropriate PROMIS Global Health Scale should be completed (in that order) by the

subject/parent before any other procedures are completed on those visit days.

For subjects from Part B continuing non-flare-up-based treatment into Part C, age-appropriate forms of the FOP-PFQ will be administered every 6 months (Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72).

For subjects from Part B starting non-flare-up-based treatment during Part C, age-appropriate forms of the FOP-PFQ will be administered at Part C Screening and every 6 months (Months 6, 12, 18, 24, 30, 36, 42 and 48).

To evaluate the effect of palovarotene on physical function, age-appropriate forms of the FOP-PFQ will be administered. The adult form of the FOP-PFQ will be completed by subjects 15 years of age and older (see Appendix 2A). Two Pediatric FOP-PFQ (FOP-PFQ-P) forms will be utilized in subjects under the age of 15 years: a self-completed form developed for 8- to 14-year-olds and a proxy-completed form developed for 5- to 14-year-olds (see Appendix 2B and Appendix 2C, respectively).

Study personnel will be trained on the administration of the instruments and subjects (and parents of subjects under the age of 15 years) will be provided specific instructions on how to complete the instrument independently.

7.4.3 PROMIS Global Health Scale

For subjects from Part B continuing non-flare-up-based treatment into Part C, age-appropriate forms of the PROMIS Global Health Scale will be administered every 6 months (Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72).

For subjects from Part B starting non-flare-up-based treatment during Part C, age-appropriate forms of the PROMIS Global Health Scale will be administered at Part C Screening and every 6 months (Months 6, 12, 18, 24, 30, 36, 42 and 48).

To evaluate the effect of palovarotene on physical and mental health in subjects ≥15 years of age and mental health in subjects <15 years of age, age-appropriate forms of the PROMIS Global Health Scales will be administered. The adult form of the PROMIS Global Health Scale will be administered to subjects 15 years of age and older (see Appendix 7A). Two PROMIS Pediatric Global Health Scale forms will be utilized in subjects under the age of 15 years: a self-completed form developed for 8- to 14-year-olds and a proxy-completed form developed for subjects under the age of 15 years (see Appendix 7B and Appendix 7C, respectively).

Study personnel will be trained on the administration of the instruments and subjects (and parents of subjects under the age of 15 years) will be provided specific instructions on how to complete the instrument independently.

7.4.4 Cumulative Analogue Joint Involvement Scale

For subjects from Part B continuing non-flare-up-based treatment into Part C, CAJIS will be administered every 6 months (Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72).

For subjects from Part B starting non-flare-up-based treatment during Part C, CAJIS will be

administered at Part C Screening and every 6 months (Months 6, 12, 18, 24, 30, 36, 42 and 48).

Range of motion will be assessed by the Investigator using CAJIS (see Appendix 1). The CAJIS should be assessed by the same Investigator at each time point. The CAJIS assessment may be performed remotely or by videoconferencing.

7.5 Pharmacokinetics

The PK of palovarotene dosing will be assessed in all subjects during non-flare-up and flare-up-based treatments.

During non-flare-up palovarotene treatment, PK blood samples will be collected at the first 3-month safety assessment. If blood samples cannot be or were not obtained during the first 3-month safety assessment, or if the subject is on flare-up-based treatment, then the non-flare-up treatment PK blood sample can be obtained during any subsequent 3-month safety visit.

Pharmacokinetics of palovarotene dosing will also be assessed twice during flare-up-based treatment: once during the 20-mg regimen at any time between Study Days 4 to 28, and once during the 10-mg regimen at any time between Study Days 32 to 84, for the first treated flare-up only. If this is not possible for the first treated flare-up, PK blood samples can be obtained during any subsequent flare-up dosing cycle.

Pharmacokinetic blood samples will be collected at pre-dose and 3, 6, 10, and 24 hours post-dose. Subjects who underwent a PK assessment for flare-up-based treatment under PVO-1A-202 Protocol Amendment 3 will not have flare-up PK assessed again. However, these subjects will require a non-flare-up treatment PK assessed at a 3-month safety visit.

The determination of palovarotene plasma concentrations will be performed using a validated LC-MS/MS method, and exploration of any relationships with palovarotene exposure will be performed. The time of sample collection as it relates to the time of dosing on the PK blood sampling days will be recorded.

Detailed instructions for collection, storage, labeling, and shipment of all samples will be provided in the Laboratory Manual.

7.6 Data Monitoring Committee

A Data Monitoring Committee (DMC) will review safety information periodically and on an ad hoc basis as outlined in the DMC Charter, which is maintained separately from the study protocol. The DMC can recommend temporary or permanent stopping of the study at any time if there are significant safety concerns. The DMC Charter includes recommended safety stopping rules. The DMC will also review the results of pre-planned interim analyses (see Section 8.7). In addition to the Investigator, the DMC will make recommendations for potential dose modifications in the event of treatment-related adverse bone effects as described in the Bone Safety Management Plan.

The DMC will include members with relevant clinical expertise, including a good understanding of the safety of retinoids. The methodology and the operating procedures for the safety reviews

will be developed by the Chairperson in collaboration with the sponsor and will be documented in the DMC Charter.

7.7 Temporary Measures (Procedures Related to COVID-19 Pandemic)

Procedures related to COVID-19 pandemic

Temporary measures put in place for the conduct of Study PVO-1A-202 during the COVID-19 pandemic and until such time as the situation resolves, at which point the protocol assessments will return to those specified. Investigators will determine the feasibility of dosing on a subject-by-subject basis, depending on the ability to conduct safety monitoring and providing subjects an adequate supply of study drug, in accordance with local requirements. These recommendations will remain in place for as long as the COVID-19 pandemic warnings are in effect in territories participating in the trial. The timing of when the pandemic is declared over may vary on a country-by-country basis as well as between sites in the same country, and as such the temporary measures may remain in place for differing periods of time per country/site.

The study visits and assessments to be conducted during this period are listed below:

Study Visits and Assessments

1) **For subjects aged under 14 years that are still participating in the study but not currently receiving palovarotene treatment as per the global partial clinical hold or for any other reason,** they will complete Part C EOT/EOS and be invited to participate in Part D and undergo assessments outlined in Table 4.

2) **For subjects aged 14 years and older who are being considered for re-starting palovarotene treatment but have NOT yet re-started,** the following minimum assessments are to be done via remote monitoring (video conference/phone calls) by the Investigator (or delegated study staff):

a. Chronic visits every 3-6 months (per protocol): assess for childbearing status (females only) and pregnancy prevention measures, CAJIS, ConMeds, adverse events, review subject diary, PROMIS Global Health Scale*, FOP-PFQ* (*assessments that can occur remotely but not required as these are not essential to ensure subjects' safety)
b. For females of childbearing status: if pregnancy testing did not continue monthly per protocol post the study drug interruption then at a minimum a self-administered urine pregnancy test is to be done within 4 weeks before re-starting palovarotene treatment.
c. All subjects should have laboratory assessments (hematology, biochemistry, urinalysis) within 4 weeks before re-starting palovarotene treatment.
d. All subjects who were skeletally immature at the last assessment will have a hand-wrist and knee radiographs within 12 weeks before re-starting palovarotene treatment. For on-treatment subjects who have not reached at least 90% skeletal maturity radiograph assessments should continue per protocol either on site or remotely

Site staff will also assess the subject's ability to restart remotely.

3) **For subjects 14 years and over that plan to reinitiate dosing, once dosing is reinitiated following the required approvals for restart (Ethics Committee and Competent Authority),** the following minimum assessments that cannot be performed via remote monitoring must be performed either at the clinical site, at the subject's home (by Symphony nursing) or at a local medical facility in order for the Investigator to adequately monitor the safety of subjects:

a. Via remote monitoring (telephone or video conferencing) by Investigator (or delegated study staff):
    i. Chronic visits (per protocol schedule every 3 and/or 6 months): C-SSRS, assess for childbearing status (females only) and pregnancy prevention measures, CAJIS, ConMeds, adverse events, PROMIS Global Health Scale*, FOP PFQ* (*assessments that can occur remotely but are not required as these are not essential to ensure subjects' safety), study drug dispensing
    ii. Flare up visits (per protocol schedule): C-SSRS, ConMeds, adverse events, study drug dispensing
b. Via home visit by Symphony nursing/local assessment
    i. Chronic visits per protocol schedule (every 3 and/or every 6 months): body weight, vital signs, hematology, biochemistry, urinalysis, self-administered pregnancy test (monthly), ConMeds, adverse events, review subject diary
    ii. Flare up visits (per protocol schedule): vital signs, body weight, hematology, biochemistry, urinalysis, self-administered pregnancy testing, ConMeds, adverse events, review subject diary

4) **Based on the known safety profile of palovarotene to date in FOP patients, the following assessments can be postponed as determined by the Sponsor and individual site Investigators, as they do not constitute assessments where a safety concern has been raised.** The below assessments were also deemed acceptable to postpone by the DMC chair.

a. To date low dose whole-body CT has not indicated a safety concern of avascular necrosis of the hip. Any concerns for avascular necrosis of the hip based on clinical assessment should be followed up;
b. For subjects who have reached at least 90% skeletal maturity radiograph assessments may be postponed given the low risk of early growth plate closure as well as growth plate abnormalities;
c. Linear height and knee height (Subjects 14 years and older are at or near adult height indicated by skeletal maturity of at least 90%);
d. ECG (FOP patients can have ECG abnormalities, ECG changes noted in subjects on Palovarotene were similar to those seen in the untreated subjects in the Natural History Study. Clinical concerns of abnormal ECG findings should continue to be followed);
e. Hearing evaluation (As a class, retinoids can cause abnormal hearing. Evaluation should be performed if there is clinical concern);
f. Physical exam (Palovarotene has been shown to cause retinoid skin reactions which can be assessed remotely)

Individual subjects may require assessments if there is a clinical concern as identified by the Investigator. Protocol deviations that have an impact on subject safety should be notified immediately to CRO/Sponsor as it may necessitate an urgent safety measure notification to competent authorities and ethics committees in some countries.

5) End of Treatment/End of Study Assessments:

a. The following assessments should be performed via remote monitoring (telephone or video conferencing) by Investigator (or delegated study staff):
    i. C-SSRS, assess for childbearing status (females only) and pregnancy prevention measures, CAJIS, Con-Meds, adverse events, PROMIS Global Health Scale, FOP PFQ
b. The following assessments should be performed at the subject's home (by Symphony nursing) or at a local medical facility: Body weight, vital signs, hematology, biochemistry, urinalysis, pregnancy test (monthly), ConMeds, adverse events, review subject diary

6) **Once on-site visits resume, the following assessments should be performed on site as well as any assessment that was not obtained via remote monitoring or Symphony nurse:**

a. X-rays, Whole-Body CT, Linear and Knee Height, Physical Exam, ECG.

7) **Informed Consent/Subject Communication:** In consultation with their site IRB/EC, Investigators are required to inform subjects of the temporary changes (during the COVID-19 global pandemic) to the study conduct and monitoring plans that could impact them and their willingness to continue participation in the trial. The method of communication to subjects (e.g., email, phone call, information letter) and documentation of subject/caregiver acknowledgement is to be performed and documented in accordance with local regulations/EC requests and guidance. All contacts with subjects must be filed in the source records.

A risk mitigation assessment will be performed for each subject at the site in order to determine how their participation may be impacted. Sites must ensure that appropriate measures are taken to ensure the safety of FOP subjects in light of the ongoing COVID-19 pandemic, taking into consideration local Ethics Committee and Competent Authority guidance, as well as the ability of individual Investigators and sites to adequately monitor subject safety.

8. STATISTICAL AND ANALYTICAL PLANS

This study is intended to assess whether a non-flare-up-based dosing regimen, combined with higher doses during times of flare-ups, will result in a lower incidence of new HO formation. As this is an open-label study with no comparator arm, use of subject data from Study PVO-1A-001 (Natural History Study [NHS]) will form the basis for a control arm. Additional analysis of the flare-up-based treatment regimen will be described in the Statistical Analysis Plan (SAP).

A summary of the general methods and strategies for analysis is provided in the sections below. A more comprehensive SAP will be written that will describe the manner in which the analysis will be performed.

8.1 General Methods

For purposes of assessing the efficacy of the non-flare-up-based dosing regimen, low-dose WBCT imaging data from Part B (after Amendment 3) and Part C will be combined.

8.2 Sample Size

The new HO volume data as assessed by low-dose WBCT scan, excluding head, from Part B (after Amendment 3) and Part C will be combined. The sample size was fixed by the number of subjects enrolled in Part B and was not based on power calculations.

8.3 Study Populations

The following populations will be analyzed under Amendment 4 and subsequent amendments:

- The Full Analysis Set (FAS) includes all enrolled subjects having a baseline HO volume measurement and at least one post-baseline HO volume measurement in the PVO-1A-202 study. For efficacy comparisons to the NHS, the FAS will also include subjects enrolled in the NHS with available baseline and at least one post-baseline HO volume measurements.

- The Per-Protocol Set (PPS) is a subset of the FAS including subjects with no major protocol deviations that are expected to interfere with assessments of the primary endpoint, and with at least 80% compliance to the study drug regimen. For efficacy comparisons to the NHS, the PPS will also include subjects in the NHS with available baseline and at least one post-baseline HO volume measurements and with no major protocol deviations that are expected to interfere with assessments of the primary endpoint.

- The Safety Analysis Set (SAS) includes all enrolled subjects receiving at least one dose of palovarotene in the PVO-1A-202 (after Amendment 3). For safety comparisons to the NHS, the SAS will also include subjects enrolled in the NHS with available post-baseline follow-up.

- The Pharmacokinetic Analysis Set (PAS) is a subset of the SAS including subjects with evaluable pharmacokinetics data.

8.4 Baseline and Disease Characteristics (including Medical History)

Baseline and disease characteristics will be tabulated descriptively (eg, number and percentage of subjects for each category for categorical parameters, and the number, mean, standard deviation, and range for continuous parameters).

8.5 Subject Disposition

Subject disposition will be listed and summarized.

8.6 Extent of Exposure

The extent (duration) of exposure will be determined from the date of first dose of study drug through the date of last dose of study drug. For times during which subjects are receiving

flare-up-based treatment, tabulation of the number of days at the higher dose(s) will be presented. An assessment of the proportion of subjects who are able to tolerate the higher doses will be performed.

8.7 Efficacy

8.7.1 Primary Efficacy

The primary efficacy endpoint is the annualized change in new HO volume (as assessed by low-dose WBCT scan, excluding head). The primary efficacy analysis comparing the annualized change in new HO volume between subjects treated with palovarotene and untreated subjects from the NHS will be conducted using a weighted linear mixed effects (wLME) model. A subject-level random effect will be used to account for the correlation among repeated measures on the same subject as subjects may contribute follow-up from the NHS and the current trial. Baseline HO volume divided by age will be the only covariate included in the model. As HO volume is non-decreasing, the LME model will be fit using only a subject's observations associated with the longest follow-up in the NHS and the current study with weights used to account for the different lengths of observed subject follow-up.

The estimated difference in the annualized change in new HO volume between subjects treated with palovarotene and untreated subjects and its associated Wald statistic will be used for hypothesis testing. Hypothesis testing will be performed using a two-sided, type I error rate of 5%.

8.7.2 Secondary Efficacy

Secondary efficacy variables for non-flare-up-based treatment will include the following: percent of subjects with new HO, change from baseline in ROM as assessed by CAJIS, change from baseline in physical function using age appropriate forms of the FOP-PFQ, and change from baseline in physical and mental function for subjects ≥15 years old and mental function for subjects <15 years old using age appropriate forms of the PROMIS Global Health Scale.

The secondary efficacy endpoints will be summarized by visit and, where applicable, compared to the relevant time point from the NHS.

8.8 Safety

The safety analysis will be descriptive in nature. Safety evaluations will include AE and SAE reporting, ECGs (for subjects receiving treatment), vital signs (temperature, respiratory rate, blood pressure, and heart rate), physical examination, body weight and height, laboratory parameters (hematology, biochemistry, and urinalysis), urine pregnancy tests for FOCBP, and concomitant medication reporting.

Evaluation of subjects with open epiphyseal growth plates at the most recent assessment will include knee (AP view) and hand/wrist (PA view) radiographs for assessment of epiphyseal growth plate; and standardized stadiometry and knee height (in triplicate) for assessment of linear growth. Any limb/joint AEs reported by these subjects will be evaluated by clinical and radiographic assessments as deemed appropriate by the Investigator.

All safety data collected and captured in the eCRF will be included in data listings sorted by domain, subject and time point, or as appropriate. Mean changes from pre-treatment to on-treatment will generally be tabulated by protocol-specified time points, while the number of subjects with potentially clinically significant values at pre-treatment and at each endpoint will be presented. The last non-missing baseline value will be used as the pre-treatment value for that parameter.

8.8.1 Adverse Events

Adverse events will be classified using the MedDRA coding dictionary. Adverse event severity will be assessed and reported according to criteria defined in the protocol (mild, moderate, severe).

Adverse events known to be associated with retinoids (eg, mucocutaneous events) will be further graded according to CTCAE, Version 4.03, 14 June 2010.

Tabulations will include an overall incidence of at least one AE, incidence within body system, and incidence by preferred term. Each subject may only contribute once (ie, first occurrence) to each of the incidence rates, regardless of the number of occurrences. Incidences (denominators and percentages) for selected gender-specific AEs will be adjusted by the number of males or females, as appropriate.

8.8.2 Suicide Ideation

The number of subjects who report any type 4 or 5 suicide ideations in the C-SSRS or any suicide behavior during the study will be presented (see Appendix 5A).

8.8.3 Clinical Laboratory Findings

Change in clinical laboratory findings, vital signs, and other continuous safety parameters will be assessed descriptively, with pre-treatment, on-treatment, and change from pre-treatment values calculated. For purposes of this analysis, pre-treatment will be the last values prior to initiation of non-flare-up-based dosing.

Group-mean plots (mean and standard error) over time will be provided.

The number and percentage of subjects with potentially clinically significant (PCS) values will be summarized. A focus will be on new-onset PCS values, ie, subjects with pre-existing PCS values at pre-treatment will not be considered to have new-onset values on-treatment.

8.9 Pharmacokinetics

Plasma palovarotene concentrations will be summarized for the PAS population by descriptive statistics of n, arithmetic mean, standard deviation (SD), coefficient of variance, geometric mean, median, minimum, and maximum.

8.10 Pharmacodynamics

Exploratory analyses will be performed to assess potential exposure relationships.

9. PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

9.1 Adverse Event and Serious Adverse Event Documentation, Severity Grading, and Reporting

9.1.1 Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product during the course of a study and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal product.

Disease, signs, symptoms, and/or laboratory abnormalities already existing prior to the use of the product are not considered AEs after administration of the study product unless they reoccur after the subject has recovered from the pre-existing condition or they represent an exacerbation in intensity or frequency.

Only a clinically significant laboratory test abnormality, physical examination finding, or other objective finding should be reported as an AE, whether it represents an exacerbation or a new abnormality.

9.1.2 Serious Adverse Event or Adverse Drug Reaction

An SAE (experience) or reaction is any untoward medical occurrence that results in any of the following outcomes and at any dose:

- Death.
- Life threatening situation (the subject was at risk of death at the time of the event). It does not refer to the hypothetical risk of death if the AE was more severe or was to progress.
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant disability/incapacity.
- Congenital anomaly/birth defect (any structural abnormality in subject offspring that occurs after intrauterine exposure to treatment).
- Other medically important event (important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon medical judgment, they may jeopardize the subject or may require intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse).

9.1.3 Adverse Event Documentation

Adverse event or SAE reports will be completed for all AEs. Signs and symptoms of each AE should be described in detail: nature, date of onset, end date, severity, relationship to study drug, and action taken and outcome.

9.1.4 Severity of Adverse Events

The term severity is used to describe the intensity of a specific event. The severity of AEs will be categorized as follows:

- Mild: events that are easily tolerated with no disruption of normal daily activity.
- Moderate: events that cause sufficient discomfort to interfere with daily activity and/or require a simple dose medication.
- Severe: events that incapacitate and prevent usual activity or require systemic drug therapy or other treatment.

Adverse events known to be associated with retinoids (eg, mucocutaneous) will be further graded according to CTCAE, Version 4.03, 14 June 2010. Sites will be provided with specific criteria for the coding of AEs.

9.1.5 Causality Assessment

Causality assessment by the Investigator in terms of relationship to study drug is required for purposes of reporting AEs. To promote consistency between the Investigators, the following definitions should be taken into consideration along with good clinical and scientific judgment when determining the relationship of study drug to an AE:

- Definitely Related: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to the study drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study drug (dechallenge) should be clinically plausible.
- Probable: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to the study drug administration, and which is unlikely to be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study drug (dechallenge) should be clinically plausible.
- Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the study drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on the study drug withdrawal (dechallenge) may be lacking or unclear.
- Not related: A clinical event that has no temporal relationship to the study drug or has a much more likely alternative etiology.

9.1.6 Action Taken With Study Drug

The action taken to remedy the reported/observed AEs will be defined as follows:

1 None

2 Study drug dosage modified

3 Study drug dosage interrupted

4 Study drug permanently discontinued

9.1.7 Outcome of Adverse Event

The outcome of the AEs will be recorded as follows:

1 Event resolved with no sequelae

2 Event resolved with sequelae

3 Event ongoing

4 Death

9.1.8 Reporting of Serious Adverse Event

All SAEs must be reported within 24 hours to the Medpace Clinical Safety Group:

Medpace SAE hotline – USA:
Tel: 1.800.730.5779, ext. 2999 **or** 1.513.579.9911, ext. 2999
Fax: 1.866.336.5320
E-mail: safetynotification@medpace.com

Medpace SAE hotline – Europe:
Tel: +49 89 89 55 718 44
Fax: +49 89 89 55 718 104
E-mail: medpace-safetynotification@medpace.com

The Investigator will be requested to complete and transmit to the sponsor or designee the SAE information using the electronic reporting form, or a paper form should the electronic system not be available.

The Investigator will inform the sponsor or designee within 24 hours of any findings with the use of the study drug that may suggest significant hazards, contraindications, SAEs, and precautions pertinent to the safety of the study drug.

The sponsor or designee will notify the regulatory authorities within the required time frames for all SAEs subject to expedited reporting, either due to their nature (“serious”) or due to the significant, unexpected information they provide.

The Investigator will notify the IRB or Independent Ethics Committee (IEC) of SAEs occurring during the trial likely to affect the safety of trial subjects or the conduct of the trial.

9.1.9 Pregnancy

If any female subject or partner of a male subject becomes or is found to be pregnant during their participation in the study, the site will submit this information on a Pregnancy Reporting Form to the sponsor or designee. The subject will be followed up through their pregnancy and the health status of the baby will be verified. The study site will record the pregnancy on the AE and the pregnancy reporting forms.

9.1.10 Follow-Up of Adverse Events and Serious Adverse Events

The AE reporting period for the non-flare-up-based treatment and the flare-up-based treatment begins at the time of informed consent and continues through study completion, The SAE, including death, reporting period for the non-flare-up-based treatment and the flare-up-based treatment begins at the time of informed consent and continues through study completion (including Part D) + 30 days.

Adverse events will be assessed at every site and remote visit. The Investigator will follow-up on all AEs observed or reported by the subject up to the end of the reporting period or the event stabilizes and follow-up is no longer necessary. The Investigator will follow-up on SAEs until they are considered resolved or the outcome is known. Limb/joint AEs reported by subjects with open epiphyses will be evaluated by clinical and radiographic assessments deemed appropriate by the Investigator.

9.2 Administrative Requirements

9.2.1 Informed Consent Form

It should be noted that the word “parents” is used throughout this protocol to denote the legally authorized representatives (eg, parents, caregivers, or legal guardians) of subjects under the age of 18 years.

Prior to participation in the clinical study, the Investigator and/or delegate must fully explain to the subjects/parents all aspects of the study that are relevant to the decision of participation in the trial. The Informed Consent Form (ICF) is documented by means of a written, signed, and dated subject/parent consent form (or age-appropriate assent form) per local requirements, prior to the start of the study. Age-appropriate assent forms will be completed for all subjects under the age of 18 years. Potential subjects/parents may undergo an IRB-approved remote consent. The ICF will be written in a language and in a form understandable to the subjects/parents. The Investigator and/or delegate will also sign the ICF. Any modifications to the ICF required by the Investigator prior to submission to the IRB/IEC or requested by the IRB/IEC must be submitted to the sponsor or designee for approval prior to the implementation of the ICF.

One signed and dated copy of the ICF will be given (or emailed/faxed in the case of remote consent) to the subject/parent and one signed and dated original copy will be maintained by the Investigator in the study file until the end of the study.

The Investigator should clearly indicate the subject's participation in a clinical trial in his/her medical chart.

Institutions, Investigators, contract research organizations (CROs), etc., under this protocol shall abide by all requirements applicable to the use and disclosure of subjects' protected health information (such as the requirements provided for under the Health Insurance Portability and Accountability Act in the United States, the Personal Information and Electronics Document Act in Canada, the European Union (EU) Directive on Data Protection, and any other similar regulations or legislation).

9.2.2 Ethical Conduct of the Study

The clinical study will be conducted in accordance with the protocol, in addition to the ethical principles that have their origin in the Declaration of Helsinki (see Appendix 8), inclusive of any subsequent amendment(s), and that are consistent with the International Council for Harmonisation (ICH) Good Clinical Practices (GCP), EU Directive 2001/20/EC, US FDA Code of Federal Regulations and other applicable local regulatory requirements, which ever affords the greater subject protection.

9.2.3 Ethics Board Approval

The IRB/IEC will be in compliance with the ICH GCP and local regulatory requirements. It will consist of at least five qualified and experienced members with varying backgrounds, including at least one member whose primary interest is in a non-scientific area and one member who is independent from the institution/site. The committee will review the science, medical aspects, and ethics of the clinical study.

The following documents will be submitted to and reviewed by the IRB/IEC:

- Final study protocol/amendment(s)
- Investigator's Brochure
- Written ICF and consent/assent form updates
- Written information to be provided to subject/parent
- Subject recruitment procedures
- Information about payments and compensation available to subjects
- Investigator's curriculum vitae and/or other documentation evidencing qualifications

Any other documents that the IRB/IEC may need to fulfill its responsibilities will be provided to the committee.

The study protocol and informed consent/assent documents to be used in the clinical study must be approved by the IRB/IEC, prior to initiation of the study. The IRB/IEC will notify the Investigator and/or the sponsor in writing, clearly identifying the study, the documents reviewed

and the date of approval. The committee will also provide a list of the members, their qualifications and affiliations. The IRB/IEC will conduct continuing review of the ongoing study at an appropriate interval.

The Investigator will be responsible for ensuring the initial approval of the clinical study protocol, written ICF, consent form updates, subject recruitment, and other documents. The Investigator and/or the sponsor is also responsible to promptly report to the IRB/IEC all changes in the research activities and all SAEs likely to affect the safety of the subjects, or the conduct of the study. The Investigator will not make any changes in the research without approval from the sponsor and without submitting for review and approval by the IRB/IEC, except where necessary to eliminate apparent immediate hazards to subjects.

9.2.4 Subject Confidentiality

Any research information obtained about the subject in this study will be kept confidential in accordance with all relevant national and international laws governing data privacy and security. The subject's name or any other identifying information will not appear in any reports published as a result of this study.

However, information obtained from individual subject's participation in the study may be disclosed with his/her express written consent to the health care providers for the purpose of obtaining appropriate medical care. The subject's medical records/charts and tests with his/her name on them may be made available to the appropriate CRO, the sponsor, its potential eventual partners, and any other regulatory authorities. This is for the purpose of verifying information obtained for this study. Confidentiality will be maintained throughout the study within the limits of the law.

A subject's name will not be given to anyone except the researchers conducting the study, who have pledged an oath of confidentiality. All identifying information will be kept behind locked doors, under the supervision of the study Investigator and will not be transferred outside of the investigator site.

A subject may take away his/her permission to collect, use, and share information about him/her at any time. If this situation occurs, the subject will not be able to remain in the study. No new information that identifies the subject will be gathered after that date. However, the information about the subject that has already been gathered and transferred may still be used and given to others as described above in order to preserve the scientific integrity and quality of the study.

9.2.5 Amendments to the Protocol

Modifications to the protocol are only possible by approved protocol amendments authorized by the study sponsor. All protocol amendments will be approved by the appropriate regulatory authorities as well as each IRB prior to implementation. The Investigator must not implement any deviations from, or changes to the protocol, except where it is necessary to eliminate an immediate hazard to the study subject.

9.2.6 Protocol Deviations

The protocol must be read thoroughly and the instructions followed exactly. Any major

deviation to the protocol has to be reported as soon as possible to the sponsor. The governing reporting guidelines for protocol deviations must be adhered to by the Investigator.

9.2.7 Study Termination

This study may be prematurely terminated, if in the opinion of the Investigator or the sponsor, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the Investigator or the sponsor by the terminating party. Circumstances that may warrant termination include, but are not limited to:

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

Should the study be closed prematurely, all study materials must be returned to the sponsor. If the study is closed prematurely due to safety concerns, all subjects exposed to the investigational drug will be followed for safety with the length of follow-up determined based on the safety risk.

9.2.8 Retention of Subject Records and Study Files

To enable evaluations and/or audits from the regulatory authorities, the appropriate CRO, or the sponsor, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eCRFs, and hospital records), all original signed ICFs, copies of all eCRFs, source documents, and detailed records of treatment disposition. The Investigator should retain these records according to federal and local regulations or as specified in the Clinical Trial Agreement, whichever is longer.

If the Investigator relocates, retires, or for any reason withdraws from the study, then the sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the sponsor. The Investigator must obtain written permission from the sponsor before disposing of any records.

9.3 Data Quality Assurance

As per GCP guidelines, the sponsor or designee will be responsible for implementing and maintaining quality assurance and quality control systems for this study.

Participating sites, the study database, and study documentation including subject medical records may be subject to a quality assurance audit during the course of the study. In addition, inspections may be conducted by regulatory bodies at their discretion.

If sites receive a request for an inspection or written or oral inquiries regarding any aspect of the institution’s or Investigator’s activities related to this study from a regulatory authority, the

Investigator must immediately notify the sponsor and the appropriate CRO of the request. Following this inspection and/or audit, the Investigator must notify the sponsor of any violation or deficiency noted by the regulatory authority.

9.4 Monitoring

The sponsor or their representative will monitor the study for compliance with GCP. The monitors will verify that the rights and well-being of subjects are respected, that the reported trial data are accurate, complete, as well as verifiable from source documents, and finally that the conduct of the trial is in accordance with the current approved protocol/amendments, GCP, and regulatory requirements.

Original subject records must be made available for reviews conducted by the sponsor or their representative.

9.5 Data Capture and Management

The sponsor or designee will provide the study sites with an electronic case report system.

Electronic CRFs will be completed for each subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data entered in each subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and document the dates and details of study procedures, AEs, and subject status.

The Investigator, or designated representative, should complete the eCRF as soon as possible after information is collected, preferably on the same day that a subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be entered immediately after the final examination. An explanation should be given for all missing data.

9.6 Liability and Insurance

The sponsor has subscribed to an insurance policy covering, in its terms and conditions, its legal liability for certain injuries to participating persons arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

9.7 Publication and Clinical Data Reporting

All information regarding palovarotene supplied by the sponsor to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without written consent from the sponsor. It is understood that there is an obligation to provide the sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of palovarotene and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. A Publications Committee, comprised of Investigators participating in the study and representatives from the sponsor, as appropriate, will be formed to oversee the publication of the study results, which will reflect the experience

of all participating study centers. Subsequently, individual Investigators may publish results from the study in compliance with their agreement with the sponsor.

9.8 Coordinating Investigator

The Coordinating Investigator will be designated from among the Primary Investigators with their agreement. The Coordinating Investigator will approve the final clinical study report for Study PVO-1A-202.

10. INVESTIGATOR AGREEMENT

I have read Protocol PVO-1A-202 Amendment 8, dated 30 November 2020:

A Phase 2, Open-Label Extension, Efficacy and Safety Study of a RARγ-Specific Agonist (Palovarotene) in the Treatment of Preosseous Flare-ups in Subjects with Fibrodysplasia Ossificans Progressiva (FOP).

I agree to conduct the study as detailed herein and in compliance with ICH Guidelines for Good Clinical Practices and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator (printed name)

_____ _____

Investigator signature Date

_____

_____

_____

Investigational site or name of institution and location (printed)

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12. APPENDICES

Appendix 1. Cumulative Analogue Joint Involvement Scale for FOP

CUMULATIVE ANALOGUE JOINT INVOLVMENT SCALE FOR FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

Subject I.D. / Initials: _____ /_____

Disability (check all that apply):

- ☐ Walks
- ☐ Wheelchair
- ☐ Needs some help with activities of daily living
- ☐ Needs complete help with activities of daily living

Assign only one score per joint:

	Not Involved (Score = 0)	Affected / Partially Involved (Score = 1)	Functionally Ankylosed / Completely Involved (Score = 2)	
Neck				
Thoraco-lumbar spine				
Jaw				
Right shoulder				
Left shoulder				
Right elbow				
Left elbow				
Right wrist				
Left wrist				
Right hip				
Left hip				
Right knee				
Left knee				
Right ankle				
Left ankle				
TOTAL				Summation:

Assessed by:	Name:	Date:___ / ___ /___
	Signature:	

Clementia Pharmaceuticals Inc.
Version: 06-Feb-2014

Protocol: PVO-1A-202

Appendix 2A. Adult FOP-Physical Function Questionnaire (Self-Completed for Subjects Age 15 Years and Older)

Fibrodysplasia Ossificans Progressiva Physical Function Questionnaire
(FOP-PFQ) for Ages 15 Years and Older
[15 Years and Older FOP-PFQ]

Please respond to each question by marking one box per row. When choosing a response, please think of your ability to do the following activities **without help from anyone and without the use of assistive devices or aids, including a wheelchair.** If you can sometimes perform an activity by yourself depending on the circumstance but sometimes cannot, then answer the question by how you can do the activity the majority of the time. Remember, complete the questions based on what you can currently do for yourself, without any help from others or by using some kind of aid or assistive device.

Please think about your current ability.

	Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
1. Are you able to button your shirt?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
2. Are you able to put on a pullover sweater?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
3. Are you able to open and close a zipper?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
4. Are you able to remove something from your back pocket?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
5. Are you able to put on a shirt or blouse?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
6. Are you able to put on and take off a coat or jacket?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
7. Are you able to put on and take off your socks?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
8. Are you able to cut your food using eating utensils?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
9. Are you able to reach into a high cupboard?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
10. Are you able to shampoo your hair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
11. Are you able to wash and dry your body?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
12. Are you able to dry your back with a towel?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
13. Are you able to sit on and get up from the toilet?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Version 1, dated 21 May 2014

	Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
14. Are you able to wipe yourself after using the toilet?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
15. Are you able to get up from the floor from lying on your back without help?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
16. Are you able to get in and out of bed?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
17. Are you able to get out of bed into a chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
18. Are you able to turn from side to side in bed?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
19. Are you able to stand up from an armless straight chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
20. Are you able to sit down in and stand up from a low, soft couch?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
21. Are you able to get in and out of a car?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
22. Are you able to climb up five steps?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
23. Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
24. Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**
25. Does your health now limit you in taking care of your personal needs (dress, comb hair, toilet, eat, bathe)?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
26. Does your health now limit you in bathing or dressing yourself?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
27. Does your health now limit you in climbing one flight of stairs?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
28. Does your health now limit you in going for a short walk (less than 15 minutes)?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Version 1, dated 21 May 2014

Appendix 2B. Pediatric FOP-Physical Function Questionnaire (Self-Completed for Subjects Ages 8 to 14 Years)

Pediatric Fibrodysplasia Ossificans Progressiva Physical Function Questionnaire (FOP-PFQ-P) Self-Completed for Ages 8 to 14
[Self 8-14 Years FOP-PFQ-P]

Instructions: Please respond to each statement by marking one box per row. When choosing a response, please think of your ability to do the following activities **without help from anyone and without the use of assistive devices or aids, including a wheelchair.**

If you can sometimes perform an activity by yourself depending on the circumstance but sometimes cannot, then complete the statement by how you can do the activity most of the time. Remember, complete the statements based on what you can currently do for yourself, without any help from others and without using some kind of aid or assistive device.

Please think about your current ability.

	With no trouble	With a little trouble	With some trouble	With a lot of trouble	Not able to do
1. I can button my shirt or pants...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
2. I can dry my back with a towel...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
3. I can go up one step...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
4. I can walk more than 15 minutes...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
5. I can get out of bed...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
6. I can pull a shirt over my head...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
7. I can zip up my clothes...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
8. I can put on my clothes...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
9. I can put on my socks...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
10. I can cut my food...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
11. I can wash and dry my body...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
12. I can get up from a regular toilet...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
13. I can get up from the floor...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Version 1, dated 08 August 2014

	With no trouble	With a little trouble	With some trouble	With a lot of trouble	Not able to do
14. I can get in and out of a car…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
15. I can walk up stairs without holding on to anything…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
16. I can put on my shoes…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
17. I can lift a cup to drink...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
18. I can brush my teeth...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
19. I can bend over to pick something up…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
20. I can get down on my knees without holding on to something…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
21. I can turn my head all the way to the side…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
22. I can wash my hair…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
23. I can reach a shelf above my head…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
24. I can write with a pen or pencil…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
25. I can wipe myself after using the toilet…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
26. I can chew my food…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Version 1, dated 08 August 2014

Appendix 2C. Pediatric FOP-Physical Function Questionnaire (Proxy-Completed for Subjects Ages 5 to 14 Years)

Pediatric Fibrodysplasia Ossificans Progressiva Physical Function Questionnaire (FOP-PFQ-P) Proxy-Completed for Ages 5 to 14
[Proxy 5-14 Years FOP-PFQ-P]

Instructions: Please respond to each statement by marking one box per row. When choosing a response, please think of your child's ability to do the following activities **without help from anyone and without the use of assistive devices or aids, including a wheelchair.** If your child can sometimes perform an activity by himself/herself depending on the circumstance but sometimes cannot, then complete the statement by how your child can do the activity most of the time. Remember, complete the statements based on what your child can currently do for himself/herself, without any help from others and without using some kind of aid or assistive device.

Please think about your child's current ability.

	With no trouble	With a little trouble	With some trouble	With a lot of trouble	Not able to do
1. My child can button his/her shirt or pants…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
2. My child can dry his/her back with a towel…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
3. My child can go up one step…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
4. My child can walk more than 15 minutes…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
5. My child can get out of bed…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
6. My child can pull a shirt on over his/her head…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
7. My child can zip up his/her clothes…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
8. My child can put on his/her clothes…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
9. My child can put on his/her socks…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
10. My child can cut his/her food…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
11. My child can wash and dry his/her body…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
12. My child can get up from a regular toilet…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
13. My child can get up from the floor…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
14. My child can get in and out of a car…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Version 1, dated 08 August 2014

	With no trouble	With a little trouble	With some trouble	With a lot of trouble	Not able to do
15. My child can walk up stairs without holding on to anything...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
16. My child can put on his/her shoes…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
17. My child can lift a cup to drink...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
18. My child can brush his/her teeth...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
19. My child can bend over to pick something up…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
20. My child can get down on his/her knees without holding on to something…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
21. My child can turn his/her head all the way to the side…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
22. My child can wash his/her hair…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
23. My child can reach a shelf above his/her head...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
24. My child can write with a pen or pencil…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
25. My child can wipe himself/herself after using the toilet…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
26. My child can chew his/her food…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Version 1, dated 08 August 2014

Appendix 3. CYP450 3A4 Strong Inducers or Inhibitors: Exclusionary Medications

INDUCERS	Half-life	INHIBITORS	Half-life
Carbamazepine [a]	18-55 hrs, 12-17 hrs	Boceprevir	3.4 hrs 5-
Phenobarbital	53-140 hrs	Clarithromycin	7 hrs 5-8
Phenytoin Rifabutin	24 hrs	Conivaptan	hrs 6 hrs
Rifampin	16-69 hrs	Delavirdine	8-28hrs
St John's Wort [b]	3-4 hrs	Fluvoxamine	NA
Troglitazone Avasimibe	43.1 hrs 16-	Grapefruit juice [c]	18-20 hrs
	34 hrs 20	Imatinib Indinavir	1.4-2.2 hrs
	hrs	Itraconazole [d]	15-27 hrs, 64 hrs
		Ketoconazole	8 hrs
		Lopinavir/ritonavir	5-6 hrs
		Mibefradil	17-25 hrs
		Nefazodone Nelfinavir	2-4 hrs
		Posaconazole	3.5-5 hrs
		Ritonavir Saquinavir	20-66 hrs
		Telaprevir	3-5 hrs
		Telithromycin	7-12 hrs
		Troleandomycin	9-11 hrs (at steady state) 10 hrs
		Voricanozole	1.05 hrs
		Suboxone	6-9 hrs (dose-dependent)
			24-42 hrs

[a] Half-life 18-55 hrs after a single dose and 12-17 hrs after multiple doses

[b] Major ingredient hyperium's half-life

[c] NA: not available

[d] Half-life 15-27 hrs after a single dose and 64 hrs at steady-state

Appendix 4. Methods of Birth Control

Highly effective methods of birth control:

- Established use of oral, transdermal, or intravaginal combined (estrogen and progesterone containing) hormonal method of contraception.
- Established use of oral (excluding mini-progesterone-only pill), injectable, or implantable progesterone-only hormonal contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
- Bilateral tubal occlusion.

Note that two hormonal forms cannot be used together.

Other effective methods of birth control include the following:

- Barrier forms (always used with spermicide) – diaphragm, cervical cap
- Barrier forms (used with or without spermicide) – male latex condom
- Others – vaginal sponge (contains

spermicide) The following are

unacceptable forms of birth control:

- Progestin only “mini-pill”
- Female condom
- Natural family planning (periodic abstinence, such as calendar, ovulation, symptothermal, post-ovulation methods; rhythm method; or breastfeeding) or withdrawal

Appendix 5A. Adult Columbia-Suicide Severity Rating Scale (Subjects Ages 12 Years and Older)

Adult C-SSRS to be used for Screening for all subjects 12 years of age and older:

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Screening

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Past 1 Month

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?

If yes, describe:

Yes ☐ No ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.
Have you actually had any thoughts of killing yourself?

If yes, describe:

Yes ☐ No ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it."*
Have you been thinking about how you might do this?

If yes, describe:

Yes ☐ No ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?

If yes, describe:

Yes ☐ No ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

If yes, describe:

Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Past 1 Year**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Adult C-SSRS to be used for visits after Screening for all subjects 12 years of age and older:

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐

If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐

If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."*
Have you been thinking about how you might do this?
Yes ☐ No ☐

If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐

If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐

If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: _____ _____
Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply; so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes No [] - [] Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes No [] - []
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes No [] - [] Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes No [] - [] Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes No [] - []
Suicidal Behavior: Suicidal behavior was present during the assessment period? **Suicide:**	Yes No [] - [] Yes No [] - []
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy; somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Appendix 5B. Pediatric Columbia-Suicide Severity Rating Scale (Subjects Ages 8 to 11 Years)

Pediatric C-SSRS to be used for Screening for subjects 8 to 11 years old:

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Screening

Version 6/23/10

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Past 1 Month**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. *Have you thought about being dead or what it would be like to be dead?* *Have you wished you were dead or wished you could go to sleep and never wake up?* *Do you ever wish you weren't alive anymore?* If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. *Have you thought about doing something to make yourself not alive anymore?* *Have you had any thoughts about killing yourself?* If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* *Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?* If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* *When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?* *This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.* If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. *Have you ever decided how or when you would make yourself not alive anymore/kill yourself? Have you ever planned out (worked out the details of) how you would do it?* *What was your plan?* *When you made this plan (or worked out these details), was any part of you thinking about actually doing it?* If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). *Most Severe Ideation:* _____ *Type # (1-5)* _____ *Description of Ideation*	Most Severe
Frequency *How many times have you had these thoughts?* *Write response*_____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____

 C-SSRS—Children's Baseline/Screening (Version 6/23/10) Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Past 1 Year
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you ever do anything to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you ever hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts: _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Has subject engaged in Self-Injurious Behavior, intent unknown?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted: _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted: _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

 C-SSRS—Children's Baseline/Screening (Version 6/23/10) Page 2 of 2

Pediatric C-SSRS to be used for visits after Screenings for subjects 8 to 11 years old:

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Since Last Visit

Version 6/23/10

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. *Have you thought about being dead or what it would be like to be dead?* *Have you wished you were dead or wished you could go to sleep and never wake up?* *Do you wish you weren't alive anymore?* If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. *Have you thought about doing something to make yourself not alive anymore?* *Have you had any thoughts about killing yourself?* If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* *Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?* If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* *When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?* *This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.* If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. *Have you decided how or when you would make yourself not alive anymore/kill yourself? Have you planned out (worked out the details of) how you would do it?* *What was your plan?* *When you made this plan (or worked out these details), was any part of you thinking about actually doing it?* If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). *Most Severe Ideation:* _____ _____ *Type # (1-5)* *Description of Ideation*	Most Severe
Frequency *How many times have you had these thoughts?* *Write response* _____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____

 C-SSRS—Children's Since Last Visit (Version 6/23/10) Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you do anything to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Has subject engaged in Self-Injurious Behavior, intent unknown?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Completed Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Appendix 6. Retinoid-Specific Adverse Events to be Assessed for Severity by CTCAE Criteria (Version 4.03, 14 June 2010)

Adverse Event	CTCAE Page Number
Corneal ulcer	22
Conjunctivitis	22
Dry eye	23
Keratitis	24
Night blindness	24
Chelitis	30
Dry mouth	33
Mucositis oral	45
Pancreatitis	48
Pharyngitis	81
Alanine aminotransferase increased	107
Aspartate aminotransferase increased	107
Blood bilirubin increased	107
Lipase increased	111
Serum amylase increased	112
Hypertriglyceridemia	116
Alopecia	179
Dry skin	179
Erythroderma	180
Photosensitivity	183
Pruritus	184
Rash maculo-papular	185
Skin and subcutaneous tissue disorders – other, specify	187

Appendix 7A. PROMIS Global Health Scale (Self-Completed for Subjects Age 15 Years and Older)

PROMIS v.1.0/1.1 – Global Health

PROMIS Global Health Scale

Please respond to each item by marking one box per row.

		Excellent	Very good	Good	Fair	Poor
Global01	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02	In general, would you say your quality of life is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03	In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04	In general, how would you rate your mental health, including your mood and your ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global05	In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global09	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

English
11 November 2013

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PROMIS v.1.0/1.1 – Global Health

		Completely	Mostly	Moderately	A little	Not at all
Global06	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
Global10	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

		None	Mild	Moderate	Severe	Very severe
Global08	How would you rate your fatigue on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Global07	How would you rate your pain on average?	☐ 0 No pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 Worst imaginable pain

English
11 November 2013

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Appendix 7B. PROMIS Pediatric Global Health Scale (Self-Completed for Subjects Ages 8 to 14 Years)

PROMIS v1.0 Pediatric Global Health

PROMIS Pediatric Global Health – Short Form 7+2

Please respond to each question or statement by marking one box per row.

		Excellent	Very Good	Good	Fair	Poor
Global01	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02	In general, would you say your quality of life is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03	In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04	In general, how would you rate your mental health, including your mood and your ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

		Never	Rarely	Sometimes	Often	Always
PedGlobal2	How often do you feel really sad?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PedGlobal5	How often do you have fun with friends?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PedGlobal6	How often do your parents listen to your ideas?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	In the past 7 days. . .	Never	Almost Never	Sometimes	Often	Almost Always
2876R1	I got tired easily.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3793R1	I had trouble sleeping when I had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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English
24 September 2014

Appendix 7C. PROMIS Pediatric Global Health Scale (Proxy-Completed for Subjects Ages Less Than 15 Years)

PROMIS v1.0 Parent Proxy –Global Health

Pediatric Global Health – Short Form 7+2

Please respond to each question or statement by marking one box per row.

		Excellent	Very Good	Good	Fair	Poor
Global01_PX	In general, would you say your child's health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02_PX	In general, would you say your child's quality of life is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03_PX	In general, how would you rate your child's physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04_PX	In general, how would you rate your child's mental health, including mood and ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

		Never	Rarely	Sometimes	Often	Always
PedGlobal2_PX	How often does your child feel really sad?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PedGlobal5_PX	How often does your child have fun with friends?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PedGlobal6_PX	How often does your child feel that you listen to his or her ideas?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	In the past 7 days…	Never	Almost Never	Sometimes	Often	Almost Always
Pf4fatigue3	My child got tired easily	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pf2pain5	My child had trouble sleeping when he/she had pain.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

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English
07 October 2014

Appendix 8. Declaration of Helsinki

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words,

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"The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by

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individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

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19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and

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standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

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27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain

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for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made

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publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

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Clementia Pharmaceuticals Inc.

Clinical Study Protocol (France-Specific)

A Phase 2, Open-Label, Efficacy and Safety Study of an RARγ-Specific Agonist (Palovarotene) to Prevent Heterotopic Ossification in Subjects with Fibrodysplasia Ossificans Progressiva (FOP)

Study Number: PVO-1A-204

Original Protocol: 13 June 2016
Amendment 1: 07 September 2016
Amendment 2: 02 November 2017
Amendment 3: 22 March 2018
Amendment 4: 08 March 2019
Amendment 5: 31 October 2019
Amendment 6: 18 December 2020

Clementia Pharmaceuticals Inc.
1000, De La Gauchetière, Suite 1200 Montreal, Quebec, Canada H3B 4W5

PROTOCOL SIGNATURE PAGE

A Phase 2, Open-Label, Efficacy and Safety Study of an RARγ-Specific Agonist (Palovarotene) to Prevent Heterotopic Ossification in Subjects with Fibrodysplasia Ossificans Progressiva (FOP)

Protocol Number: PVO-1A-204
(France-Specific)

Signature of Approval for Protocol PVO-1A-204 (Amendment 6: 18 December 2020)

CLEMENTIA PHARMACEUTICALS INC.

PPD

NAME: PPD

SIGNATURE: _____ **DATE:** Dec 18, 2020

PROTOCOL AMENDMENT SUMMARY

This sixth amendment to the protocol for Study PVO-1A-204 was finalized on 18 December 2020.

Location/Section Number	Change	Rationale
Major changes that affected the clinical conduct of the study:		
Protocol Synopsis Tables 1, 2 and 4 Section 3.1 Overview of Study Design Part D is also mentioned in 1.1.3.2.2, 3.2, 5.7, 9.1.10 Section 1.1.3.2.2 Palovarotene Phase 2 Interventional Studies Section 2.3 Secondary Objectives Section 3.2 Study Rationale Section 5.7 Subject Withdrawal or Early Termination from the Study Section 7.2.2 Physical Examination Section 7.2.3 Body Weight and Linear Growth Section 7.2.4 Vital Sign Section 7.2.9 Concomitant Medications Section 7.3.2 Knee and Hand/Wrist Radiographs Section 7.4.1 Low-dose Whole Body Computed Tomography Section 9.1.10 Follow-up of Adverse Events and Serious Adverse Events	References to Parts B/C/D are to PVO-1A-202 Parts B/C/D which corresponds to PVO-1A-204, ongoing in France. Part D was added for skeletally immature subjects who stopped taking study medication for any reason before completion of Part A/B/C. Part D includes yearly visits for up to a 2-year follow-up period following last dose. No dosing will occur during Part D. Assessments obtained in Part D include yearly linear height, knee height, weight, physical exam, vital signs, radiographic assessments of the knee and hand/wrist, low-dose WBCT imaging excluding head, adverse events (AEs), and concomitant medications. Participation in Part D will continue as long as subjects remain skeletally immature. The up to 2-year period would begin the last day the subject stopped receiving study drug in Part A/B/C. The total duration of participation, in Part C and Part D, is a maximum of 4 years. Secondary objective added for Part D to monitor longer-term safety in skeletally immature subjects off treatment. Safety will be summarized for Part D.	To implement safety measures based on DMC recommendations. Preliminary data suggest that the risk of premature epiphyseal fusion is higher in subjects with open epiphyseal growth plates who have received the flare-up dosing regimen. Decreasing the interval between radiographic assessments will allow earlier detection of potential growth plate abnormalities in skeletally immature subjects treated with the palovarotene flare-up dosing regimen. A 2-year follow up is an adequate timeframe to assess growth and epiphyseal changes off palovarotene treatment.
Protocol Synopsis Tables 1 and 2 Sections 2.3 Secondary Objectives Section 3.1 Overview of Study Design Section 4.2 Secondary Endpoints Section 7.1 Screening, Recruitment, and Informed Consent	References to Parts B/C/D are to PVO-1A-202 Parts B/C/D which corresponds to PVO-1A-204, ongoing in France. In Part C, subjects may continue on the study for up to an additional 12 months.	To allow for provision of study medication until commercial availability.

Location/Section Number	Change	Rationale
Section 7.2.2 Physical Examination Section 7.2.3 Body Weight and Linear Growth Section 7.2.4 Vital Signs Section 7.2.5 Electrocardiogram Section 7.2.6 Clinical Laboratory Test Section 7.3.1 Columbia-Suicide Severity Rating Scale Section 7.3.2 Knee and Hand/Wrist Radiographs Section 7.4 Efficacy Assessments Section 7.4.1 Low-dose Whole Body Computed Tomography Section 7.4.2 FOP-Physical Function Questionnaire Section 7.4.3 PROMIS Global Health Scale Section 7.4.4 Cumulative Analogue Joint Involvement Scale		
Synopsis Section 3.1 Overview of Study Design Section 3.2 Study Rationale Section 5.1 Study Population (Adult and Pediatric Cohorts – Original Protocol and Amendment 1) Section 6.4 Administration Section 7.1 Screening, Recruitment, and Informed Consent	As of 04 December 2019, all subjects <14 years of age were required to interrupt study drug due to a partial clinical hold placed on the palovarotene clinical development program by the US FDA. Treatment will subsequently not be restarted in children <14 years of age.	As a consequence of the FDA partial clinical hold subjects remained off treatment for a prolonged period of time. As such, a significant gap in dosing occurred which would render any further data to inform additional benefit/risk uninterpretable in this patient population. Part D was added to ensure continued collection of safety data off treatment for these subjects and any subjects who stopped treatment for any other reason.
Section 7.3.3 Bone Safety Management Plan	Added assessments for spinal health carried out on low dose WBCT scans collected in the study.	Emerging data from PVO-2A-201 trial in the multiple osteochondroma indication has suggested a potential effect of palovarotene on bone mineral accrual. As such assessments were added to further characterize this risk in FOP subjects.
Section 7.1 Screening, Recruitment, and Informed Consent	Integrated protocol amendment 5 addendum previously created to describe temporary measures applied during the COVID pandemic.	To integrate protocol amendment 5 for addendum. To assess skeletal maturity in subjects ≥14 years re-initiating treatment in

Location/Section Number	Change	Rationale
Section 7.7 Temporary Measures (Procedures Related to the COVID Pandemic)	Additional update to these temporary measures to clarify that radiographic assessments are required for subjects ≥14 years (who were skeletally immature at their last assessment) as part of the minimal safety procedures prior to re-initiation of palovarotene.	order to ensure appropriate safety follow up as well as determine if weight-based dosing is required.
Changes that did not affect the clinical conduct of the study:		
Global	References to Parts B/C/D are to PVO-1A-202 Parts B/C/D which corresponds to PVO-1A-204, ongoing in France.	Clarification of alignment with PVO-1A-202.
Global	Replaced "chronic" with "non-flared-up-based"	Maintain consistency across palovarotene program
Synopsis Table 2 Section 7 Study Procedures and Assessments Section 7.3.2 Knee and Hand/Wrist Radiographs Section 8.8 Safety	Specified that knee (A/P) and hand/wrist radiographs are anterior/posterior and posterior/anterior views, respectively	Clarified radiograph views by anatomic structure
Section 1.1.3.1.1 Palovarotene Pharmacokinetics	Added new exposure information	Update with current information
Section 3.1 Overview of Study Design	Added radiographs for subjects who receive flare-up-based treatment and have not reached 100% skeletal maturity.	Integration of administrative change from protocol amendment 5 addendum #1.
Section 7.2.3 Body Weight and Linear Growth Assessments	Added missing evaluated month for linear growth assessments and knee height measurements.	Integration of administrative change from protocol amendment 5 addendum #1.
Section 7.6 Data Monitoring Committee	Added DMC language.	Clarifying DMC oversight
Section 7.2.8 Adverse Events Section 9.1.10 Follow up of Adverse Events and Serious Adverse Events	Collection of SAE reports, including deaths, will continue until 30 days past end of study.	Clarification of end date of collection of SAEs, including death reports.
Section 9.8 Coordinating Investigator	Added statement about Coordinating Investigator.	Integration of administrative change from protocol amendment 5 addendum #1.
Table 1	Assessment added designating annual site visits should be included at Months 12, 24, 36, 48, 60, 72, EOT, and EOS (±1 month) for the	Integration of administrative change from protocol amendment 5 addendum #2.

Location/Section Number	Change	Rationale
	assessment/procedure of low-dose WBCT scan, excluding head.	
Table 2	Deleted the reference to footnote 14 for the assessment/procedure of Low-dose WBCT scan, excluding head.	Integration of administrative change from PVO-1A-204 Protocol Amendment 5 Addendum #2.
General	Corrected minor errors and formatting irregularities.	To provide a consistent presentation.

GROUPS RESPONSIBLE FOR STUDY CONTACT

Task	Vendor or Responsible Group
Trial Oversight and Management Medical Writing	Clementia Pharmaceuticals Inc. 1000, De La Gauchetière Suite 1200 Montreal, Quebec, Canada, H3B 4W5 Tel: PPD Fax: PPD
Data Management Clinical Monitoring Biostatistics Statistical Programming Electronic Data Capture System	Medpace, Inc. 5375 Medpace Way Cincinnati, Ohio 45227 USA Tel: PPD Fax: PPD
Medical Monitoring	PPD Medpace 5375 Medpace Way Cincinnati, Ohio 45227 Tel: PPD Fax: PPD Email: PPD
Central Laboratory	Medpace Reference Laboratories LLC 5365 Medpace Way Cincinnati, Ohio 45227 USA Tel: PPD Fax: PPD
Central Electrocardiogram Laboratory	Medpace Cardiovascular Core Laboratory 5365 Medpace Way Cincinnati, Ohio 45227 USA Tel: PPD Fax: PPD
Imaging Core Laboratory	PAREXEL Informatics 195 West Street Waltham, MA 02451 Tel: PPD Fax: PPD

PROTOCOL SYNOPSIS

Title	A Phase 2, Open-Label, Efficacy and Safety Study of an RARγ-Specific Agonist (Palovarotene) to Prevent Heterotopic Ossification in Subjects with Fibrodysplasia Ossificans Progressiva (FOP).
Sponsor	Clementia Pharmaceuticals Inc.
Objectives	Primary Objective • To evaluate the safety and efficacy of different palovarotene dosing regimens in subjects with FOP. Efficacy will be based on the ability of palovarotene to prevent the formation of new heterotopic ossification (HO) as assessed by low-dose whole body computed tomography (WBCT) scan, excluding head. Secondary Objectives • To evaluate the effect of palovarotene on range of motion (ROM) as assessed by the Cumulative Analogue Joint Involvement Scale (CAJIS) for FOP. • To evaluate the effect of palovarotene on physical function using age-appropriate forms of the FOP-Physical Function Questionnaire (PFQ). • To evaluate the effect of palovarotene on physical and mental health using age- appropriate forms of the Patient Reported Outcomes Measurement Information System (PROMIS) Global Health Scale. • To evaluate the pharmacokinetics of palovarotene. Secondary Objective (Part D) • To implement safety measures based on the Data Monitoring Committee (DMC) recommendations in order to ensure that assessments of safety continue for up to 2 years post last dose of study treatment for skeletally immature subjects.
Study Design	A Phase 2, single-center, open-label study that will explore different dosing regimens of palovarotene in adult and pediatric subjects with FOP. References to Parts B/C/D are to PVO-1A-202 Parts B/C/D which corresponds to PVO-1A-204, ongoing in France. Under the original protocol and Amendment 1, subjects who successfully completed Study PVO-1A-201 as well as up to two new adult subjects were followed for up to 24 months. Subjects who participated under Amendment 1 will be followed for up to an additional 48 months. No new subjects will be enrolled. **Non-Flare-up Based Treatment** All subjects will receive non-flare-up based treatment of 5 mg palovarotene once daily (weight-adjusted doses for skeletally immature subjects [see table below and Table 5]). Note: all weight-based dosing, both non-flare-up-based and flare-up, will cease when subjects become skeletally mature, but radiographic assessment of the growth plate (performed every 6 months) will continue until these subjects achieve 100% skeletal maturity as defined as growth plate closure at both knee and hand/wrist locations. Additional radiographic assessments will be performed every 3 months in those subjects who (1) received the flare-up dosing regimen in the period of time since their last radiographic assessment; and (2) had not achieved 100% skeletal maturity on their last radiographic assessment. Subjects will follow all assessments as outlined in Table 1, Table 2 and Table 3. Subjects who cannot receive non-flare-up based treatment will only undergo annual assessments (clinical laboratory tests will not be performed). In the event of a flare-up, these subjects will receive flare-up-based treatment and undergo all flare-up based assessments, including clinical laboratory tests and radiographs if they have not reached 100% skeletal maturity.

Study Design (cont.)

Subjects from Amendment 1 Continuing Non-Flare-Up Based Treatment
Subjects who began non-flare-up based treatment prior to this amendment will continue the same visit schedule, and will receive non-flare-up based treatment for up to an additional 48 months. Therefore, these subjects may undergo non-flare-up based treatment for up to 72 months over the entire study.
Subjects continuing Amendment 3 (dated 22 March 2018) and subsequent amendments will follow all procedures and undergo all assessments as specified in the Schedule of Assessments in Table 1, including low-dose WBCT scan (excluding head) at all annual site visits (Months 12, 24, 36, 48, 60 and 72). Non-flare-up Day 1 is the first day that non-flare-up based treatment was initiated prior to Amendment 2, and total duration of treatment will continue under Amendment 3 and subsequent amendments.
Remote visits (eg, at home or at a local medical facility; and via telephone contact from clinical site personnel) will occur every 3 months unless the Investigator deems that a site visit is necessary; urine pregnancy tests will be performed each month for females of childbearing potential (FOCBP).

Subjects from Amendment 1 Starting Non-Flare-Up Based Treatment
Subjects who will start non-flare-up based treatment will receive non-flare-up based treatment for up to 48 months. These subjects will follow all procedures and undergo all assessments as specified in the Schedule of Assessments in Table 2, including low-dose WBCT scan (excluding head) at Screening for this amendment and at all annual site visits (Months 12, 24, 36 and 48). Non-flare-up Day 1 is the first day that non-flare-up based treatment is initiated under this amendment for these subjects.
Remote visits (eg, at home or at a local medical facility; and via telephone contact from clinical site personnel) will occur every 3 months unless the Investigator deems that a site visit is necessary; urine pregnancy tests will be performed each month for FOCBP.

Part D:

Annual post last dose of study treatment assessments for up to 2 years will be obtained in subjects who were skeletally immature at the time of study treatment discontinuation in order to obtain longer-term safety data. No new subjects will be enrolled into Part D. Subjects who were enrolled in Parts A, B or C who have discontinued the study and were skeletally immature at their last assessment will be invited back to participate in the off-treatment Part D safety follow-up. These subjects will follow all procedures and undergo all assessments as specified in the Schedule of Assessments in Table 4.

Flare-Up Based Treatment
Subjects will report potential flare-up symptoms to site personnel; such symptoms include, but are not limited to, pain, swelling, redness, decreased range of motion, stiffness, and warmth. Only one symptom is required to define a flare-up. If these symptoms are consistent with previous flare-ups, include a subject-reported onset date, and are confirmed by the Investigator as associated with a flare-up, subjects will immediately receive open-label palovarotene treatment as follows:

- 20 mg for 4 weeks (28 days) once daily. The first dose will be taken upon flare-up confirmation by the Investigator. To be followed by:
- 10 mg for 8 weeks (56 days) once daily, for a total flare-up treatment duration of 12 weeks (84 days); 10 mg treatment may be extended if the flare-up is ongoing and continue until the flare-up resolves. Dosing will be extended in 4-week intervals and be based on clinical signs and symptoms as assessed by the Investigator.

Subjects under the age of 18 years will receive weight-adjusted doses of 20 mg palovarotene (for 28 days) and 10 mg palovarotene (for 56 days) as shown in Table 5. (Note: all weight-based flare-up dosing will cease when subjects are 18 years old, but radiographic assessment of the growth plate will continue until these subjects achieve 100% skeletal maturity at both knee and hand/wrist locations.)

Flare-up-based dosing should also be initiated if the Investigator confirms the presence of a substantial high-risk traumatic event likely to lead to a flare-up.

Study Design (cont.)	Should a subject experience an intercurrent flare-up, or other substantial traumatic event likely to lead to a flare-up, at any time during flare-up-based treatment, the 12-week dosing regimen will restart upon new intercurrent flare-up confirmation by the Investigator (ie, 4 weeks of 20 mg palovarotene followed by 8 weeks of 10 mg palovarotene [or weight-based equivalent]). A Flare-up Cycle will include the first flare-up or traumatic event and any subsequent intercurrent flare-ups or traumatic events during the same dosing period. Flare-Up Cycle Safety Day 1 is defined as the first day that study drug is administered for the first flare-up or traumatic event during that cycle. Safety assessments will be performed at Flare-up Cycle Safety Day 1 and then every 12 weeks thereafter until treatment of the last flare-up or traumatic event in the cycle is completed. If any flare-up in a cycle has not resolved after 12 weeks, treatment and safety assessments will be extended and 10 mg palovarotene (or the weight- based equivalent) will be administered in 4-week intervals until all the flare-ups or traumatic events resolve and flare-up-based treatment has been completed. It is possible that subjects may experience more than one Flare-up Cycle during the study. Subjects receiving flare-up-based treatment will follow all procedures and undergo all assessments as specified in the Schedule of Assessments in Table 3. All assessments will occur remotely, unless the Investigator deems it necessary to evaluate subjects at the clinical site. Once all flare-ups in a cycle have resolved and flare-up-based treatment has been completed, subjects will resume non-flare-up-based treatment with 5 mg palovarotene once daily (weight-adjusted doses for skeletally immature subjects). The pharmacokinetics of palovarotene dosing will be assessed at the first 3-month safety assessment during non-flare-up-based treatment; if samples cannot be obtained during the first 3-month safety assessment, or if subjects are on flare-up-based treatment, then blood samples for non-flare-up treatment pharmacokinetics can be obtained during any subsequent 3-month safety visit. Pharmacokinetics of palovarotene dosing will also be assessed twice during flare-up-based treatment: once during the 20-mg regimen at any time between Study Days 4 to 28, and once during the 10-mg regimen at any time between Study Days 32 to 84, for the first treated flare-up only. If this is not possible for the first treated flare-up, pharmacokinetic blood samples can be obtained during any subsequent flare-up dosing cycle. Pharmacokinetic blood samples will be collected at pre-dose and 3, 6, 10, and 24 hours post-dose. Subjects who underwent a pharmacokinetic assessment for flare-up-based treatment prior to Amendment 3 will not have flare-up pharmacokinetics assessed again. However, these subjects will need to have non-flare-up treatment pharmacokinetics assessed at a 3-month safety visit. As of 04 December 2019, all subjects <14 years of age were required to interrupt study drug due to a partial clinical hold placed on the palovarotene clinical development program by the US FDA. Treatment will subsequently not be restarted in children <14 years of age. Off Treatment Part D: No study drug will be administered in Part D. For skeletally immature subjects in Part D, added Year 1 (Y1) and Year 2 (Y2) post last dose of study treatment assessments that include linear height, knee height, weight, physical exam, vital signs, radiographic assessments of the knee and hand/wrist, low-dose WBCT imaging, adverse events (AEs), and concomitant medications. Once subjects reach skeletal maturity their participation in Part D will end. The total duration of participation in Part C and Part D combined is a maximum of 4 years (±1 month).

Number of Subjects	A total of approximately nine subjects will be enrolled: ▪ Up to seven subjects enrolled under Amendment 1 from Study PVO-1A-201. ▪ Up to two new adult subjects enrolled under Amendment 1 who did not previously participate in Study PVO-1A-201 or Study PVO-1A-202. Note: No new subjects will be enrolled under this amendment.
Total Number of Sites	One investigational site in France.
Study Population (Adult and Pediatric Cohorts – Original Protocol and Amendment 1)	Inclusion Criteria 1. Completion of Study PVO-1A-201 (through Study Day 84), including any subject from Study PVO-1A-202); or Adult Cohort subjects not enrolled in Study PVO-1A-201, have the confirmed R206H genetic mutation consistent with FOP, have had at least two acute symptomatic flare-ups in the past 2 years but no flare-up symptoms within the past 4 weeks (including at the time of enrollment), have a CAJIS score of 6 to 16, inclusive, and able to receive non-flare-up-based dosing. 2. For the Adult Cohort, subjects under the age of 18 must have knee and hand/wrist radiographs confirming ≥90% skeletal maturity. 3. Written, signed, and dated subject/parent informed consent; and, for subjects who are minors, age-appropriate assent (this must be performed according to local regulations). Exclusion Criteria 1. Simultaneous participation in another clinical research study (except for Studies PVO-1A-201, PVO-1A-202, PVO-1A-203, or PVO-1A-001) within 4 weeks prior to Screening. 2. Any reason that, in the opinion of the Investigator, would lead to the inability of the subject and/or family to comply with the protocol.
Study Population for Non-Flare-up-based Treatment (Adult Cohort – Original Protocol and Amendment 1)	Inclusion Criteria 1. Females of child-bearing potential (FOCBP) must have a negative blood or urine pregnancy test (with sensitivity of at least 50 mIU/mL) prior to administration of palovarotene. Male and FOCBP subjects must agree to remain abstinent during treatment and for 1 month after treatment or, if sexually active, to use two highly effective methods of birth control during and for 1 month after treatment. Additionally, sexually active FOCBP subjects must already be using two highly effective methods of birth control 1 month before treatment is to start. Specific risk of the use of retinoids during pregnancy, and the agreement to remain abstinent or use two highly effective methods of birth control will be clearly defined in the informed consent and the subject or legally authorized representatives (eg, parents, caregivers, or legal guardians) must specifically sign this section. 2. Subjects must be accessible for treatment with palovarotene and follow-up. Subjects living at distant locations from the investigational site must be able and willing to travel to a site for the initial and all on-site follow-up visits. Exclusion Criteria 1. Weight <20 kg. 2. Intercurrent known or suspected non-healed fracture at any location. 3. If currently using vitamin A or beta carotene, multivitamins containing vitamin A or beta carotene, or herbal preparations, fish oil, and unable or unwilling to discontinue use of these products during palovarotene treatment. 4. Exposure to synthetic oral retinoids other than palovarotene in the past 30 days prior to Screening (signature of the informed consent). 5. Concurrent treatment with tetracycline or any tetracycline derivatives due to the potential increased risk of pseudotumor cerebri. 6. History of allergy or hypersensitivity to retinoids or lactose

Study Population for Non-Flare-up-based Treatment (Adult Cohort – Original Protocol and Amendment 1) (cont.)	7. Concomitant medications that are inhibitors or inducers of cytochrome P450 (CYP450) 3A4 activity). 8. Amylase or lipase >2x above the upper limit of normal (ULN) or with a history of chronic pancreatitis. 9. Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5x ULN. 10. Fasting triglycerides >400 mg/dL with or without therapy. 11. Female subjects who are breastfeeding. 12. Subjects with uncontrolled cardiovascular, hepatic, pulmonary, gastrointestinal, endocrine, metabolic, ophthalmologic, immunologic, psychiatric, or other significant disease. 13. Subjects experiencing suicidal ideation (type 4 or 5) or any suicidal behavior within the past month as defined by the Columbia Suicide Severity Rating Scale (C-SSRS).
Study Population for Flare-up-based Treatment (Adult and Pediatric Cohorts - Original Protocol and Amendment 1)	<u>Inclusion Criteria</u> 1. Symptomatic onset of a flare-up within 7 days before the first dose of study drug and defined by the presence of at least two of the following symptoms: pain, soft tissue swelling, decreased ROM, stiffness, redness, and warmth. Symptoms must be reported by the subject, be consistent with their previous flare-ups, and include a subject-reported onset date, and flare-up must be confirmed by the Investigator. 2. Flare-up is at an appendicular area (upper or lower extremity), abdomen, chest, neck, or lower back; and subject has received, is receiving, or is willing to receive treatment per standard of care, which may or may not include prednisone (2 mg/kg PO to a maximum dose of 100 mg daily) for 4 days. 3. Females of child-bearing potential (FOCBP) must have a negative blood or urine pregnancy test (with sensitivity of at least 50 mIU/mL) prior to administration of palovarotene. Male and FOCBP subjects must agree to remain abstinent during treatment and for 1 month after treatment or, if sexually active, to use two highly effective methods of birth control during and for 1 month after treatment. Additionally, sexually active FOCBP subjects must already be using two highly effective methods of birth control 1 month before treatment is to start. Specific risk of the use of retinoids during pregnancy, and the agreement to remain abstinent or use two highly effective methods of birth control will be clearly defined in the informed consent and the subject or legally authorized representatives (eg, parents, caregivers, or legal guardians) must specifically sign this section. 4. Subjects must be accessible for treatment with palovarotene and follow-up. Subjects living at distant locations from the investigational site must be able and willing to travel to a site for the initial and all on-site follow-up visits. <u>Exclusion Criteria</u> 1. Weight <20 kg. 2. Intercurrent known or suspected non-healed fracture at any location. 3. Complete immobilization of joint at site of flare-up. 4. Inability of the subject to undergo imaging assessments using plain radiographs. 5. Currently using vitamin A or beta carotene, multivitamins containing vitamin A or beta carotene, or herbal preparations, fish oil, and unable or unwilling to discontinue use of these products during palovarotene treatment. 6. Exposure to synthetic oral retinoids other than palovarotene in the past 30 days prior to Flare-up Screening (signature of the informed consent). 7. Concurrent treatment with tetracycline or any tetracycline derivatives due to the potential increased risk of pseudotumor cerebri. 8. History of allergy or hypersensitivity to retinoids or lactose. Concomitant medications that are inhibitors or inducers of CYP450 3A4 activity (see Section 5.6.1).

Study Population for Flare-up-based Treatment (Adult and Pediatric Cohorts - Original Protocol and Amendment 1) (cont.)	9. Any subject with clinically significant elevations in amylase, lipase, AST, ALT, or fasting triglycerides during the most recent clinical laboratory assessment will require re-test prior to immediate flare-up-based dosing with palovarotene per the Investigator. If upon re-test, the laboratory value in question remains clinically significant abnormal, then the subject will not receive flare-up-based treatment for this flare-up. 10. Female subjects who are breastfeeding. 11. Subjects with uncontrolled cardiovascular, hepatic, pulmonary, gastrointestinal, endocrine, metabolic, ophthalmologic, immunologic, psychiatric, or other significant disease. 12. Subjects experiencing suicidal ideation (type 4 or 5) or any suicidal behavior within the past month as defined by the C-SSRS. 13. Any reason that, in the opinion of the Investigator, would lead to the inability of the subject and/or family to comply with the protocol.
Study Population (All Subjects - Amendment 2 and Amendment 3)	Inclusion Criteria 1. Prior participation in Amendment 1 of the current study (PVO-1A-204). 2. Written, signed, and dated subject/parent informed consent; and, for subjects who are minors, age-appropriate assent (this must be performed according to local regulations). 3. Females of child-bearing potential must have a negative blood or urine pregnancy test (with sensitivity of at least 50 mIU/mL) prior to administration of palovarotene. Male and FOCBP subjects must agree to remain abstinent from heterosexual sex during treatment and for 1 month after treatment or, if sexually active, to use two effective methods of birth control during and for 1 month after treatment. Additionally, sexually active FOCBP subjects must already be using two effective methods of birth control 1 month before treatment is to start. Specific risk of the use of retinoids during pregnancy, and the agreement to remain abstinent or use two effective methods of birth control will be clearly defined in the informed consent and the subject or legally authorized representatives (eg, parents, caregivers, or legal guardians) must specifically sign this section. Exclusion Criteria 1. Any reason that, in the opinion of the Investigator, would lead to the inability of the subject and/or family to comply with the protocol.
Study Population of Subjects Starting Non-Flare-up-based Treatment During Amendment 3	Inclusion Criteria 1. Subjects must be accessible for treatment with palovarotene and follow-up. Subjects living at distant locations from the investigational site must be able and willing to travel to a site for the initial and all on-site follow-up visits. 2. Subjects must be able to undergo low-dose WBCT scan, excluding head. Exclusion Criteria 1. Amylase or lipase >2x above the upper limit of normal (ULN) or with a history of chronic pancreatitis. 2. Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5x ULN. 3. Fasting triglycerides >400 mg/dL with or without therapy. 4. Subjects experiencing suicidal ideation (type 4 or 5) or any suicidal behavior within the past month as defined by the Columbia Suicide Severity Rating Scale (C-SSRS).
Investigational Product	Palovarotene supplied as powder-filled hard gelatin capsules. The capsules may be swallowed whole or opened and the contents added onto specific food: apple sauce, pudding, or yogurt.
Dose/Route/Regimen for Non-Flare-Up Based Treatment	Palovarotene: 5 mg daily or weight-based equivalent for skeletally immature subjects (upon entry into the study) / taken orally with food / at approximately the same time each day. For 5 mg palovarotene, weight equivalent doses for 20 to <40 kg, 40 to <60 kg, and ≥60 kg will be 3 mg, 4 mg, and 5 mg, respectively.

Dose/Route/Regimen for Flare-up-based Treatment

Palovarotene initiated at the start of a flare-up for subjects 18 years of age and older: 20 mg for 4 weeks (28 days) once daily, 10 mg for 8 Weeks (56 days) once daily for a total of 12 weeks (84 days) (may be extended in 4-week intervals if flare-up is ongoing and continue until flare-up resolves) / weight-adjusted for subjects under the age of 18 years / taken orally with food / at approximately the same time each day.
The weight-adjusted palovarotene doses and dose de-escalation for flare-up and non-flare-up-based dosing are:

Weight range category	20-mg Equivalent	15-mg Equivalent*	10-mg Equivalent	7.5-mg Equivalent*	5-mg Equivalent*	2.5 mg Equivalent
20 to <40 kg	12.5 mg	10 mg	6 mg	4 mg	3 mg	1.5 mg
40 to <60 kg	15 mg	12.5 mg	7 5 mg	5 mg	4 mg	2 mg
≥60 kg	20 mg	15 mg	10 mg	7.5 mg	5 mg	2.5 mg

* In the event of dose de-escalation from 20-mg, 10-mg, or 5-mg equivalent, respectively.

Comparator Product Dose/Route/Regimen

Not Applicable – this is an open-label study.

Assessments of Efficacy

Primary Efficacy Endpoint

1. Annualized change in new HO volume as assessed by low-dose WBCT scan, excluding head. The annualized change from the original protocol, and Amendments 1 and 2, will be compared to data collected from the NHS.

Secondary Endpoints (Note: baseline is Non-flare-up Day 1. Some subjects may be assessed for up to 72 months):

1. Percent of subjects with new HO at Months 12, 24, 36, 48, 60, 72 and overall.
2. Change from baseline in ROM as assessed by CAJIS at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, and 72.
3. Change from baseline in physical function using age-appropriate forms of the FOP-PFQ at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72.
4. Change from baseline in physical and mental function for subjects ≥15 years old and mental function for subjects <15 years old using age-appropriate forms of the PROMIS Global Health Scale at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72.

Assessments of Safety

Safety evaluations will include AE and serious AE (SAE) reporting, electrocardiograms (for subjects receiving treatment), vital signs (temperature, respiratory rate, blood pressure, and heart rate), physical examination, body weight and height, laboratory parameters (hematology, biochemistry, and urinalysis), urine pregnancy tests for FOCBP, and concomitant medication reporting. Concomitant medications will include treatment per standard of care, which may or may not include corticosteroids (eg, prednisone at 2 mg/kg PO to a maximum dose of 100 mg daily) for 4 days.
Evaluation of subjects under the age of 18 with open epiphyses at the last assessment will include knee (anterior/posterior [A/P]) and hand/wrist radiographs (posterior/anterior [P/A] view) for assessment of epiphyseal growth plate; and standardized stadiometry and knee height for assessments of linear growth (in triplicate). If there is evidence of premature growth plate closure (with or without linear growth deceleration) the Investigator may require that study drug be continued, interrupted, de-escalated, or discontinued. Dose modification decisions will be made by the Investigator upon review of the subject's clinical and radiographic information, and following discussion of the risk/benefit with the subject/parent. The Investigator may consult with the sponsor and the DMC.
In addition, bilateral hand/wrist and knee growth plate morphology will be assessed by WBCT scan safety reads. Bilateral hip growth plate morphology will also be assessed for avascular necrosis in all subjects.
Limb/joint AEs in these subjects will be evaluated by clinical and radiographic assessments as deemed appropriate by the Investigator.

	Adverse event severity will be assessed and reported according to criteria defined in the protocol (mild, moderate, severe). Adverse events known to be associated with retinoids (eg, mucocutaneous events) will be further graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03, 14 June 2010. Subjects 8 years of age and older will be assessed for suicidal ideation and behavior every 3 months using the age-appropriate C-SSRS and at all visits during a Flare-up Cycle. The DMC will assess the safety of the subjects during the course of the study. The DMC can recommend temporary or permanent stopping of the study at any time if there are significant safety concerns. The DMC can also make recommendations for potential dose modifications for individual subjects in the event of treatment-related adverse bone effects. The DMC Charter includes recommended safety stopping rules.
Statistical Analysis (Amendment 3 and subsequent amendments)	The primary efficacy endpoint implemented for Amendment 3 and subsequent amendments is the annualized change in new HO volume (as assessed by low-dose WBCT scan, excluding head). The annualized change will be compared to data collected from a natural history study using a weighted linear mixed effects model with baseline HO volume divided by age as the only covariate and weights used to account for the different lengths of observed subject follow-up. A subject-specific random effect will be included to account for within-subject correlation.

Table 1 Schedule of Assessments During Non-Flare-up-based Treatment (Subjects from Amendment 1 Continuing Non-Flare-up-based Treatment)

Assessment/Procedure	Amendment 3 Consent/Assent[1] (Remote Visit)	Every Month Remote Visit[1,2,] (±1 week)	Every 3 Months Remote Visit[1,2,3] (±2 weeks)	Months 6, 18, 30, 42, 54, 66 Remote Visit[1,2,4] (±1 month)	Months 12, 24, 36, 48, 60 72/EOT/EOS[1,4,5] Site Visit (±1 month)
Informed consent/assent[1]	X				
Inclusion/exclusion	X				
Knee and hand/wrist radiographs[6]			X[7]	X	X
Linear growth assessment (stadiometry, knee height; subjects <18 years of age)[6]				X	X
Physical examination					X
Body weight			X	X	X
Electrocardiogram					X
Study drug dispensing	As needed from Non-flare-up Day 1 through Month 72				
Study drug treatment	Continuous from Non-flare-up Day 1 through Month 72[8]				
Dispense/review subject diary	Dispense diary as needed and review at every subject contact				
Vital signs			X	X	X
C-SSRS (age-appropriate)			X	X	X
Hematology[9]				X	X
Biochemistry (includes lipids, serum pregnancy test)[9]				X	X
Urinalysis[10]				X	X
Pregnancy test[11]		X			
FOP-PFQ[12]				X	X
PROMIS Global Health Scale[12]				X	X
CAJIS				X[13]	X
Low-dose WBCT scan, excluding head[14]					X
Prior/concomitant medications	At every subject contact				
Adverse events	At every subject contact				
Pharmacokinetic blood sample[15]			Month 3 only		
Telephone contact[3]			X		

1 Visits can be combined with flare-up visits when appropriate.

2 Remote visits, except for knee and hand/wrist radiographs, will be performed at the subject's home by qualified study personnel, or at a local medical facility, or via video-conferencing or telephone contact, unless the Investigator deems that a site visit is necessary. Remote visits that occur every 3 months should align with the remote visits at Months 6, 18, 30, 42, 54 and 66. Monthly remote visits will only be conducted for FOCBP subjects.

3 At the time of a remote visit, subjects will be contacted by telephone every 3 months from the time of informed consent until study completion to assess AEs and concomitant medications. Every effort should be made to conduct the telephone contact on the same day as the remote visit completed every 3 months. However, the visit window of ±2 weeks will allow for flexibility in scheduling if needed.

4 Non-flare-up Day 1 is the first day that non-flare-up-based treatment was initiated prior to Amendment 3, and total duration of treatment will continue into Amendment 3. Subjects who began non-flare-up-based treatment prior to Amendment 3 will continue this visit schedule into Amendment 3 and all subsequent amendments, and will receive non-flare-up-based treatment for up to an additional 48 months. Therefore, these subjects may undergo non-flare-up-based treatment for up to 72 months over the entire study. Subjects who decide to stop treatment more than 1 month after an annual visit but who remain in the study will undergo all assessments included in an annual visit as part of their EOT assessments. If the next annual visit is in less than 6 months, the EOT will serve as their EOS assessments and will conclude their participation in the study if subjects decide not to participate in Part D. If the next annual visit is in more

than 6 months, these subjects will be assessed again at the next annual visit and undergo all assessments included in an annual visit. This will serve as their EOS assessment and will conclude their participation in the study if subjects decide not to participate in Part D. If the Part C EOS visit (at completion of the trial) is >6 months from the last annual visit, this visit will serve as the EOT/EOS site visit, will include all annual assessments and will end their participation in the study.

5 Adult subjects who cannot receive non-flare-up-based treatment will only undergo annual assessments (clinical laboratory tests will not be performed).

6 Subjects with open epiphyseal growth plates at the most recent assessment will be evaluated at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72. As the linear growth assessments cannot be performed remotely, all assessments scheduled at these time points will be performed at the clinical site. Limb/joint AEs in these subjects will be evaluated by clinical and radiographic assessments deemed appropriate by the Investigator. Once a subject has achieved 100% skeletal maturity (confirmed by radiography as complete closure of the growth plate), knee and hand/wrist radiographs will no longer be required. If 100% skeletal maturity is not achieved at both locations, then only the location that is still maturing would need to be monitored. In addition, once a subject is 18 years old, linear growth assessments in triplicate and knee height will no longer be required.

7 These additional knee and hand/wrist radiograph assessments will be performed every 3 months (±2 weeks) in those subjects who (1) received flare-up dosing in the period of time since their last assessment; and (2) had not achieved 100% skeletal maturity on their last assessment. Radiographic assessments required because of flare-up status at the time of a remote visit will instead be conducted at the clinical site unless the Investigator determines they can be performed at a local medical facility. All remote assessments will be performed at the clinical site if the radiographs cannot be performed locally.

8 Continuous non-flare-up-based treatment unless flare-up-based treatment is initiated.

9 Analysis of samples can be completed at a local, qualified laboratory. The investigative site should notify the study team if the local laboratory cannot test all the analytes listed in Table 6. If the total thyroxine (Total T4), free T4, uric acid, gamma glutamyl transferase, inorganic phosphorous, very low-density lipoprotein, or globulin parameters are not available through the local laboratory, and alternative arrangements cannot be made, testing of these analytes may be omitted provided other subject-assessments of thyroid function (ie, thyroid-stimulating hormone), lipid metabolism (ie, triglycerides, low-density lipoprotein, high-density lipoprotein, and total cholesterol), and protein metabolism (ie, total protein and albumin) are available and confirmed to be stable as per the Investigator. Alternative arrangements to test the listed analytes are to be made if the Investigator, Medical Monitor, or sponsor determines that they have the potential to impact subject safety. In the event the local laboratory is unable to test any other analytes, they may be omitted in exceptional circumstances after consultation with the sponsor. Such exceptions will not be applied to any of the key safety analytes (see Section 7.2.6).

10 If urinalysis results are abnormal, then a microscopic evaluation will be completed.

11 Pregnancy testing will be performed monthly for females of child-bearing potential. Urine pregnancy test will be performed only when a serum pregnancy test is not obtained.

12 Age-appropriate versions of the FOP-PFQ and PROMIS Global Health Scale will be used.

13 CAJIS assessment may be performed remotely or by videoconferencing.

14 Baseline for low-dose WBCT scan, excluding head, was performed under the original protocol or under Amendment 1 (ie, prior to the initiation of non-flare-up-based dosing under Amendment 3).

15 Blood samples for pharmacokinetic assessment of non-flare-up dosing will be collected at the first 3-month safety assessment at predose and 3, 6, 10, and 24 hours post-dose; if samples cannot be obtained at the 3-month safety assessment, or if a subject is on flare-up-based treatment, then the blood sample for non-flare-up-based treatment pharmacokinetics can be obtained during any subsequent 3-month safety visit.

Note: study procedures that require sedation will not be performed.

AE = adverse event, CAJIS = Cumulative Analogue Joint Involvement Scale for FOP, C-SSRS = Columbia Suicide Severity Rating Scale, EOS = end of study, EOT = end of treatment; FOP-PFQ = Fibrodysplasia Ossificans Progressiva physical function questionnaire, PROMIS = Patient Reported Outcomes Measurement Information System, WBCT = whole body computed tomography.

Table 2 Schedule of Assessments During Non-Flare-up-based Treatment (Subjects from Amendment 1 Starting Non-Flare-up-based Treatment)

Assessment/ Procedure	Amendment 3 Screening/ Non-Flare-Up Day 1[1]/ Site Visit (-1 month)	Non-Flare-Up Day 7 (±3 days)	Every Month Remote Visit[1,2] (±1 week)	Every 3 Months Remote Visit[1,2,3] (±2 weeks)	Months 18, 30 42 Remote Visit[1,2] (±1 month)	Months 6, 12, 24, 36, 48/EOT/ EOS[1,4,5] Site Visit (±1 month)
Informed consent/assent[1]	X					
Inclusion/exclusion	X					
Knee and hand/wrist radiographs for assessment of epiphyseal growth plate[6]	X			X[7]	X	X
Linear and knee height growth assessments (<18 years of age)[6]	X				X	X
Physical examination	X					X
Body weight	X			X	X	X
Electrocardiogram	X	X[8]				X
Study drug dispensing	As needed from Non-flare-up Day 1 through Month 48					
Study drug treatment	Continuous from Non-flare-up Day 1 through Month 48[9]					
Dispense/review subject diary	Dispense diary as needed and review at every subject contact					
Vital signs	X			X	X	X
C-SSRS (age-appropriate)	X			X	X	X
Hematology[10]	X				X	X
Biochemistry (includes lipids)[10]	X				X	X
Urinalysis	X				X	X
Pregnancy test[12]			X			
FOP-PFQ[13]	X				X	X
PROMIS Global Health Scale[13]	X				X	X
CAJIS	X				X[14]	X
Low-dose WBCT scan, excluding head	X					X[15]
Prior/concomitant medications	At every subject contact					
Adverse events	At every subject contact					
Pharmacokinetic blood sample[16]				Month 3 only		
Telephone contact[3]				X		

1 A visit will be scheduled as soon as possible after Amendment 3 is approved at the clinical site and non-flare-up-based treatment will be started during that visit (Non-flare-up Day 1). Visits can be combined with flare-up visits when appropriate.

2 Remote visits, except for knee and hand/wrist radiographs, will be performed at the subject's home by qualified study personnel, at a local medical facility, or via video-conferencing or telephone contact unless the Investigator deems that a site visit is necessary. Remote visits that occur every 3 months should align with the remote visits at Months 18, 30 and 42. Monthly remote visits will only be conducted for FOCBP subjects.

3 At the time of a remote visit, subjects will be contacted by telephone every 3 months from the time of informed consent until study completion to assess AEs and concomitant medications. Every effort should be made to conduct the telephone contact on the same day as the remote visit completed every 3 months. However, the visit window of ±2 weeks will allow for flexibility in scheduling if needed.

4 Subjects who decide to stop treatment more than 1 month after an annual visit but who remain in the study will undergo all assessments included in an annual visit as part of their EOT assessments. If the next annual visit is in less than

6 months, the EOT will serve as their EOS assessments and will conclude their participation in the study. If the next annual visit is in more than six months, these subjects will be assessed again at the next annual visit and undergo all assessments included in an annual visit. This will serve as their EOS assessment and will conclude their participation in the study. If the Part C EOS visit (at completion of the trial) is > 6 months from the last annual visit, this visit will serve as the EOT/EOS site visit, will include all annual assessments and will end their participation in the study.

5 Adult subjects who cannot receive non-flare-up-based treatment will only undergo annual assessments (clinical laboratory tests will not be performed).

6 Subjects with open epiphyseal growth plates at the most recent assessment will undergo knee (A/P) and hand/wrist radiographs (P/A view) and measurements of linear and knee height (in triplicate) at Amendment 3 Screening and/or Non-flare-up Day 1. As the linear growth assessments cannot be performed remotely, all assessments scheduled at these time points will be performed at the clinical site. Subjects for whom radiographs were performed within the last 3 months will not need to repeat radiographs at Screening. Subjects with open epiphyseal growth plates at this assessment will also be evaluated at Months 6, 12, 18, 24, 30, 36, 42 and 48. Limb/joint AEs in these subjects will be evaluated by clinical and radiographic assessments deemed appropriate by the Investigator. Once a subject has achieved 100% skeletal maturity (confirmed by radiography), knee and hand/wrist radiographs will no longer be required. If 100% skeletal maturity is not achieved at both locations, then only the location that is still maturing would need to be monitored. In addition, once a subject is 18 years old, linear growth assessments in triplicate and knee height will no longer be required.

7 These additional knee and hand/wrist radiograph assessments will be performed every 3 months (±2 weeks) in those subjects who (1) received flare-up dosing in the period of time since their last assessment; and (2) had not achieved 100% skeletal maturity on their last assessment. Radiographic assessments required because of flare-up status at the time of a remote visit will instead be conducted at the clinical site unless the Investigator determines they can be performed at a local medical facility. All remote assessments will be performed at the clinical site if the radiographs cannot be performed locally.

8 ECG may be performed at the subject's home by qualified study personnel, at a local medical facility, or at the clinical site.

9 Continuous non-flare-up-based treatment unless flare-up-based treatment is initiated.

10 Analysis of samples can be completed at a local, qualified laboratory. The investigative site should notify the study team if the local laboratory cannot test all the analytes listed in Table 6. If the total thyroxine (Total T4), free T4, uric acid, gamma glutamyl transferase, inorganic phosphorous, very low-density lipoprotein, or globulin parameters are not available through the local laboratory, and alternative arrangements cannot be made, testing of these analytes may be omitted provided other subject-assessments of thyroid function (ie, thyroid-stimulating hormone), lipid metabolism (ie, triglycerides, low-density lipoprotein, high-density lipoprotein, and total cholesterol), and protein metabolism (ie, total protein and albumin) are available and confirmed to be stable as per the Investigator. Alternative arrangements to test the listed analytes are to be made if the Investigator, Medical Monitor, or sponsor determines that they have the potential to impact subject safety. In the event the local laboratory is unable to test any other analytes, they may be omitted in exceptional circumstances after consultation with the sponsor. Such exceptions will not be applied to any of the key safety analytes (see Section 7.2.6).

11 If urinalysis results are abnormal, then a microscopic evaluation will be completed.

12 Pregnancy testing will be performed monthly for females of child-bearing potential. Urine pregnancy test will be performed only when a serum pregnancy test is not obtained.

13 Age-appropriate versions of the FOP-PFQ and PROMIS Global Health Scale will be used.

14 CAJIS assessment may be performed remotely or by videoconferencing.

15 Baseline for low-dose WBCT scan, excluding head, will be at Amendment 3 Screening (ie, when the subject provides informed consent/assent for Amendment 3). The low-dose WBCT scans, excluding head, will only be performed during annual visits (not at the 6-month visit).

16 Blood samples for pharmacokinetic assessment of non-flare-up dosing will be collected at the first 3-month safety assessment at predose and 3, 6, 10, and 24 hours post-dose; if samples cannot be obtained during the first 3-month safety assessment, or if the subject is on flare-up-based treatment, then the blood sample for non-flare-up-based treatment pharmacokinetics can be obtained during any subsequent 3-month safety visit.

Note: study procedures that require sedation will not be performed.

AE = adverse event, A/P = anterior/posterior, CAJIS = Cumulative Analogue Joint Involvement Scale for FOP, C-SSRS = Columbia Suicide Severity Rating Scale, EOS = end of study, EOT = end of treatment, FOP-PFQ = Fibrodysplasia Ossificans Progressiva physical function questionnaire, P/A = posterior/anterior; PK = pharmacokinetic(s), PROMIS = Patient Reported Outcomes Measurement Information System, WBCT = whole body computed tomography.

Table 3 Schedule of Assessments for Flare-up-based Treatment (Subjects with a Flare-Up)

Assessment/Procedure		FLARE-UP CYCLE SAFETY ASSESSMENTS Remote Visits[1,2] (±5 days)	
	Flare-Up Cycle Safety Day 1[3]	Flare-Up Cycle Safety Day 7	Every 12 Weeks[3]
Vital signs and body weight	X		X
ECG[4]	X	X	X
Hematology[5,6]	X		X
Biochemistry (includes lipids)[5,6]	X		X
Urinalysis[5,6,7]	X		X
C-SSRS (age appropriate)	X		X
Pregnancy testing[8]	X		Every 4 weeks
Study drug dispensing		As needed from Cycle Day 1 to end of treatment of last flare-up cycle[9,10]	
Study drug treatment		Continuous from Cycle Day 1 to end of treatment of last flare-up cycle[3,9,10]	
Dispense/review subject diary		Dispense diary as needed and review at every subject contact	
Flare-up(s) status and end date confirmation[11]	X		At every subject contact
Prior/concomitant medications			At every subject contact
Adverse events			At every subject contact

Treatment/Assessment	FLARE-UP TREATMENT[9] AND PHARMACOKINETICS			
	Flare-Up Day 1[5,12,14]	High Dose Treatment	Low Dose Treatment	
Flare-up (first flare-up or restart for intercurrent flare-up)[11,12]	X	Week 1 to 4 (4 weeks)	Week 4 to 12 (8 weeks)	4-Week Extension (if applicable)
Pharmacokinetic blood sample		X[13]	X[13]	
Telephone contact[14]			End of Week 12	End of each 4-week extension

1 All visit windows are ±5 days, except the End of Flare-Up Cycle Safety Assessments of the first flare-up, which is -5 days because a blood draw is required for pharmacokinetic analysis.

2 Remote visits will be performed at the subject's home by qualified study personnel or at a local medical facility, unless the Investigator deems that a site visit is necessary. Remote visits during treatment extension, if applicable, will occur every 12 weeks until all the flare-ups within a cycle have resolved and treatment has been completed.

3 A Flare-up Cycle will include the first flare-up and any subsequent intercurrent flare-ups or traumatic events during the same dosing period. Flare-Up Cycle Safety Day 1 is defined as the first day that study drug is administered for the first flare-up or traumatic event upon confirmation by the Investigator. Flare-up cycle safety assessments will be performed on Flare-up Cycle Safety Day 1 and then every 12 weeks thereafter until treatment of the last flare-up or traumatic event within a Flare-up Cycle is completed. If treatment of the last flare-up or traumatic event in a cycle resolves within 4 weeks of the last flare-up cycle safety assessment, then another flare-up cycle safety visit does not need to be performed. Once all flare-ups or traumatic events in a cycle have resolved and flare-up-based treatment has been completed, subjects will resume non-flare-up-based treatment with 5 mg palovarotene once daily (weight-adjusted doses for skeletally immature subjects). It is possible that subjects may experience more than one Flare-up Cycle during Amendment 3 and all subsequent amendments of the study.

4 For the first flare-up only. The ECG may be performed at the subject's home by qualified study personnel, at a local medical facility, or at the clinical site.

5 Flare-up-based treatment can begin immediately after the Investigator confirms the presence of a flare-up or traumatic event and prior to availability of safety laboratory results, unless the Investigator determines that the results are required prior to treatment initiation (eg, clinically significant abnormal laboratory test results requiring follow-up). Analysis of samples can be completed at a local, qualified laboratory. The investigative site should notify the study team if the local laboratory cannot test all the analytes listed in Table 6. If the total thyroxine (Total T4), free T4, uric acid, gamma glutamyl transferase, inorganic phosphorous, very low-density lipoprotein, or globulin parameters are not available through the local laboratory, and alternative arrangements cannot be made, testing of these analytes may be omitted provided other subject-assessments of thyroid function (ie, thyroid-stimulating hormone), lipid metabolism (ie, triglycerides, low- density lipoprotein, high-density lipoprotein, and total cholesterol), and protein metabolism (ie, total

protein and albumin) are available and confirmed to be stable as per the Investigator. Alternative arrangements to test the listed analytes are to be made if the Investigator, Medical Monitor, or sponsor determines that they have the potential to impact subject safety. In the event the local laboratory is unable to test any other analytes, they may be omitted in exceptional circumstances after consultation with the sponsor. Such exceptions will not be applied to any of the key safety analytes (see Section 7.2.6).

6 Subjects with normal or non-clinically significant abnormal safety laboratory results observed within 1 month of flare-up based treatment will not need to have laboratory tests performed at Flare-up Cycle Safety Day 1. The Investigator will determine whether subjects with clinically significant abnormal laboratory results in the most recent assessment will need to be re-assessed prior to beginning flare-up-based treatment. The only exception is for pregnancy testing, which must be performed at the start of each Flare-up Cycle and every 4 weeks thereafter until the end of the cycle. However, if a pregnancy test was performed within 4 weeks prior to the start of treatment for a flare-up/trauma, treatment of the flare-up/trauma will not be delayed pending repeat pregnancy testing.

7 If urinalysis results are abnormal, then a microscopic evaluation should be completed.

8 Pregnancy testing will be performed monthly for females of child-bearing potential. A urine pregnancy test will be performed only when a serum pregnancy test is not obtained.

9 A flare-up, or substantial high-risk traumatic event likely to lead to a flare-up, will be treated with a minimum of 4 weeks (28 days) of 20 mg palovarotene once daily followed by 8 weeks (56 days) of 10 mg palovarotene once daily (or weight-based equivalent) for a total of 12 weeks (84 days). If the flare-up has not resolved after 12 weeks, treatment will be extended in 4-week intervals until the flare-up resolves.

10 Should a subject experience an intercurrent flare-up, or other substantial high-risk traumatic event likely to lead to a flare-up, at any time during flare-up-based treatment, the 12-week (84 day) dosing regimen will restart upon confirmation by the Investigator (ie, 4 weeks of 20 mg palovarotene followed by 8 weeks of 10 mg palovarotene [or weight-based equivalent]). This may occur more than once during a Flare-up Cycle.

11 At each contact, flare-up status will be assessed for every flare-up and flare-up end date will be recorded when a flare-up resolves. Flare-up status will also be assessed at Week 12 of the initial flare-up (if only one flare-up) or the last ongoing intercurrent flare-up (if more than one flare-up); if any flare-up is still ongoing, the on-going flare-up(s) will be assessed every 4 weeks until the last flare-up has resolved.

12 Flare-up Day 1 is the first day of treatment for a flare-up/substantial high-risk traumatic event (upon confirmation by the Investigator).

13 Pharmacokinetics of palovarotene dosing will be assessed twice: once during the 20-mg regimen at any time between Study Days 4 to 28, and once during the 10-mg regimen at any time during Study Days 32 to 84, for the first treated flare-up only. If not possible for the first treated flare-up, pharmacokinetic blood samples can be obtained during any subsequent flare-up dosing cycle. Blood samples will be collected at pre- dose and 3, 6, 10, and 24 hours post-dose. Subjects who underwent a flare-up dosing pharmacokinetic assessment prior to Amendment 3 will not have flare-up treatment pharmacokinetics assessed again under Amendment 3 or subsequent amendments. However, these subjects will require a pharmacokinetic assessment for non-flare-up palovarotene dosing at a 3-month safety visit.

14 Flare-up will be evaluated remotely, or by telephone or video-conferencing, unless the Investigator deems that a site visit is necessary. This will include subject-reported current flare-up location, symptoms, and probable causes.

C-SSRS = Columbia Suicide Severity Rating Scale, PK = pharmacokinetic(s)

Table 4 Schedule of Assessments for Part D

Assessment/Procedure	Y1 and Y2 Post Treatment Site Visit[1]
Informed consent[2,3]	X
Knee and hand/wrist radiographs[4,5]	X
Linear and knee height growth assessments (<18 years of age)[4]	X
Physical examination	X
Body weight[2]	X
Vital signs[2]	X
Low-dose, WBCT scan (excluding head)	X
Prior/concomitant medications[2]	At every subject contact
Adverse events[2,6]	At every subject contact

1 Year 1 (Y1) and Year 2 (Y2) visits following the last dose of study drug will be done within the total study duration from enrolment from Part A.
Y1 to be completed in the window of ≥ 6 to < 18 months post last dose of study medication.
If Part A, B or C EOS date is within the Y1 window then the EOS will serve as the Y1 visit.
If Part A, B or C EOS date is prior to Y1 window then Y1 should be scheduled ≥ 6 months from Part A, B or C EOS date but still within the Y1 window.
Y2 to be completed ≥18 – 24 months post last dose of study medication.
If Part A, B or C EOS date is within the Y2 window then the EOS will serve as the Y2 visit.
If Part A, B or C EOS date or Y1 date (if applicable) is prior to Y2 window then Y2 should be scheduled ≥ 6 months from the Part A, B or C EOS date or the Y1 date, whichever is later, but still within the Y2 window.
If subjects had their last dose of study medication and completed Part A, B or C EOS more than 2 years prior to their consent for Part D, then these subjects will only complete Y2 following their consent for Part D.

2 Assessments may be performed remotely (eg, at the subject's home by qualified study personnel, at a local medical facility, or via videoconference or telephone contact from clinical site personnel) unless the Investigator deems that a site visit is necessary.

3 Part D informed consent is required prior to conducting Part D assessments/procedures.

4 Subjects found to be skeletally immature will continue knee and hand/wrist radiographs, and linear and knee height measurements (all in triplicate) at Year 1 (Y1) and Year 2 (Y2). Limb/joint AEs in these subjects will be evaluated by any clinical and radiographic assessments deemed appropriate by the Investigator. Once a subject has achieved 100% skeletal maturity (confirmed by radiography and defined by growth plate closures), knee and hand/wrist radiographs will no longer be required, and this will serve as their Part D study completion. In addition, once a subject is 18 years old, linear and knee height growth assessments will no longer be required. If 100% skeletal maturity is not achieved at both locations, then only the location that is still maturing would need to be monitored.

5 Knee and hand/wrist radiograph assessments will be conducted at the clinical site unless the Investigator determines they can be performed at a local medical facility. All assessments will be performed at the clinical site if the radiographs cannot be performed locally.

6 At each AE assessment, the Investigator must ask the subject about any joint-related complaints.

Note: References to Parts B/C/D are to PVO-1A-202 Parts B/C/D which corresponds to PVO-1A-204, ongoing in France.

AE = adverse event; WBCT = whole-body computed tomography; Y = year;

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACVR1/ALK2	activin receptor type IA/activin-like kinase 2
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
A/P	anterior/posterior view
AST	aspartate aminotransferase
AUC	area under the curve
AVN	avascular necrosis
BMP	bone morphogenetic protein
CAJIS	Cumulative Analogue Joint Involvement Scale for FOP
CI	confidence interval
C_{max}	maximum or peak measured plasma concentration
COPD	chronic obstructive pulmonary disease
COVID	Corona virus disease
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interaction
DMC	Data Monitoring Committee
EAP	early access program
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	end of study
EOT	end of treatment
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FOCBP	female of child-bearing potential

Abbreviation	Definition
FOP	Fibrodysplasia Ossificans Progressiva
FOP-PFQ	FOP-Physical Function Questionnaire
FOP-PFQ-P	Pediatric FOP-PFQ
GCP	Good Clinical Practices
GGT	gamma glutamyl transferase
HDL	high-density lipoprotein
HED	human equivalent dose
HO	heterotopic ossification
IC_{50}	concentration of drug producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LDL	low-density lipoprotein
LME	linear mixed effects
LOQ	limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSC	mesenchymal stem cell
NHS	Natural History Study
OMIM	Online Mendelian Inheritance in Man
P/A	posterior/anterior view
PAS	Pharmacokinetic Analysis Set
PCS	potentially clinically significant
PK	pharmacokinetic(s)
PO	per os
PPS	Per-Protocol Set
PROMIS	Patient Reported Outcomes Measurement Information System
RAR	retinoic acid receptor
RARγ	retinoic acid receptor gamma

Abbreviation	Definition
ROM	range of motion
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Set
SD	standard deviation
$t_{½}$	apparent terminal elimination half-life
T_{max}	time of maximum or peak measured plasma concentration at steady-state
ULN	upper limit of normal
US	United States
VLDL	very low-density lipoprotein
WBCT	whole body computed tomography
wLME	weighted linear mixed effects

1 INTRODUCTION

1.1 Background

1.1.1 Fibrodysplasia Ossificans Progressiva

Fibrodysplasia Ossificans Progressiva (FOP) (OMIM #135100) is a rare, severely disabling disease characterized by heterotopic ossification (HO) in muscles, tendons, and ligaments often associated with painful, recurrent episodes of soft tissue swelling (flare-ups). Lesions begin in early childhood and lead to progressive ankyloses of major joints with resultant loss of movement. Prognosis is poor and life expectancy is reduced. FOP is caused by an activating mutation in the bone morphogenetic protein (BMP) type I receptor, or activin receptor type IA (ACVR1), also known as activin-like-kinase 2 (ALK2) type I receptor. Most patients with FOP (approximately 97%) have the same point mutation, R206H. The International FOP Association, a US-based patient group organization, reports approximately 800 confirmed cases of FOP globally.[1] The prevalence is estimated at approximately 1.36 per million individuals, with no geographic, ethnic, racial, or gender preference.[2] FOP is misdiagnosed approximately 80% of the time resulting in great harm to patients.[3] The preosseous flare-ups that characterize the disease have been misinterpreted as lymphedema, soft tissue sarcoma, or juvenile fibromatosis, often resulting in harmful diagnostic biopsies that exacerbate the progression of the disease, and/or unnecessary chemotherapeutic interventions. Individuals with FOP appear normal at birth except for the pathognomonic malformation of the great toes, which are typically short (lack a phalange) and deviated in hallux valgus.[4]

Heterotopic ossification is episodic and cumulative throughout life, resulting in segments, sheets, and ribbons of extra bone developing throughout the body and across joints, progressively restricting movement. Rapidly growing bony spurs have been known to protrude through the skin causing pain and a risk of infections.[5] Only the tongue, heart, and diaphragm muscle are spared for reasons that have yet to be elucidated. Asymmetric HO in the rib cage and subsequent contralateral growth can lead to a rapid progression in spinal deformity and cause respiratory insufficiency. Ankyloses of the temporomandibular joints results in severe tooth decay and malnutrition. Periods of flare-up activity are interspersed with variable-length intervals of apparently quiescent disease in the absence of obvious clinical symptoms. In some subjects, the presence of substantial soft tissue edema and muscle necrosis observed in imaging performed within 7 days of flare-up symptom-onset suggests that the process that ultimately leads to new HO formation starts before clinical symptoms are reported. Fibrodysplasia Ossificans Progressiva might be similar to other chronic diseases that are characterized by acute exacerbations/relapses, followed by variable-length periods of apparent disease quiescence (eg, relapsing/remitting multiple sclerosis) without clinical symptoms.

The majority of FOP patients are confined to a wheelchair by the third decade of life, and require caregiver assistance to perform daily living activities. The median age of survival is approximately 56 years with mortality often resulting from complications of respiratory insufficiency.[6,7]

1.1.2 Current Therapeutic Options for Fibrodysplasia Ossificans Progressiva

Currently there are no effective medical treatment options to prevent the formation of heterotopic bone in FOP, nor have there been well-controlled trials of other therapeutics in this disease.

Treatments are aimed at the symptomatic management of the disease. Removal of heterotopic bone and other trauma are avoided. Surgical trauma to tissues is likely to induce additional bone formation;[3,8] and intramuscular immunizations; blocks for dental work; muscle fatigue; blunt muscle trauma from bumps, bruises, or falls; or influenza-like viral illnesses can trigger flare-ups leading to HO formation.[9] Falls are a severe form of trauma; in one survey of FOP patients, flare-ups were induced in two-thirds of falls and resulted in permanent loss of movement in 93% of patients.[10] Glucocorticoids are used to manage symptoms of flare-ups affecting major joints of the appendicular skeleton and jaw, especially when used immediately after the onset of a flare-up. Non-steroidal anti-inflammatory agents, cyclooxygenase-2 inhibitors, mast cell stabilizers, and leukotriene inhibitors are reported by patients to manage chronic pain and ongoing disease progression.

The identification of the recurrent point mutation that causes FOP in all classically affected individuals provides a specific target for drug development.[11] An innovative therapeutic approach that can be evaluated in FOP includes diverting the responding mesenchymal stromal cells to a soft tissue fate.[12,13,14] This pathway is the mechanism by which palovarotene is believed to prevent HO in animal models of FOP.

1.1.3 Overview of Palovarotene

Palovarotene is 4-[(E)-2-(5,5,8,8-tetramethyl-3-pyrazol-1-ylmethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-benzoic acid. Palovarotene is an orally bioavailable retinoic acid receptor gamma (RARγ) selective agonist licensed from Roche following the completion of Phase 2 studies in COPD patients (program discontinued due to lack of efficacy), and is being developed by Clementia Pharmaceuticals Inc. as a re-purposed drug for the treatment of FOP.

RARγ agonists potently impair heterotopic endochondral ossification by redirecting prechondrogenic mesenchymal stem cells (MSCs) to a nonosseous soft tissue fate. The rationale for testing retinoids as inhibitors of HO was based on the observation that retinoid signaling is a strong inhibitor of chondrogenesis[15] and that unliganded RAR transcriptional repressor activity is needed for chondrogenic differentiation.[16,17] Inhibition of HO with non-selective retinoids or RARα receptor agonists has also been achieved but to a lesser degree.[13]

RARγ is expressed in chondrogenic cells and chondrocytes[18] where it also operates as an unliganded transcriptional repressor.[19] Hence, an RARγ agonist-based anti-HO therapy could be very effective because it would target both chondrogenic cells and chondrocytes. It has been shown that RARγ agonists exert their action on bone formation through post-translational regulation of BMP signaling by inhibiting Smad phosphorylation and promoting proteasome-regulated degradation of Smads specific to the BMP signaling pathway. Thus, RARγ agonists could directly prevent the activating (R206H) mutation in the BMP type I receptor of FOP patients. Inhibition of both prechondrogenic and chondrogenic cells is also thought to occur through possible stimulation of Wnt-β-catenin signaling.[20,21]

The process of HO consists of two major phases: a catabolic phase of inflammation and tissue destruction followed by an anabolic phase of tissue neogenesis involving the formation of a transient cartilaginous scaffold and its replacement with mature heterotopic bone. A key feature of all HO is the formation of a bridging cartilaginous scaffold that is under control of the BMP and possibly the Wnt–β-catenin signaling pathways. RARγ agonists affect both BMP and Wnt-β-catenin signaling and interfere with the building of the cartilaginous scaffold, thereby disrupting the bridge and derailing HO.[12]

Palovarotene has been evaluated in various animal models of HO including a BMP-implant model, a constitutively-active receptor model (Q207D), and a highly physiological human mutation knock-in model (R206H). Following injury, the results consistently demonstrate dose-dependent reductions in HO with palovarotene across the models, and significant reduction in spontaneous (non-injury) HO with non-flare-up-based treatment. The data from the injury-based Q207D mouse model of FOP demonstrated that a human equivalent dose (HED) of 20 mg palovarotene may be required for the greatest inhibition of HO across all injury conditions.

In addition to the injury-based model, palovarotene has also been effective in preventing HO formation in a spontaneous HO model (*Prrx1-R206H* model) that recapitulates many of the phenotypic features of FOP seen in patients including malformed great toes. An average HED of approximately 5 mg palovarotene administered daily by oral gavage to young *Prrx1-R206H* mice markedly reduced the formation of spontaneous HO, suggesting that daily dosing with palovarotene may be an important component of the treatment regimen in humans.

1.1.3.1 Nonclinical Data

The toxicology of palovarotene has been extensively characterized in rodent and non-rodent studies, including single-dose, repeat-dose (sub-chronic and chronic), reproductive toxicity, genotoxicity, and phototoxicity studies in support of clinical studies in humans. Toxicity studies of four metabolites of palovarotene were also performed. A detailed summary of these studies and the observed effects is provided in the Investigator's Brochure.

The toxicology profile of palovarotene in animals is similar to that which is expected for a retinoid based on the extensive data available for compounds in this class of agents.[22] The toxic potential of this molecule was evaluated in rats dosed daily for up to 6 months and in dogs dosed daily for up to 9 months. Initial chronic toxicity studies at dose levels up to 0.15 mg/kg/day in rats (6-month study) and 0.006 mg/kg/day in dogs (9-month study) did not induce any observed palovarotene-related changes. These studies identified these top doses as the no-observed-effect-level for chronic exposure. Further studies at higher dose levels characterized the toxic potential of this molecule after similar chronic administration periods in these two species. The maximum tolerated dose following chronic exposure was 0.6 mg/kg/day in rats and 0.04 mg/kg/day in dogs. Moreover, in order to evaluate the toxicity profile of metabolites at high exposure levels, 6-month studies were conducted in rats and 9-month studies were conducted in dogs with a mixture of metabolites M2, M3, M4a, and M4b given orally. The toxicity profile of these metabolites was similar to that of parent drug in rats and dogs.

The dose limiting toxicities in adult animals were primarily mucocutaneous effects, with mild/moderate and reversible chondrodystrophy observed at the clinically relevant dose of 1 mg/kg/day in 7 to 8-week old rats. The toxicity of palovarotene has also been evaluated in a 6-week repeat-dose oral toxicity study in juvenile rats (3 weeks old at the start of dosing). These results did not reveal any toxicities not observed in older animals, with the primary toxicologic effects related to bone. At a dose level that produced systemic exposures similar to those predicted in patients, skeletal effects were relatively limited and mild and showed evidence of reversing when dosing stopped, even though juvenile rats were exposed to palovarotene over a period of skeletal development that would be similar to chronic daily dosing from age 2 to 12 years in humans.

In rat and dog mass balance studies, recovery of the administered [^{14}C]-palovarotene dose was complete within 7 days, and elimination of the dose, which was mostly complete within the

first 24 hours after dosing, was exclusively biliary/fecal. At least 68% and 50% of the administered dose was absorbed in rats and dogs, respectively.

After the once-daily [^{14}C]-palovarotene oral dose administration for 5 days in rats, radioactivity was slowly, but extensively distributed into tissues, with the highest exposures seen in the adrenal cortex, adrenal medulla, liver, and the walls of the small intestine and caecum.

Radioactivity in all tissues decreased 8 hours after the last dose, except for the radioactivity in the adrenal cortex.

Inhibition of the six human CYP450 isoforms by palovarotene was moderate, suggesting a low probability that palovarotene would inhibit the clearance of concomitantly administered drugs. The IC_{50} values for all metabolites against human CYP450 3A4 were very high (>100 μM). The oxidative metabolism of the parent drug was primarily by CYP450 3A4.

1.1.3.2 Clinical Data

1.1.3.2.1 Palovarotene Pharmacokinetics

The data describing the clinical pharmacokinetics (PK) of palovarotene are based on 12 completed Phase 1 clinical pharmacology studies in healthy subjects, including a single ascending dose study; a multiple ascending dose study; five drug-drug interaction (DDI) studies with ketoconazole (a strong cytochrome P450 [CYP] 3A4 inhibitor), rifampicin (a strong CYP3A4 inducer), inhibition and induction potential with midazolam (a CYP3A4 substrate), and prednisone (a weak CYP3A4 inhibitor); a bioequivalence study; a [^{14}C]-radiolabeled single-dose mass balance study; a single-dose age and sex study; a single-dose bridging study in Japanese and non-Asian subjects; a definitive food-effect/mode of administration study (as part of the midazolam induction potential study mentioned above); and a thorough QT study and a study evaluating the concentration of palovarotene in seminal fluid.

Pharmacokinetic data were also collected in two multiple-dose studies in subjects with COPD, and three multiple-dose studies in subjects with FOP (one completed Phase 2 study, one ongoing Phase 2 study, and one ongoing Phase 3 study). A population PK model was developed for palovarotene using data obtained after single- and multiple-dose oral administration to healthy volunteers and subjects with COPD and FOP.

To date, over 1200 subjects have received at least one dose of palovarotene across the following indications:

- 309 healthy volunteers received single or multiple doses between 0.02 and 50 mg for up to 4 weeks
- 611 subjects with COPD received multiple doses between 0.2 and 5 mg daily for up to 24 months
- 164 subjects with FOP received multiple doses between 2.5 and 20 mg once daily for up to 4 years, and
- approximately 129 subjects with MO received multiple doses of 2.5 or 5.0 mg once daily for up to 18 months.
- 7 FOP subjects received palovarotene in an early access program (EAP)

In healthy subjects, the palovarotene pharmacokinetics were linear and dose-proportional up to a single dose of 50 mg or a multiple dose of 10 mg under a fed condition. The plasma palovarotene T_{max} was approximately 4 hours and its $T_{½}$ was approximately 8 hours. The

calculated effective half-life was between 5 to 10 hours. With repeated administration, steady-state palovarotene plasma concentrations were attained by day 3.

In a study of Japanese versus non-Asian healthy volunteers, mean plasma concentrations after 5 and 10 mg palovarotene peaked at 4 hours post-dose for both subject populations; the mean terminal half-life ranged from 9.7 to 13 hours. Palovarotene was absorbed and eliminated in a similar manner for both populations, and pharmacokinetic parameters were similar at both dose levels based on geometric mean ratios and CIs for C_{max}, $AUC_{(0-\infty)}$, and $AUC_{(0-t)}$.

Palovarotene was primarily metabolized by CYP3A4. Five metabolites, 6,7-dihydroxy (M1), 6- hydroxy (M2), 7-hydroxy (M3), 6-oxo (M4a), and 7-oxo (M4b) were observed for palovarotene in the clinical pharmacology studies. M1 was present in very low concentrations, usually below the limit of quantification (LOQ). Following administration of ^{14}C-radiolabeled palovarotene, 97% of the dose was recovered in the feces and 3.2% in the urine. Overall, the metabolite profile was qualitatively similar to that reported in all the animal species.

In healthy subjects, palovarotene exposure at steady-state increased approximately three-fold with ketoconazole (a strong CYP3A4 inhibitor), decreased approximately 10-fold with rifampicin (a strong CYP3A4 inducer), decreased slightly by 14% with prednisone (a weak CYP3A4 inhibitor), and did not change consistently with midazolam (a CYP3A4 substrate). Palovarotene did not impact the pharmacokinetics of concomitantly administered drugs, including oral prednisone and midazolam.

Co-administration of palovarotene with food resulted in a 40% increase in $AUC_{0-\infty}$ and a 16% increase in C_{max} compared with administration under fasted conditions. Additionally, T_{max} appeared to be slightly shorter for fasted subjects dosed with palovarotene. Opening the capsule and sprinkling the contents onto soft food did not affect the PK of palovarotene. No clinically relevant differences in palovarotene pharmacokinetics were found between young males and elderly males and between elderly males and elderly females.

A population PK model was used to simulate palovarotene administration in pediatric patients in order to assess the appropriateness of weight-based dosing in skeletally immature children. The simulations identified weight-adjusted doses that provide derived steady-state exposures ($AUC_{0-\tau}$, $C_{max,ss}$, and $C_{min,ss}$) within the range of those for adults after receiving the 10- and 20-mg doses.

1.1.3.2.2 Palovarotene Phase 2 Interventional Studies

The Phase 2 interventional studies for which subjects with FOP have received treatment include:

- Study PVO-1A-201 provided a preliminary assessment of palovarotene efficacy across two different dosing regimens following 6 weeks of treatment for a flare-up relative to placebo (ie, flare-up only regimen). Forty subjects were randomized (3:3:2) within 1 week of a flare-up to receive either 10 mg palovarotene daily for 2 weeks followed by 5 mg daily for 4 weeks (10/5 mg); 5 mg palovarotene for 2 weeks followed by 2.5 mg for 4 weeks (5/2.5 mg); or placebo for 6 weeks. After the 6-week treatment period, subjects began a 6-week follow-up period during which no study drug was administered.
- Study PVO-1A-202/Part A, an open-label extension of Study PVO-1A-201, evaluated the long-term safety and efficacy of prior palovarotene treatment after an additional 12 months of follow-up. Open-label palovarotene was administered to all subjects, including any randomized to placebo during Study PVO-1A-201, experiencing

additional eligible flare-ups (ie, flare-up only regimens). Subjects were treated with high dose palovarotene (10 mg palovarotene for 2 weeks followed by 5 mg for 4 weeks) regimen for 6 weeks, followed by a 6-week period in which no study drug was administered.

- Study PVO-1A-202/Part B (corresponds to Study PVO-1A-204 in France) included non-flare-up-based daily doses (5 mg) of palovarotene in subjects with at least 90% skeletal maturity. During a flare-up, all subjects received higher dose/longer duration treatment with palovarotene (20 mg for 4 weeks followed by 10 mg for 8 weeks). This "non-flare-up-based/flare-up" regimen is the dosing regimen employed in Study PVO-1A 202/Part C that will include non-flare-up-based dosing for skeletally mature as well as skeletally immature subjects. This corresponds to the current study, PVO-1A-204 Amendment 3 in France, that also includes non-flare-up-based dosing (weight-adjusted for skeletally immature subjects).
- Study PVO-1A-202/Part C (corresponds to Study PVO-1A-204 in France, ongoing) extends the non-flare-up-based/flare-up palovarotene regimen to all subjects, including skeletally immature children.
- Study PVO-1A-202/Part D (corresponds to Study PVO-1A-204 in France, ongoing) is adding annual post last dose of study treatment assessments for up to 2 years in subjects who were skeletally immature at the time of study treatment discontinuation in order to obtain longer-term safety data.

1.1.3.2.3 Palovarotene Safety

Consistent with other retinoids, the most commonly reported adverse events across all palovarotene dosing regimens in the FOP interventional studies were mucocutaneous and dermatologic events such as dry skin and lips, erythema, and pruritus. In general, the incidence, total number, duration and severity of mucocutaneous and dermatologic events increased with increasing palovarotene dose. These AEs generally resolved without sequelae after completion of palovarotene treatment. Musculoskeletal events such as arthralgia, pain in extremity, and condition aggravated (the Medical Dictionary for Regulatory Activities [MedDRA] preferred term used to capture reports of FOP flare-ups) were also commonly reported.

The majority of AEs in the palovarotene Phase 2 studies in FOP were mild or moderate in severity.

In the current study, and in the ongoing FOP Phase 2 study, subjects enrolled with open epiphyses undergo knee (anterior/posterior [AP] view) and hand/wrist radiographs (posterior/anterior [PA] view) for assessment of epiphyseal growth plate; and linear and knee height measurements for assessment of growth. The most common epiphyseal growth plate abnormality is growth recovery lines (dense metaphyseal lines) at both baseline and post-baseline time points. Potential premature closure of the epiphysis is closely monitored and data are reviewed quarterly by an independent Data Monitoring Committee (DMC). Premature epiphyseal closure has been observed in subjects in the interventional FOP studies that have been reported as serious adverse events. Analysis of the SAEs suggests that the risk of premature epiphyseal fusion is higher in subjects with open epiphyseal growth plates who have received the flare-up dosing regimen. The finding of premature epiphyseal closure has been seen across all ages although the potential impact on growth is likely to be greater in the youngest, most skeletally immature subjects, given limitations in time to attain a greater percent of their final adult height.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is:

- To evaluate the safety and efficacy of different palovarotene dosing regimens in subjects with FOP. Efficacy will be assessed based on the ability of palovarotene to prevent the formation of new heterotopic ossification (HO) as assessed by low-dose whole body computed tomography (WBCT) scan, excluding head.

2.2 Secondary Objectives

- To evaluate the effect of palovarotene on range of motion (ROM) as assessed by the Cumulative Analogue Joint Involvement Scale (CAJIS) for FOP.
- To evaluate the effect of palovarotene on physical function using age-appropriate forms of the FOP Physical Function Questionnaire (PFQ).
- To evaluate the effect of palovarotene on physical and mental health using age-appropriate forms of the Patient Reported Outcomes Measurement Information System (PROMIS) Global Health Scale.
- To evaluate the pharmacokinetics of palovarotene.

2.3 Secondary Objective (Part D)

- To implement safety measures based on DMC recommendations in order to ensure that assessments of safety continue for up to 2 years post last dose of study treatment for skeletally immature subjects.

3 STUDY DESIGN

3.1 Overview of the Study Design

This is a Phase 2, single-center, open-label study that will explore different dosing regimens of palovarotene in adult and pediatric subjects with FOP. References to Parts B/C/D are to PVO-1A-202 Parts B/C/D which corresponds to PVO-1A-204, ongoing in France.

Under the original protocol and Amendment 1, subjects who successfully completed Study PVO-1A-201 as well as up to two new adult subjects were followed for up to 24 months.

Subjects who participated under Amendment 1 will be followed for up to an additional 48 months. No new subjects will be enrolled under this amendment.

All subjects will receive non-flare-up based treatment of 5 mg palovarotene once daily (weight-adjusted doses for skeletally immature subjects). Note: all weight-based dosing will cease when subjects become skeletally mature, but radiographic assessment of the growth plate will continue until these subjects achieve 100% skeletal maturity at both knee and hand/wrist locations performed at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60 and 72. Additional radiographic assessments will be performed at Months 3, 9, 15, 21, 27, 33, 39, 45, 51, 57, 63, 66, or 69 in those subjects who (1) received the flare up dosing regimen in the period of time since their last radiographic assessment; and (2) had not achieved 100% skeletal maturity on their last radiographic assessment.

Subjects will follow all assessments as outlined in Table 1 and Table 2. Adult subjects who cannot receive non-flare-up based treatment will only undergo annual assessments (clinical laboratory tests will not be performed). In the event of a flare-up or traumatic event, these subjects will receive flare-up-based treatment and undergo all flare-up-based assessments, including clinical laboratory tests and radiographs if they have not reached 100% skeletal maturity.

Adverse events will be assessed at every site and remote visit during both non-flare-up based and flare-up-based treatment. In case of early termination or withdrawal of a subject, every reasonable effort will be made by the study staff to have the subject return to the site in order to complete all end of treatment (EOT) and end of study (EOS) evaluations.

Travel arrangements to the site for subjects and caregivers will take into consideration subjects' disability in a manner that will minimize any possible injury to subjects. For example, ground travel could utilize an ambulance if deemed necessary; air travel could consist of first-class seating or use of a private jet or air ambulance; and hotel accommodations could consist of disability accessible rooms. It should be noted that all travel arrangements are to be made in consultation with the Investigator so that the safety of the subject is always fully considered.

As of 04 December 2019, all subjects <14 years of age were required to interrupt study drug due to a partial clinical hold placed on the palovarotene clinical development program by the US FDA. Treatment will subsequently not be restarted in children <14 years of age.

Subjects from Amendment 1 Continuing Non-Flare-Up Based Treatment

Subjects who began non-flare-up based treatment under Amendment 1 will continue this visit schedule, and will receive non-flare-up based treatment for up to an additional 48 months.

Therefore, these subjects may undergo non-flare-up based treatment for up to 72 months over the entire study.

These subjects will follow all procedures and undergo all assessments as specified in the Schedule of Assessments in Table 1, including low-dose WBCT scan (excluding head) at all annual site visits (Months 12, 24, 36, 48, 60 and 72). Non-flare-up Day 1 is the first day that non-flare-up based treatment was initiated, and total duration of treatment will include participation under this amendment.

Remote visits (eg, at home or at a local medical facility; and via telephone contact from clinical site personnel) will occur every 3 months unless the Investigator deems that a site visit is necessary; urine pregnancy tests will be performed each month for females of childbearing potential (FOCBP).

Subjects from Amendment 1 Starting Non-Flare-Up Based Treatment

Subjects from Amendment 1 who will start non-flare-up based treatment will receive

non-flare-up based treatment for up to 48 months. These subjects will follow all procedures and undergo all assessments as specified in the Schedule of Assessments in Table 2, including

low-dose WBCT scan (excluding head) at Amendment 3 Screening and at all annual site visits (Months 12, 24, 36 and 48). Non-flare-up Day 1 is the first day that non-flare-up based treatment is initiated under Amendment 3 for these subjects.

Remote visits (eg, at home or at a local medical facility; and via telephone contact from clinical site personnel) will occur every 3 months unless the Investigator deems that a site visit is necessary; urine pregnancy tests will be performed each month for FOCBP.

Part D:

Annual post last dose of study treatment assessments for up to 2 years will be obtained in subjects who were skeletally immature at the time of study treatment discontinuation in order to obtain longer-term safety data. No new subjects will be enrolled into Part D. Subjects who were enrolled in Parts A, B or C who have discontinued the study and were skeletally immature at their last assessment will be invited back to participate in the off-treatment Part D safety follow-up. These subjects will follow all procedures and undergo all assessments as specified in the Schedule of Assessments in Table 4.

Assessments will include knee and hand/wrist radiographs, linear and knee height growth assessments, physical examination, body weight, vital signs, low-dose WBCT scan (excluding head), prior/concomitant medications, and adverse events.

Flare-Up Based Treatment

Subjects and/or their parents/caregivers will report potential flare-up symptoms to site personnel; such symptoms include, but are not limited to, pain, swelling, redness, decreased range of motion, stiffness, and warmth. Only one symptom is required to define a flare-up. If these symptoms are consistent with previous flare-ups, include a subject-reported onset date, and are confirmed by the Investigator as associated with a flare-up, subjects will immediately receive open-label palovarotene treatment as follows:

- 20 mg for 4 weeks (28 days) once daily. The first dose will be taken upon flare-up confirmation by the Investigator. To be followed by:
- 10 mg for 8 weeks (56 days) once daily, for a total flare-up treatment duration of 12 weeks (84 days); 10 mg treatment may be extended if the flare-up is ongoing and continue until the flare-up resolves. Dosing will be extended in 4-week intervals and be based on clinical signs and symptoms as assessed by the Investigator.

Subjects under the age of 18 years will receive weight-adjusted doses of 20 mg palovarotene (for 28 days) and 10 mg palovarotene (for 56 days) as shown in Table 5. (Note: all weight-based flare-up dosing will cease when subjects are 18 years old, but radiographic assessment of the growth plate will continue until these subjects achieve 100% skeletal maturity at both knee and hand/wrist locations.)

Table 5 Weight-Adjusted Palovarotene Doses and Dose De-escalation

Weight Range Category	20-mg Equivalent	15-mg Equivalent*	10-mg Equivalent	7.5-mg Equivalent*	5-mg Equivalent*	2.5-mg Equivalent*
20 to <40 kg	12.5 mg	10 mg	6 mg	4 mg	3 mg	1.5 mg
40 to <60 kg	15 mg	12.5 mg	7.5 mg	5 mg	4 mg	2 mg
≥60 kg	20 mg	15 mg	10 mg	7.5 mg	5 mg	2.5 mg

* In the event of dose de-escalation from 20-mg, 10-mg, or 5-mg equivalent, respectively.

If the subject experiences intolerable side effects, the dose may be reduced to the next lower dose as shown in Table 5; if the subject is already receiving the lowest possible dose, then study drug will be discontinued. Treatment may be extended after the 84-day treatment period (flare-up based dosing) if the flare-up is ongoing and continue until the flare-up resolves. Dosing will be extended in 4-week intervals based on clinical signs and symptoms as assessed by the Investigator, with remote visits performed every 2 weeks while on treatment. In the event the subject required dose de-escalation due to an intolerable side effect for a previous flare-up, then the dose the subject will receive for a subsequent flare-up will be determined by the Investigator and the Medical Monitor. If there is evidence of partial or complete premature growth plate closure (with or without growth deceleration) study drug may be continued, interrupted, de-escalated, or discontinued. Dose modification decisions will be made by the Investigator upon review of the subject's clinical and radiographic information, and following discussion of the risk/benefit with the subject/parent. The Investigator may also consult with the sponsor and the DMC.

Should a subject experience an intercurrent flare-up (defined as a new flare-up or marked worsening of the original flare-up), or if the Investigator confirms the presence of a substantial high-risk traumatic event likely to lead to a flare-up, at any time during flare-up based treatment, the 12-week dosing regimen will restart upon new intercurrent flare-up confirmation by the Investigator (ie, 4 weeks of 20 mg palovarotene followed by 8 weeks of 10 mg palovarotene [or weight-based equivalent]). A Flare-up Cycle will include the first flare-up or traumatic event and any subsequent intercurrent flare-ups or traumatic events during the same dosing period.

Flare-Up Cycle Safety Day 1 is defined as the first day that study drug is administered for the first flare-up or traumatic event during that cycle. Safety assessments will be performed on Flare-up cycle Safety Day 1 and every 12 weeks thereafter until treatment of the last flare-up or traumatic event in the flare-up cycle is completed. If any flare-up in a cycle has not resolved after 12 weeks, treatment and safety assessments will be extended and 10 mg palovarotene (or the weight-based equivalent) will be administered in 4-week intervals until all the flare-ups resolve and flare-up-based treatment has been completed. It is possible that subjects may experience more than one Flare-up Cycle during the study.

Subjects receiving flare-up-based treatment will follow all procedures and undergo all assessments as specified in the Schedule of Assessments in Table 3. All assessments will occur remotely, unless the Investigator deems it necessary to evaluate subjects at the clinical site.

Once all flare-ups or traumatic events in a cycle have resolved and flare-up based treatment has been completed, subjects will resume non-flare-up based treatment with 5 mg palovarotene once daily (weight-adjusted doses for skeletally immature subjects as shown in Table 5).

Pharmacokinetics of palovarotene dosing will be assessed twice during flare-up based treatment: once during the 20-mg regimen at any time between Study Days 4 to 28, and once during the 10- mg regimen at any time between Study Days 32 to 84, for the first treated flare-up only. If this is not possible for the first treated flare-up, pharmacokinetics blood samples can be obtained during any subsequent flare-up dosing cycle. Pharmacokinetic blood samples will be collected at pre-dose and 3, 6, 10, and 24 hours post-dose. Subjects who underwent a prior flare-up pharmacokinetic assessment will not have flare-up treatment pharmacokinetics

assessed again. However, these subjects will require a pharmacokinetic assessment during non-flare-up palovarotene treatment at a 3-month safety assessment (see Section 7.5).

3.2 Study Rationale

Study PVO-1A-202 followed subjects who rolled over from Study PVO-1A-201 and provided open-label active treatment to any subject who experienced a subsequent flare-up. This allowed for the collection of long-term efficacy and safety data of palovarotene (10 mg for 14 days, followed by 5 mg for 28 days), and provided active treatment to all subjects experiencing eligible flare-ups including those who were randomized to placebo during Study PVO-1A-201. Clinical data obtained from the Phase 2 interventional studies, as well as recent animal pharmacology data, have contributed to the understanding of FOP disease progression, the risk factors leading to HO formation, and the potential utility of palovarotene in preventing HO formation.

Fibrodysplasia Ossificans Progressiva is a disease that is characterized by HO that may develop spontaneously or after soft tissue trauma, vaccinations, or influenza infections. The HO accumulates throughout life, resulting in segments, sheets, and ribbons of extra bone throughout the body and across joints, progressively restricting movement. While HO formation may be preceded by signs and symptoms of a flare-up such as pain, swelling, redness, decreased range of motion, stiffness, and warmth, the biological process that results in the formation of HO may begin before the onset of symptoms. Thus, the optimal treatment for FOP might be similar to other non-flare-up-based diseases that are characterized by acute exacerbations/relapses, followed by variable-length periods of apparent disease quiescence (eg, relapsing/remitting multiple sclerosis) during which clinical symptoms are not observed.

It is hypothesized that daily treatment in the absence of flare-up symptoms, which will ensure exposure to palovarotene when the endochondral process starts, together with increasing the dose immediately upon symptom onset (the non-flare-up-based/flare-up regimen), may be a better approach than treating only when clinical symptoms are present (the flare-up only regimen). Under the original protocol and Amendment 1, adult subjects initiated non-flare-up based daily treatment with palovarotene, which was extended to the Pediatric Cohort subjects under Protocol Amendment 2. In addition, subjects experiencing an eligible intercurrent flare-up will restart flare-up based dosing in order to continue exposure to palovarotene and provide an optimal treatment for all flare-ups that may occur during the study.

As of 04 December 2019, all subjects <14 years of age were required to interrupt study drug due to a partial clinical hold placed on the PVO clinical development program by the US FDA. Treatment will subsequently not be restarted in children <14 years of age as subjects remained off treatment for such a prolonged period of time as to render any further data to inform additional benefit/risk uninterpretable in this patient population.

Given the serious identified risk of premature physeal closure, Part D was added to implement safety measures based on DMC recommendations in order to ensure that assessments of safety continue for up to 2 years post last dose of study treatment in Part A/B/C for skeletally immature subjects, who stopped treatment for any reason.

3.3 Dose Justification

Fibrodysplasia Ossificans Progressiva is an extremely rare, chronic, severely disabling disease characterized by periods of relative disease quiescence interspersed with episodic flare-ups and the formation of HO that is irreversible, and the disability is permanent. Because the risks of

under-treatment are very high, FOP should be treated aggressively in order to evaluate the maximal potential treatment benefit, while carefully monitoring for potential safety concerns. The dose regimens selected for the current study address these aspects of the disease and are based on emerging nonclinical and clinical data:

- **Chronic dosing regimen:** In a non-injury-based mouse model of FOP that recapitulates much of the clinical phenotype observed in patients, including spontaneous HO formation, chronic daily treatment with palovarotene at an HED of approximately 5 mg prevented HO formation. Importantly in this R206H FOP-relevant animal model, the dosing regimen did not impair long bone growth but partially normalized the abnormal growth plate histology and shortened long bones that are key phenotypic features of this model. The results raised the possibility that chronic daily palovarotene dosing may be a major component of an optimized clinical dosing strategy.
- **Flare-up dosing regimen:** The rationale for increasing the non-flare-up-based palovarotene dose at the time of a flare-up comes from both the animal pharmacology and available clinical trial results. The nonclinical data from two different mouse models of FOP demonstrated a dose-related decrease in HO volume; and suggested that flare-up-based treatment using an HED of 20 mg may be necessary to optimally prevent HO following an injury (equivalent to a flare-up in humans). The Phase 2 program has evaluated four different palovarotene dosing regimens, three flare-up based episodic treatment regimens and one non-flare-up-based/flare-up regimen. Preliminary clinical data on 103 prospectively assessed flare-ups demonstrated an approximate 45% reduction in the proportion of flare-ups with new HO, and an approximate 75% decrease in new HO volume, in those flare-ups treated with palovarotene 10/5 mg over 6 weeks compared to placebo/untreated flare-ups; and an approximate 65% reduction in proportion of flare-ups with new HO and an approximate 98% reduction in HO volume in those flare-ups treated with the non-flare-up-based/flare-up regimen 20/10 mg over 12 weeks (the regimen in the current study) compared to placebo/untreated flare-ups. These data provide a strong rationale for the continued evaluation of palovarotene as a potential treatment of FOP, and the selection of non-flare-up-based daily administration of 5 mg palovarotene, with dose escalation to 20 mg once daily for 4 weeks followed by 10 mg for 8 weeks (with treatment extension possible per Investigator discretion for persistent flare-ups) for all subjects. The flare-up dosage will be adjusted for weight in subjects under the age of 18 years.
- While it is recognized that flare-ups can occur in the absence of any apparent causative factor, there is a high risk that substantial traumatic events such as surgery, intramuscular immunizations, mandibular blocks for dental work, muscle fatigue, blunt muscle trauma from bumps, bruises, falls, or influenza-like viral illnesses can induce flare-ups and progressive HO formation.[9] In one survey of FOP patients, flare-ups were induced in two-thirds of falls and resulted in permanent loss of movement in 93% of patients.[10] Thus, subjects experiencing substantial high-risk traumatic events that the Investigators deem likely to lead to a flare-up will be treated with the flare-up regimen.

It is acknowledged that palovarotene plasma exposure in humans receiving treatment with this regimen will be similar to or greater than the threshold for adverse effects in juvenile rats, adult rats, or adult dogs. The toxicological effects were primarily mucocutaneous (in adult animals) and skeletal (in juvenile animals after chronic exposure). Current safety monitoring in the

current Phase 2 and Phase 3 studies has confirmed mucocutaneous adverse effects that are managed with prophylactic treatment or dose reduction. In addition, monitoring of the growth plate revealed that the most common finding was dense metaphyseal lines in approximately 70% of subjects at both baseline and post-baseline time points. Premature epiphyseal closure has also been observed in the current Phase 2 and Phase 3 studies. Therefore, careful safety monitoring and dose modification procedures for intolerable side effects will be employed in the current study.

3.4 Appropriateness of Measurements

3.4.1 Imaging

A number of different imaging modalities have been utilized in patients presenting with soft tissue swelling/masses including plain radiographs, computed tomography (CT) scan,[23] magnetic resonance imaging (MRI),[24] and radionuclide bone scan.[25] Most are performed at the time of the initial flare-up as part of the diagnostic evaluation and prior to the diagnosis of FOP. Following the accurate diagnosis of FOP, imaging is not routinely performed[4] as such imaging does not play a role in the supportive care offered to patients. Although most of the experience with documentation of HO following a flare-up has been with x-ray, it has been noted that CT scans may allow earlier detection of new areas of HO.[26]

Flare-up site, low-dose CT scan was found to be more sensitive to the detection and quantification of new HO following a flare-up in the initial interventional Phase 2 study (PVO-1A-201) compared to plain radiograph. The Natural History Study (PVO-1A-001)

demonstrated the utility of WBCT at documenting the presence, location, and quantification of whole body HO, including new HO formation at 12-months. This also assesses HO in areas remote to flare-up symptoms, which more accurately reflects the status of the subject at follow-up. For these reasons, the imaging modality utilized in the current study to assess the primary and secondary endpoints will be low-dose WBCT scan (excluding head).

In order to ensure consistency and standardization, interpretation of the acquired images will be performed by a central imaging laboratory. The clinical trial imaging methodology will be documented (eg, imaging charter and imaging guideline) prior to study initiation.

3.4.2 Measures of Functional Disability and General Health

Two key measures of functional disability include:

- The CAJIS for FOP is an objective measure of joint movement completed by the Investigators to document total joint involvement. This scale, which was developed by the Investigators from the Center for Research in FOP and Related Disorders, assesses functional disability by categorizing range of motion across 12 joints (shoulder, elbow, wrist, hip, knee, ankle on both right and left), and three body regions (cervical spine [neck], thoracic/lumbar spine and jaw) with each joint/region assessed as: 0=uninvolved; 1=affected; 2=functionally ankylosed. The total score range is 0-30. The CAJIS is provided in Appendix 1.
- The FOP-PFQ is a disease-specific patient-reported outcome measure of physical impairment. The FOP-PFQ was developed by Clementia based on the FDA Guidance for

Industry, "Patient Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims". This patient-reported outcome instrument was developed to assess the relationship between patient reports of physical impairment due to HO, thereby providing evidence of HO as a clinically meaningful endpoint. Age-appropriate forms provide a measure of functional impairment experienced by subjects and include questions related to activities of daily living and physical performance. These data are analyzed as a percent of the total possible score, with higher percentages representing greater functional impairment. The adult and pediatric versions of the FOP-PFQ are provided in Appendix 2.

4 STUDY ENDPOINTS

4.1 Primary Endpoints

The primary endpoint is:

(1) Annualized change in new HO volume as assessed by low-dose WBCT scan, excluding head. The annualized change from the original protocol, and Amendments 1 and 3, will be compared to data collected from the NHS.

4.2 Secondary Endpoints

Note: Baseline is Non-flare-up Day 1. Some subjects may be assessed for up to 72 months.

(1) Percent of subjects with new HO at Months 12, 24, 36, 48, 60, 72 and overall.
(2) Change from baseline in ROM as assessed by CAJIS at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72.
(3) Change from baseline in physical function using age-appropriate forms of the FOP-PFQ at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, and 72.
(4) Change from baseline in physical and mental function for subjects ≥15 years old and mental function for subjects <15 years old using age-appropriate forms of the PROMIS Global Health Scale at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72.

5 SELECTION OF STUDY POPULATION

The target study population consists of up to nine subjects with FOP who have completed Study PVO-1A-201 (through Study Day 84), including subjects from Study PVO-1A-202, as well as up to two new subjects who did not participate in Study PVO-1A-201 or Study PVO-1A-202. No new subjects will be enrolled under this amendment. References to Parts B/C/D are to PVO-1A-202 Parts B/C/D which corresponds to PVO-1A-204, ongoing in France.

5.1 Study Population (Adult and Pediatric Cohorts – Original Protocol and Amendment 1)

As of 04 December 2019, all subjects <14 years of age were required to interrupt study drug due to a partial clinical hold placed on the palovarotene clinical development program by the US FDA. Treatment will subsequently not be restarted in children <14 years of age.

5.1.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

(1) Completion of Study PVO-1A-201 (through Study Day 84), including any subject from Study PVO-1A-202; or Adult Cohort subjects not enrolled in Study PVO-1A-201, have the confirmed R206H genetic mutation consistent with FOP, have had at least two acute symptomatic flare-ups in the past 2 years but no flare-up symptoms within the past 4 weeks (including at the time of enrollment), have a CAJIS score of 6 to 16, inclusive, and able to receive non-flare-up based dosing.

(2) For the Adult Cohort, subjects under the age of 18 must have knee and hand/wrist radiographs confirming ≥90% skeletal maturity.

(3) Written, signed, and dated subject/parent informed consent; and, for subjects who are minors, age-appropriate assent (this must be performed according to local regulations).

5.1.2 Exclusion Criteria

(1) Simultaneous participation in another clinical research study (except for Studies PVO-1A-201, PVO-1A-202, PVO-1A-203, or PVO 1A-001) within the 4 weeks prior to Screening.

(2) Any reason that, in the opinion of the Investigator, would lead to the inability of the subject and/or family to comply with the protocol.

5.2 Study Population for Non-Flare-Up Based Treatment (Adult Cohort - Original Protocol and Amendment 1)

5.2.1 Inclusion Criteria

(1) Females of child-bearing potential (FOCBP) must have a negative blood or urine pregnancy test (with sensitivity of at least 50 mIU/mL) prior to administration of palovarotene. Male and FOCBP subjects must agree to remain abstinent during treatment and for 1 month after treatment or, if sexually active, to use two highly effective methods of birth control during and for 1 month after treatment. Additionally, sexually active FOCBP subjects must already be using two highly effective methods of birth control 1 month before treatment is to start. Specific risk of the use of retinoids during pregnancy, and the agreement to remain abstinent or use two highly effective methods of birth control will be clearly defined in the informed consent, and the subject or legally authorized representative (eg, parents, caregivers, or legal guardians) must specifically sign this section.

(2) Subjects must be accessible for treatment with palovarotene and follow-up. Subjects living at distant locations from the investigational site must be able and willing to travel to a site for the initial and all on-site follow-up visits.

5.2.2 Exclusion Criteria

(1) Weight <20 kg.

(2) Intercurrent known or suspected non-healed fracture at any location.

(3) Currently using vitamin A or beta carotene, multivitamins containing vitamin A or beta carotene, or herbal preparations, fish oil, and unable or unwilling to discontinue use of these products during palovarotene treatment.

(4) Exposure to synthetic oral retinoids other than palovarotene in the past 30 days prior to Screening (signature of the informed consent).

(5) Concurrent treatment with tetracycline or any tetracycline derivatives due to the potential increased risk of pseudotumor cerebri.

(6) History of allergy or hypersensitivity to retinoids or lactose.

(7) Concomitant medications that are inhibitors or inducers of cytochrome P450 (CYP450) 3A4 activity (see Appendix 3).

(8) Amylase or lipase >2x above the upper limit of normal (ULN) or with a history of chronic pancreatitis.

(9) Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5x ULN.

(10) Fasting triglycerides >400 mg/dL with or without therapy.

(11) Female subjects who are breastfeeding.

(12) Subjects with uncontrolled cardiovascular, hepatic, pulmonary, gastrointestinal, endocrine, metabolic, ophthalmologic, immunologic, psychiatric, or other significant disease.

(13) Subjects experiencing suicidal ideation (type 4 or 5) or any suicidal behavior within the past month as defined by the Columbia Suicide Severity Rating Scale (C-SSRS).

5.3 Study Population for Flare-up Based Treatment (Adult and Pediatric Cohorts - Original Protocol and Amendment 1)

5.3.1 Inclusion Criteria

(1) Symptomatic onset of a flare-up within 7 days before the first dose of study drug and defined by the presence of at least two of the following symptoms: pain, soft tissue swelling, decreased ROM, stiffness, redness, and warmth. Symptoms must be reported by the subject, be consistent with their previous flare-ups, and include a subject-reported onset date, and flare-up must be confirmed by the Investigator.

(2) Flare-up is at an appendicular area (upper or lower extremity), abdomen, chest, neck, or lower back; and subject has received, is receiving, or is willing to receive treatment per standard of care, which may or may not include prednisone (2 mg/kg PO to a maximum dose of 100 mg daily) for 4 days.

(3) Females of child-bearing potential (FOCBP) must have a negative blood or urine pregnancy test (with sensitivity of at least 50 mIU/mL) prior to administration of palovarotene. Male and FOCBP subjects must agree to remain abstinent during treatment and for 1 month after treatment or, if sexually active, to use two highly effective methods of birth control during and for 1 month after treatment. Additionally, sexually active FOCBP subjects must already be using two highly effective methods of birth control 1 month before treatment is to start. Specific risk of the use of retinoids during pregnancy, and the agreement to remain abstinent or use two highly effective methods of birth control will be clearly defined in the informed consent and the subject or legally authorized representatives (eg, parents, caregivers, or legal guardians) must specifically sign this section.

(4) Subjects must be accessible for treatment with palovarotene and follow-up. Subjects living at distant locations from the investigational site must be able and willing to travel to a site for the initial and all on-site follow-up visits.

5.3.2 Exclusion Criteria

(1) Weight <20 kg.

(2) Intercurrent known or suspected non-healed fracture at any location.

(3) Complete immobilization of joint at site of flare-up.

(4) The inability of the subject to undergo imaging assessments using plain radiographs.

(5) Currently using vitamin A or beta carotene, multivitamins containing vitamin A or beta carotene, or herbal preparations, fish oil, and unable or unwilling to discontinue use of these products during palovarotene treatment.

(6) Exposure to synthetic oral retinoids other than palovarotene in the past 30 days prior to Flare-up Screening (signature of the informed consent).

(7) Concurrent treatment with tetracycline or any tetracycline derivatives due to the potential increased risk of pseudotumor cerebri.

(8) History of allergy or hypersensitivity to retinoids or lactose.

(9) Concomitant medications that are inhibitors or inducers of CYP450 3A4 activity (see Appendix 3).

(10) Any subject with clinically significant elevations in amylase, lipase, AST, ALT, or fasting triglycerides during the most recent clinical laboratory assessment will require re-test prior to immediate flare-up-based dosing with palovarotene per the Investigator. If upon re-test, the laboratory value in question remains clinically significant abnormal, then the subject will not receive flare-up-based treatment for this flare-up.

(11) Female subjects who are breastfeeding.

(12) Subjects with uncontrolled cardiovascular, hepatic, pulmonary, gastrointestinal, endocrine, metabolic, ophthalmologic, immunologic, psychiatric, or other significant disease.

(13) Subjects experiencing suicidal ideation (type 4 or 5) or any suicidal behavior within the past month as defined by the Columbia Suicide Severity Rating Scale (C-SSRS).

(14) Any reason that, in the opinion of the Investigator, would lead to the inability of the subject and/or family to comply with the protocol.

5.4 Study Population (All Subjects – Amendments 2 and 3)

5.4.1 Inclusion Criteria

Subjects must meet the following inclusion criterion to be eligible for enrollment:

(1) Prior participation in Amendment 1 of the current study (PVO-1A-204).

(2) Written, signed, and dated subject/parent informed consent; and, for subjects who are minors, age-appropriate assent (this must be performed according to local regulations).

(3) Females of child-bearing potential must have a negative blood or urine pregnancy test (with sensitivity of at least 50 mIU/mL) prior to administration of palovarotene. Male and FOCBP subjects must agree to remain abstinent from heterosexual sex during treatment and for 1 month after treatment or, if sexually active, to use two effective methods of birth control during and for 1 month after treatment. Additionally, sexually active FOCBP subjects must already be using two effective methods of birth control 1 month before treatment is to start. Specific risk of the use of retinoids during pregnancy, and the agreement to remain abstinent or use two effective methods of birth control will be clearly defined in the informed consent and the subject or legally

authorized representatives (eg, parents, caregivers, or legal guardians) must specifically sign this section.

5.4.2 Exclusion Criteria

Subjects with the following exclusion criterion will not be eligible for enrollment:

(1) Any reason that, in the opinion of the Investigator, would lead to the inability of the subject and/or family to comply with the protocol.

5.5 Study Population of Subjects Starting Non-Flare-Up Based Treatment During Amendment 3

5.5.1 Inclusion Criteria

Subjects must meet the following inclusion criterion to be eligible for enrollment:

(1) Subjects must be accessible for treatment with palovarotene and follow-up. Subjects living at distant locations from the investigational site must be able and willing to travel to a site for the initial and all on-site follow-up visits.
(2) Subjects must be able to undergo low-dose WBCT scan, excluding head.

5.5.2 Exclusion Criteria

Subjects with the following exclusion criterion will not be eligible for enrollment:

(1) Amylase or lipase >2x above the upper limit of normal (ULN) or with a history of chronic pancreatitis.
(2) Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5x ULN.
(3) Fasting triglycerides >400 mg/dL with or without therapy.
(4) Subjects experiencing suicidal ideation (type 4 or 5) or any suicidal behavior within the past month as defined by the Columbia Suicide Severity Rating Scale (C-SSRS).

5.6 Prior and Concomitant Medications and Other Study Restrictions

5.6.1 Prior and Concomitant Medications for Subjects Receiving Palovarotene

Subjects must be willing to receive treatment per the standard of care as noted in the FOP Treatment Guidelines 2011 which, for acute flare-ups, may or may not include corticosteroids (eg, prednisone at 2 mg/kg PO to a maximum dose of 100 mg daily) for 4 days.[27] Ideally, corticosteroids will have been initiated within 24 hours after the start of a flare-up. Initiation of corticosteroids after 24 hours will be based on the clinical judgment of the Investigator taking into consideration the subject's flare-up symptoms and location, and in consultation with the subject's primary physician, if necessary. Other standard-of-care medications are also permitted.

The following medications are not allowed during palovarotene treatment (flare-up or non-flare-up based):

- Vitamin A or beta carotene, multivitamins containing vitamin A or beta carotene, herbal preparations, or fish oil are not permitted from the day before the start of treatment until the last day of treatment.

- Synthetic oral retinoids other than palovarotene are not permitted in the 30 days prior to treatment until the last day of treatment.
- Concomitant use of tetracyclines and retinoids has been associated with benign intracranial hypertension. Therefore, use of tetracycline or tetracycline derivatives is prohibited during the study. If the subject experiences a medical condition that requires treatment with tetracycline and/or doxycycline, study drug should be discontinued for the duration of tetracycline treatment and the Medical Monitor should be notified. Prior to restarting treatment with palovarotene an appropriate wash-out period of 3 days must be considered.
- Strong inhibitors of cytochrome CYP450 3A4 are known to alter the metabolism of palovarotene. Thus, concurrent oral medications identified as strong inhibitors of CYP450 3A4 (see Appendix 3) or kinase inhibitors, such as imatinib, are excluded. If during the study, the subject must take a strong inhibitor of CYP450 3A4, the study drug is to be discontinued for the duration of treatment. Prior to restarting treatment with palovarotene, an appropriate wash-out period (five half-lives) must be considered (see Appendix 3).
- Strong inducers of cytochrome CYP450 3A4 are also known to alter the metabolism of palovarotene. Thus, concurrent oral medications identified as inducers of CYP450 3A4 (see Appendix 3) are excluded. If during the study, the subject must take a strong inducer of CYP450 3A4, the study drug may continue, but the Medical Monitor should be notified.

Skin and mucous membrane reactions are the most common side effects associated with treatment with retinoids, therefore a subject leaflet describing recommended treatment for the most common mucocutaneous AEs will be distributed to each subject at the initiation of study treatment. These treatments may also be recommended as prophylaxis per Investigator discretion.

5.6.2 Other Restrictions

Male and FOCBP subjects must either commit to true abstinence from heterosexual sex or agree to use two effective methods of birth control during treatment, and for 1 month after treatment has ended. Sexually active FOCBP subjects must already be using two effective methods of birth control 1 month before treatment is to start. Abstinence from heterosexual sex is only acceptable as "true abstinence." True abstinence occurs when it is in line with the preferred and usual lifestyle of the subject. Periodic abstinence from heterosexual sex (such as calendar, ovulation, symptothermal, post-ovulation methods), the rhythm method, and withdrawal are not acceptable methods of contraception.

Specific risks of the use of retinoids during pregnancy, and the agreement to remain abstinent from heterosexual sex or to use two effective methods of birth control will be clearly defined in the informed consent form. Subjects or legally authorized representatives (eg, parents, caregivers, or legal guardians) must sign this specific section. Two effective forms of birth control consist of the concurrent use of at LEAST one highly effective method of birth control as described in Appendix 4.

In the unlikely event of a pregnancy, a female subject must be instructed to stop taking the study drug and immediately inform the Investigator. Pregnancies occurring up to 30 days after the completion of the study drug must also be reported to the Investigator. The Investigator should report all pregnancies within 24 hours to the sponsor. The Investigator should counsel the

subject and discuss the risks of continuing with the pregnancy, and the possible effects on the fetus. Monitoring of the subject should continue until conclusion of the pregnancy.

5.7 Subject Withdrawal or Early Termination from Study

Subjects can voluntarily withdraw from the study at any time for any reason. All reasonable efforts should be made by the study personnel to determine the reason for withdrawal. Subjects will be considered lost to follow-up if no response is received in spite of repeated attempts to contact them.

Study drug administration for individual subjects can be discontinued by the Investigator if he/she believes the subject's safety is at risk. Additional details regarding study drug dose modification are provided in Section 6.5.

If any subject enrolled in Part D chooses to enroll in another clinical trial, all reasonable efforts should be made by the study personnel to have the subject continue participation in Study PVO-1A-204 until their final EOS visit.

In the event of an early termination or discontinuation of study drug, all reasonable efforts should be made by the study personnel to have the subject complete all study assessments per the Schedule of Assessments for non-flare-up based treatment (Table 1 and Table 2), and if appropriate, for flare-up based treatment (Table 3), including those assessments subsequent to early termination or study drug discontinuation.

5.8 Replacement of Subjects

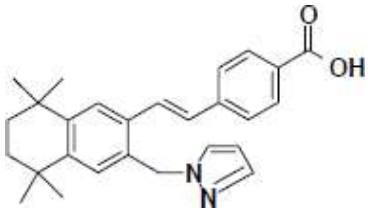
Subjects who drop out will not be replaced.

6 STUDY DRUG ADMINISTRATION

6.1 Identity of Study Drug

Palovarotene is a white to off-white crystalline powder with the chemical name 4-[(E)-2-(5,5,8,8-tetramethyl-3-pyrazol-1-ylmethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-benzoic acid. Palovarotene is an orally bioavailable RARγ selective agonist. The structure of palovarotene is shown in Figure 1.

Figure 1 Chemical Structure of Palovarotene



6.2 Packaging, Labeling, and Storage

Study drug supplies provided for this study will be manufactured under Good Manufacturing Practices and will be suitable for human use. Palovarotene will be provided in powder-filled opaque hard gelatin capsules using standard USP/EP grade excipients in the following dosage strengths: 10, 5, 4, 3, 2.5, 2, and 1.5 mg (see Section 3.1). Capsules will be packaged in appropriately sized bottles designed for maximum protection.

Study drug will be stored in a secured area at the study site with limited access. All study drug is to be stored at room temperature (not above 30°C/86°F) and protected from light and humidity.

6.3 Randomization and Blinding

This is an open-label study and does not involve randomization or blinding.

6.4 Administration

All subjects will receive non-flare-up based treatment of 5 mg palovarotene once daily (weight-adjusted doses for skeletally immature subjects). The first day that subjects receive non-flare-up based treatment will be Non-Flare-Up Day 1. Details for handling, preparing, storing, and discarding study drug will be provided to subjects.

Subjects who began non-flare-up based treatment under Amendment 1 will continue this visit schedule, and will receive non-flare-up based treatment for up to an additional 48 months.

Subjects who will start non-flare-up based treatment will receive non-flare-up based treatment for up to 48 months. Subjects who cannot receive non-flare-up based treatment will only undergo annual assessments (clinical laboratory tests will not be performed). In the event of a flare-up, these subjects will receive flare-up-based treatment and undergo all flare-up based assessments, including clinical laboratory tests.

Flare-up based treatment can begin immediately after the Investigator confirms the presence of a flare-up or the presence of a substantial high-risk traumatic event likely to lead to a flare-up.

Subjects with normal or non-clinically significant abnormal safety laboratory results observed within 1 month of flare-up based treatment will not need to have laboratory tests performed at Flare-up Day 1. The Investigator will determine whether subjects with clinically significant abnormal laboratory results in the most recent assessment will need to be re-assessed prior to beginning flare-up based treatment. The only exception is for pregnancy testing, which must be performed monthly. For subjects receiving flare-up based treatment, Flare-up Day 1 is defined as the first day that flare-up based treatment with study drug is administered.

Subjects will report potential flare-up symptoms or traumatic events to site personnel, and if confirmed by the Investigator as associated with a flare-up or, in the case of trauma, likely to lead to a flare-up, subjects will immediately begin flare-up based treatment with palovarotene 20 mg for 4 weeks (28 days) once daily followed by palovarotene 10 mg for 8 weeks (56 days) once daily (or weight-based equivalent), for a total duration of 12 weeks (84 days). Based on clinical signs and symptoms as determined by the Investigator, treatment may be extended in 4-week intervals while on-treatment with 10 mg palovarotene, and continue until the flare-up resolves and 4-week extension treatment has been completed. Flare-up dosing will be weight-adjusted for subjects under the age of 18 years (Section 3.1). Subjects will be provided with the appropriate dose of study drug to be used to initiate treatment with palovarotene when a flare-up or traumatic event is confirmed by the Investigator. Should a subject experience a new intercurrent flare-up or traumatic event at any time during flare-up based treatment, the 12-week dosing regimen will restart upon confirmation by the Investigator (ie, 4 weeks of 20 mg palovarotene followed by 8 weeks of 10 mg palovarotene [or weight-based equivalent]).

Once all flare-ups or traumatic events in a cycle have resolved and flare-up based treatment has been completed, subjects will resume non-flare-up based treatment with 5 mg palovarotene once daily (weight-adjusted doses for skeletally immature subjects).

The dose of study drug taken each day will be documented in the subject dosing diary.

Many FOP patients experience difficulty swallowing intact capsules or tablets due to ankylosis of the jaw. In order to facilitate drug administration, subjects or caregivers may sprinkle the contents of the capsule onto specific foods as specified in the dosing instructions. Subjects should be instructed to take study drug orally following a full meal at approximately the same time each day and to avoid foods that are known to induce or inhibit the activity of the CYP3A4 enzyme (eg, grapefruit, pomelo, or juices containing these fruits). Due to the potential for dermal absorption of study drug, subjects and caregivers will be instructed to wear protective gloves when handling the study drug capsule.

6.5 Dose Modification

Should a subject experience an AE that is not tolerated but would not require immediate discontinuation of study drug (eg, skin rash), the subject will be instructed to contact the study site immediately. The Investigator will assess the AE and if appropriate, will instruct the subject to decrease the dose of study drug to the next lower dose as shown in Table 5 (Section 3.1).

Dose modification may also be required due to potential bone safety findings as described in the Bone Safety Management Plan (see Section 7.3.3).

If the subject does not have the proper dosage strength in his/her possession, the clinical site will make immediate arrangements to ship the appropriate study drug to the subject. If the subject is already receiving the lowest possible dose, then study drug will be discontinued. The subject should then be followed until resolution or improvement of the AE. Should the AE remain intolerable despite dose reduction, then study drug will be discontinued, and the subject will continue to be followed with all study procedures performed per protocol.

Should a subject experience an AE that requires immediate discontinuation of study drug (eg, acute pancreatitis), then study drug will be discontinued. The Investigator will follow up on all AEs observed or reported by the subject up to the end of the reporting period or until follow-up is no longer necessary. In the event the subject required dose de-escalation due to an intolerable side effect for a previous flare-up, then the dose the subject will receive for a subsequent flare-up will be determined by the Investigator and the Medical Monitor.

If there is evidence of partial or complete premature growth plate closure (with or without growth deceleration) study drug may be continued, interrupted, de-escalated, or discontinued. Dose modification decisions will be made by the Investigator upon review of the subject's clinical and radiographic information, and following discussion of the risk/benefit with the subject/parent. The Investigator may also consult with the sponsor and the DMC.

6.6 Study Drug Accountability

The Investigator has the ultimate responsibility for the study drug accountability at the study site. The Investigator or a designated individual (eg, pharmacist or another appropriate person) will maintain records of the study drug's delivery to the study site and to the subject, the inventory at the site (used and unused product containers), the use by each subject, and the return to the sponsor or alternative disposition of unused medication. The study drug must be kept in a locked area that is monitored for temperature at least once per day. Access to study drug will be restricted to authorized study personnel and used only in accordance with the approved protocol. At the conclusion of the study, any remaining study drug supplies will be returned to the sponsor or its designee. The sponsor or its designee will ensure that a final report of study drug accountability is prepared and maintained by the Investigator. The Investigator

agrees not to supply or administer study drug to any person except those subjects participating in this study.

6.7 Assessment of Subject Compliance

Compliance will be based on the amount of study drug dispensed to the subject and returned to the site. In addition, subjects with flare-up-based treatment will be provided diaries to record the date study drug was taken. The diaries will be collected by the study personnel at the end of the dosing period.

7 STUDY PROCEDURES AND ASSESSMENTS

Under Amendment #5 and subsequent amendments, subjects with open epiphyseal growth plates will undergo knee (A/P) and hand/wrist radiographs (P/A view) at the clinical site every 6 months. Additional knee and hand/wrist radiograph assessments will also be performed every 3 months (±2 weeks) in skeletally immature subjects who (1) received flare up dosing in the period of time since their last assessment; and (2) had not achieved 100% skeletal maturity on their last assessment. These radiographic assessments will not be performed remotely unless the Investigator determines they can be performed at a local medical facility. A description of the knee and hand/wrist radiograph assessments is provided in Section 7.3.2.

References to Parts B/C/D are to PVO-1A-202 Parts B/C/D which corresponds to PVO-1A-204, ongoing in France.

7.1 Screening, Recruitment, and Informed Consent

Once the PVO-1A-204 Protocol Amendment 6 is approved at the clinical site, subjects currently enrolled in the study will be contacted, informed about the Amendment 6 changes, and given the opportunity to enrol under this amendment. PVO-1A-202 Parts B/C/D corresponds to PVO-1A-204, ongoing in France.

Subjects who began non-flare-up based treatment during the original protocol or Amendment 1 will continue this visit schedule, and will receive non-flare-up based treatment for up to an additional 48 months. Subjects who started non-flare-up based treatment under Amendment 3 will receive non-flare-up based treatment for up to 48 months.

Potential subjects/parents wishing to participate must sign the informed consent/assent per local requirements prior to undergoing any study-related procedures.

Part D was added for skeletally immature subjects who stopped taking study medication for any reason before completion of Part A/B/C. Part D includes yearly visits for up to a 2-year follow-up period following last dose. Maximum length of study is 72 months. No dosing will occur during Part D.

As per the global addendum (dated 15Apr2020) to Study PVO-1A-202 Amendment 5, Investigators, in consultation with their site IRB/EC, are required to inform subjects of the temporary changes (during the COVID-19 global pandemic) to the study conduct and monitoring plans that could impact them and their willingness to continue participation in the trial. The method of communication to subjects (e.g., email, phone call, information letter) and documentation of subject/caregiver acknowledgement is to be performed and documented in accordance with local regulations/EC requests and guidance. All contacts with subjects must be filed in the source records.

7.2 Safety Assessments

Subjects will follow all procedures and undergo all assessments as outlined in the Schedule of Assessments in Table 1, Table 2, Table 3 and Table 4, as appropriate, unless a subject is unable to undergo a procedure due to safety concerns (eg, risk of flare) or physical limitation (pain or locked position).

7.2.1 Medical History

No new subjects will be enrolled under Amendment 5 and a repeat medical history is not necessary.

For subjects receiving flare-up-based treatment, the flare-up assessment will include subject-reported current flare-up location, symptoms, and probable causes, documented on Flare-up Day 1.

7.2.2 Physical Examination

For subjects from Amendment 1 continuing non-flare-up based treatment, a physical examination of all body systems is to be documented at Months 12, 24, 36, 48, 60 and 72.

For subjects from Amendment 1 starting non-flare-up based treatment, a physical examination of all body systems is to be documented at Amendment 2 Screening and at Months 6, 12, 24, 36 and 48.

For subjects in Part D, a physical examination of all body systems is to be documented at Year 1 and Year 2 post last dose of study treatment.

The physical examination will monitor for objective changes and for possible adverse reactions associated with therapy. Any post-baseline abnormal physical examination findings assessed as clinically significant will be recorded as AEs.

7.2.3 Body Weight and Linear Growth Assessments

For subjects from Amendment 1 continuing non-flare-up based treatment, body weight will be documented every 3 months (Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69 and 72).

For subjects from Amendment 1 starting non-flare-up based treatment, body weight will be documented at Amendment 3 Screening and every 3 months (Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45 and 48).

For subjects receiving flare-up-based treatment, body weight will be recorded at Flare-up Cycle Safety Day 1 and every 12 weeks thereafter during safety assessments until treatment of the last flare-up or traumatic event in the flare-up cycle is completed.

Subjects from Amendment 1 continuing non-flare-up based treatment with open epiphyseal growth plates at the most recent assessment will have linear growth assessments (in triplicate) by stadiometer and knee height measurements (in triplicate) at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, and 72.

Subjects from Amendment 1 starting non-flare-up based treatment that are under the age of 18 years and who enrolled with open epiphyseal growth plates at the most recent assessment will have linear growth assessments (in triplicate) by stadiometer and knee height

measurements (in triplicate) at Screening. Subjects with open epiphyseal growth plates at this assessment will also be evaluated at Months 6, 12, 18, 24, 30, 36, 42 and 48.

For subjects in Part D, body weight will be documented at Year 1 and Year 2 post last dose of study treatment. Subjects in Part D will have linear growth assessments (in triplicate) by stadiometer and knee height measurements (in triplicate) at Year 1 and Year 2 post last dose of study treatment.

Once a subject is 18 years old, triplicate linear growth and knee height assessments will no longer be required. In Part D subjects will stop participation once they reach 18 years of age.

Linear growth measurements will be performed by trained and qualified study personnel. The stadiometric measurement instructions will include practices that reduce measurement error including calibration of equipment, proper subject positioning, and measurement capture. The same examiner should be used whenever possible to standardize the performance of procedures and minimize the inter-examiner variability. Measurement of knee height will also be standardized.

7.2.4 Vital Signs

Vital signs (temperature, respiratory rate, blood pressure, and heart rate) will be assessed for all subjects.

For subjects from Amendment 1 continuing non-flare-up based treatment, vital signs (temperature, respiratory rate, blood pressure, and heart rate) will be assessed every 3 months (Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69 and 72).

For subjects from Amendment 1 starting non-flare-up based treatment, vital signs will be assessed at Amendment 3 Screening and every 3 months (Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, and 48).

For subjects receiving flare-up based treatment, vital signs will be assessed at Flare-up Cycle Safety Day 1 and every 12 weeks thereafter during safety assessments until treatment of the last flare-up or traumatic event in the flare-up cycle is completed.

For subjects in Part D, vital signs will be assessed at Year 1 and Year 2 post last dose of study treatment.

Blood pressure will preferably be measured on the same arm at the same position and with the same instrument at each visit. If a subject is unable to have blood pressure performed on the same arm, the alternate arm or leg will be used. Blood pressure and heart rate will be obtained following a resting period of at least 5 minutes. Automatic blood pressure devices are not allowed due to the risk of over-inflation and potential tissue injury.

7.2.5 Electrocardiogram

For subjects from Amendment 1 continuing non-flare-up based treatment, a 12-lead electrocardiogram (ECG) will be performed at Months 12, 24, 36, 48, 60, and 72.

For subjects from Amendment 1 starting non-flare-up based treatment, an ECG will be performed at Amendment 3 Screening, Non-flare-up Day 7, and at Months 6, 12, 24, 36, and 48.

For subjects receiving flare-up based treatment, an ECG will be performed at Flare-up Cycle Safety Day 1, Flare-up Cycle Safety Day 7, and at the End of Flare-up Cycle Safety Assessments.

To ensure consistent generation and interpretation of results, a central ECG laboratory will perform the analysis using standardized procedures. The Investigator will be provided ECG interpretations from the central ECG laboratory, and will review and assess all abnormal results for clinical significance. Any post-baseline ECG abnormalities assessed as clinically significant will be recorded as AEs.

7.2.6 Clinical Laboratory Tests

Blood and urine samples will be collected for hematology, biochemistry (includes lipids), and urinalysis testing.

For subjects from Amendment 1 continuing non-flare-up based treatment, blood and urine samples will be collected every 6 months (Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72).

For subjects from Amendment 1 starting non-flare-up based treatment, blood and urine samples will be collected at Amendment 3 Screening and every 6 months (Months 6, 12, 18, 24, 30, 36, 42 and 48).

For subjects receiving flare-up-based treatment, blood and urine samples will be collected at Flare-up Safety Day 1 and every 12 weeks thereafter during safety assessments until treatment of the last flare-up or traumatic event in the flare-up cycle is completed. Subjects with normal or non-clinically significant abnormal safety laboratory results observed within 1 month of flare-up-based treatment will not need to have laboratory tests performed at Flare-up Day 1. The Investigator will determine whether subjects with clinically significant abnormal laboratory results in the most recent assessment will need to be re-assessed prior to beginning flare-up-based treatment. The only exception is for pregnancy testing, which must be performed monthly during non-flare-up based treatment; and at the start of each flare-up cycle and every 4 weeks thereafter until treatment of the last flare-up or traumatic event in the flare-up cycle is completed. However, if a pregnancy test was performed within 4 weeks prior to the start of a flare-up or traumatic event, treatment of the flare-up or traumatic event will not be delayed pending repeat pregnancy testing.

Blood and urine samples may be collected remotely (eg, at the subject's home) by qualified study personnel or at a local medical facility according to standard operating procedures and applicable regulations. When possible, samples will be collected under fasting conditions. Samples will be packaged and shipped to the designated laboratory for testing. To ensure consistent generation and interpretation of results, a central testing laboratory will perform the analysis of clinical laboratory samples. If urinalysis results are abnormal, a microscopic evaluation will be completed. If results are needed promptly (eg, Screening for eligibility), analysis of samples can be completed at a local, qualified laboratory.

The total blood volume drawn from a subject from Amendment 1 continuing non-flare-up based treatment over the course of the entire study (up to 72 months) will range from approximately 60 mL (in the case of no flare-ups) to 170 mL (in the case of two flare-ups treated per year, or a total of 12 flare-ups treated during the entire study). The total blood volume drawn from a subject from Amendment 1 starting non-flare-up based treatment during Amendment 2 over the course of the entire study (up to 48 months) will range from approximately 42 mL (in the case

of no flare-ups) to 120 mL (in the case of two expected flare-ups treated per year, or a total of eight flare-ups treated during the entire study). In the event that the total drawn blood volume exceeds the limits established by the clinical site for pediatric subjects, then priority will be given to the key safety laboratory tests, as outlined in the clinical safety laboratory manual. This will ensure that the total blood volume drawn is within the established limits.

The Investigator will be provided all laboratory results and will review and assess out-of-range findings for clinical significance. Any post-baseline abnormal laboratory value assessed as clinically significant will be recorded as an AE. It is recognized that performing phlebotomy in subjects with FOP is very challenging due to their multiple ankyloses and the potential to cause injury resulting in a flare-up following multiple attempts. The Investigator will be notified about any protocol-specified safety laboratory test that could not be obtained despite at least two attempts. Should this occur, or for those samples that were drawn but were not usable (eg, quantity not sufficient, clotted, sample lost, etc.), the Investigator will assess the subject's condition and determine whether repeated attempts should be made to obtain the missing laboratory data for that timepoint, or reassessed at the next scheduled timepoint based on the subject's current clinical status (eg, AEs, vital signs) and previous laboratory measures.

If a local laboratory is utilized, the investigative site should notify the study team if the local laboratory cannot test all the analytes listed in Table 6. If the total thyroxine (Total T4), free T4, uric acid, gamma glutamyl transferase, inorganic phosphorous, very low-density lipoprotein, or globulin parameters are not available through the local laboratory, and alternative arrangements cannot be made, testing of these analytes may be omitted provided other subject-assessments of thyroid function (ie, thyroid-stimulating hormone), lipid metabolism (ie, triglycerides, low-density lipoprotein, high-density lipoprotein, and total cholesterol), and protein metabolism (ie, total protein and albumin) are available and confirmed to be stable as per the Investigator.

Alternative arrangements to test the listed analytes are to be made if the Investigator, Medical Monitor, or sponsor determines that they have the potential to impact subject safety. In the event the local laboratory is unable to test any other analytes, they may be omitted in exceptional circumstances after consultation with the sponsor. Such exceptions will not be applied to any of the key safety analytes, as outlined below and in the clinical safety laboratory manual.

For subjects with two or more consecutive missing assessments of key safety laboratory analytes, including triglycerides, ALT, AST, bilirubin, lipase, and amylase (as outlined in Section 7.3, Special Safety Assessments), blood collection for evaluation of missing analytes should be performed as soon as possible. If such analytes have not been evaluated over a prolonged period of time (>6 months during non-flare-up-based treatment or >8 weeks during flare-up treatment), a successful repeat assessment should be performed within 1 month. If key safety laboratory tests cannot be evaluated within 1 month, the subject should be discussed with the Medical Monitor and the EC/IRB, as necessary. If the subject is unable to have venous specimens collected, use of microliter collection techniques and capillary specimens, where available, may be utilized to assess subject safety. Local laboratory results should be promptly documented in the appropriate eCRF.

Table 6 presents the clinical laboratory parameters that will be assessed in this study.

Table 6 Clinical Laboratory Parameters

Biochemistry:	
Sodium	Globulin
Potassium	Alkaline phosphatase (ALP)
Chloride	Aspartate aminotransferase (AST)
Bicarbonate	Alanine aminotransferase (ALT)
Blood urea nitrogen	Gamma glutamyl transferase (GGT)
Creatinine	Uric acid
Calcium	Total thyroxine (T4)
Inorganic phosphorous	Free T4
Glucose	Thyroid-stimulating hormone
Total bilirubin	Amylase
Total proteins	Lipase
Albumin	
Lipid Profile:	
Triglycerides	High-density lipoprotein (HDL)
Total cholesterol	Low-density lipoprotein (LDL)
	Very low-density lipoprotein (VLDL)
Hematology:	
Hemoglobin	Platelets
Hematocrit	White blood cell count (including differentials)
Red blood cell count	Neutrophils
Packed cell volume	Lymphocytes
Mean corpuscular volume	Monocytes
Mean corpuscular hemoglobin	Eosinophils
Mean corpuscular hemoglobin concentration	Basophils
Urinalysis1:	
pH	Blood (free hemoglobin)
Protein	Nitrite
Glucose	Urobilinogen
Ketones	Specific gravity
Bilirubin	Color & appearance

1 If results are abnormal, then a microscopic evaluation will be completed.

7.2.7 Pregnancy Testing

For females of child bearing potential receiving palovarotene, a blood or urine pregnancy test (with sensitivity of at least 50 mIU/mL) will be conducted monthly in Parts A, B and C. If the Screening test is positive, the subject will not be eligible for study participation. Any positive pregnancy test during study participation will result in immediate discontinuation of study drug. If a subject becomes pregnant during the study, she will be followed throughout her pregnancy and the health status of the baby will be verified.

7.2.8 Adverse Events

Adverse event (AE) monitoring will be conducted throughout the study for all subjects. Adverse events will be assessed at every site and remote visit during both non-flare-up-based and flare-up-based treatment. The AE, serious adverse event (SAE) and death reporting period begins at the time of informed consent and continues through study completion. Adverse events, SAEs, and deaths will be assessed at every site and remote visit during non-flare-up-based treatment, flare-up-based treatment, Part C or SC and EOT/EOS + 30 days.

The Investigator will follow-up on all AEs observed or reported by the subject up to the end of the reporting period or until follow-up is no longer necessary. Limb/joint AEs reported by

subjects with open epiphyses will be evaluated by clinical and radiographic assessments deemed appropriate by the Investigator.

Definitions, documentation, and reporting of AEs are described in Section 9.1. Serious adverse events (SAEs) must be reported within 24 hours as described in Section 9.1.8.

7.2.9 Concomitant Medications

Concomitant medications will be assessed at every site and remote visit during both non-flare-up based and flare-up-based treatment and in Part D.

See Section 5.6.1 for restrictions for concomitant medications.

7.3 Special Safety Assessments

In light of the established safety profile of the currently marketed oral systemic retinoids and hypothesized potential concerns, clinical and laboratory monitoring of selected AEs and laboratory abnormalities in subjects in this study is indicated. The following potential safety issues will be monitored in the study.

7.3.1 Columbia-Suicide Severity Rating Scale

In accordance with the Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials, 2012, all subjects 8 years of age and older who are receiving palovarotene will be assessed for suicidal ideation and behavior every 3 months using the age-appropriate C-SSRS and at all visits during the Flare-up Cycle Safety Assessments (see Appendix 5). The adult form will be used for subjects 12 years and older and the pediatric form will be used for subjects 8 to 11 years old. Study personnel administering the questionnaire will receive formal training to ensure accuracy and consistency in application of the instrument.

For subjects from Amendment 1 continuing non-flare-up based treatment, assessment using the C-SSRS will occur every 3 months (Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69 and 72).

For subjects from Amendment 1 starting non-flare-up based treatment, assessment using the

C-SSRS will occur at Amendment 3 Screening and every 3 months (Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45 and 48). Any subject reporting a type 4 or 5 suicidal ideation or any suicidal behavior within 1 month prior to Amendment 3 Screening will not be eligible to receive study drug.

Any subject experiencing a type 4 or 5 suicidal ideation or any suicidal behavior while receiving study drug will have study drug immediately withheld. All such subjects will be referred by the Investigator to a mental health professional for evaluation and counselling as appropriate.

7.3.2 Knee and Hand/Wrist Radiographs

Due to the potential for palovarotene to cause adverse effects on long-bone growth, all subjects at the time of enrolment into Study PVO-1A-204 with open epiphyseal growth plates at Screening had knee (A/P) and hand/wrist radiographs (P/A).

For subjects from Amendment 1 continuing non-flare-up based treatment with open epiphyseal growth plates at the most recent assessment, knee (A/P) and hand/wrist radiographs (P/A view, preferable on the left side) will be performed at the clinical site at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72.

For subjects from Amendment 1 starting non-flare-up based treatment with open epiphyseal growth plates at the most recent assessment, knee (A/P) and hand/wrist radiographs (P/A) view, preferable on the left side) will be performed at Amendment 3 Screening. Subjects for whom radiographs were performed within the last 3 months will not need to repeat radiographs at Screening. Subjects with open epiphyseal growth plates at this assessment will also be evaluated at the clinical site at Months 6, 12, 18, 24, 30, 36, 42 and 48 at the clinical site.

Subjects who are skeletally immature at the time of study drug discontinuation and entering Part D (Y1 and Y2 post last dose of study treatment) will have follow-up knee (A/P view) and hand/wrist radiographs (P/A view, preferably on the left side) every year.

Additional knee and hand/wrist radiograph assessments will also be performed every 3 months (±2 weeks) in skeletally immature subjects who (1) received flare-up dosing in the period of time since their last assessment; and (2) had not achieved 100% skeletal maturity on their last assessment. The 3-month radiographic assessments will be performed at the clinical site unless the Investigator determines they can be performed at a local medical facility. Once a subject has achieved 100% skeletal maturity (defined as closure of all assessed growth plates) as determined by the knee and hand/wrist radiographs, further radiographs will no longer be necessary. If 100% skeletal maturity is not achieved at both locations, then only the location that is still maturing would need to be monitored.

All radiographs will be read by a central imaging laboratory to ensure consistent assessment of the radiographs. The Investigator will be provided all results and will review and assess abnormal results for clinical significance. Any post-baseline abnormal results assessed as clinically significant will be recorded as an AE. Limb/joint AEs in these subjects will be evaluated by clinical and radiographic assessments deemed appropriate by the Investigator.

7.3.3 Bone Safety Management Plan

To enhance subject safety monitoring, a Bone Safety Management Plan has been developed to supplement per-protocol safety monitoring and will be followed under Amendment 3 and subsequent amendments of Study PVO-1A-204. Of note, in addition to the knee and hand/wrist radiographs described in Section 7.3.2, WBCT scans acquired from subjects under the age of 18 years will be reviewed in a blinded fashion by two independent radiologists to assess the growth plate morphology of bilateral hands/wrists and knees. Reviews of WBCT scans from all subjects regardless of age will also monitor hip morphology for signs of avascular necrosis (AVN), warranted due to the association of corticosteroids with AVN and the presence of AVN of the femoral head in wild-type rats treated with high dose palovarotene. WBCT scans will be reviewed for spinal health including fracture assessment.

The Bone Safety Management Plan will be provided to each clinical site, must be signed by the clinical site Investigator, and will be appended to the Data Monitoring Committee Charter.

Safety findings of these bone images may trigger additional follow-up images and/or dose modification, as discussed in the Bone Safety Management Plan.

7.3.4 Mucocutaneous Effects (Skin and Mucous Membrane Toxicity Profile)

At every study visit during palovarotene treatment, subjects will be assessed for AEs, including mucocutaneous AEs (eg, dry skin, itching, redness, rash, flaking and peeling of the skin, dry lips, chapped lips, cheilitis, dry eyes, and conjunctivitis). In addition to the severity assessments of mild, moderate, and severe (Section 9.1.4), all mucocutaneous AEs will be rated according to the most recent version of the Common Terminology Criteria for Adverse Events (CTCAE),

Version 4.03, 14 June 2010 (see Appendix 6). In the event of a subject-report of a mucocutaneous AE, dermatologic photographs may be taken for review by a dermatologist. Permission to obtain dermatologic photographs will be requested in the informed consent/assent document(s).

If any mucocutaneous effects are observed, symptomatic therapy (eg, analgesics, skin emollients, lip moisturizers, artificial tears, or other helpful treatments) may be administered if deemed necessary by the Investigator. In addition, the Investigator may recommend prophylactic use of these therapies at the start of palovarotene treatment. Dose reduction as described in Section 6.5 is recommended for intolerable mucocutaneous effects that would otherwise result in study drug discontinuation. If a subject is already receiving the lowest possible dose, then study drug will be discontinued.

Although palovarotene has not been proven to be phototoxic, precautionary measures for phototoxicity are recommended for subjects who are receiving palovarotene. Excessive exposure to sun should be avoided and protection from sunlight when it cannot be avoided (use of sunscreens, protective clothing, and use of sunglasses).

7.3.5 Serum Lipids

A complete lipid profile will be performed as part of the biochemistry testing (see Section 7.2.6) for all subjects in Part C.

If, during the palovarotene treatment, serum triglyceride levels are ≥800 mg/dL, the study drug should be immediately discontinued, with follow-up assessments performed per protocol.

7.3.6 Liver Enzymes

Liver enzymes will be monitored as part of the biochemistry testing (see Section 7.2.6) for all subjects in Part C.

During palovarotene treatment, drug therapy should be discontinued if any of the following occur:

- AST or ALT ≥5× ULN
- Jaundice is observed
- ALT >3× ULN if accompanied with any bilirubin increase >2× ULN, unexplained abdominal pain, malaise, nausea, and/or vomiting

Liver toxicity evaluation will follow the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009).

7.3.7 Lipase/Amylase

Amylase and lipase will be monitored as part of the biochemistry testing (see Section 7.2.6) for all subjects in Part C.

Lipase and/or amylase increases during the course of the study should be further evaluated to exclude the occurrence of pancreatitis. With symptoms of pancreatitis or with persistent elevations that cannot be explained, the study drug should be discontinued as per the Investigator's judgment, with follow-up assessments performed per protocol.

7.3.8 Central Nervous System

Retinoid use has been associated with a number of cases of benign intracranial hypertension (also known as pseudotumor cerebri), some of which involved concomitant use of tetracyclines.

The cases of benign intracranial hypertension were manifested with symptoms and signs such as severe headache, nausea and vomiting, and visual disturbances, and may be associated with papilledema. Headache generally occurs within 3 to 4 hours of starting therapy and remits spontaneously.

However, headache of unusual characteristics (eg, severity, location, pattern) to the subject should lead to contacting the Investigator. In case of such headache, it is at the discretion of the Investigator to refer subjects receiving palovarotene treatment for neurological and/or ophthalmological examination to rule out benign intracranial hypertension. Headache will be assessed using the standard AE severity scale (see Section 9.1).

7.3.9 Hearing and Visual Disturbances

Impaired hearing has been reported in subjects taking retinoids. The Investigator should refer subjects receiving palovarotene treatment who experience tinnitus or hearing impairment to specialized care for further evaluation. The subject with a confirmed diagnosis of hearing impairment (felt to be related to the study drug) will be discontinued from treatment.

An ophthalmological examination should be carried out in all subjects receiving palovarotene treatment who are experiencing unexplained visual difficulties.

Corneal opacities have occurred in subjects receiving retinoids and were reversible upon drug discontinuation. Subjects receiving palovarotene treatment with corneal opacities should be assessed by an ophthalmologist.

Decreased night vision has been reported during retinoid therapy. The onset in some subjects can be sudden; therefore, subjects receiving palovarotene treatment should be informed and warned to be cautious when driving or operating vehicles at night.

7.3.10 Teratogenicity

Palovarotene must not be used by female subjects who are or may become pregnant. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking palovarotene in any amount, even for short periods of time. Potentially any fetus exposed during pregnancy can be affected. There are no accurate means of determining whether an exposed fetus has been affected.

Birth defects that have been documented following exposure to retinoids include abnormalities of the face, eyes, ears, skull, central nervous system, cardiovascular system, and thymus and parathyroid glands. Cases of IQ scores less than 85 with or without other abnormalities have been reported. There is an increased risk of spontaneous abortion, and premature births have been reported.

Documented external abnormalities with other retinoids include: skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia); facial dysmorphia; and cleft palate. Documented internal abnormalities with other retinoids include: central nervous system abnormalities (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit); cardiovascular abnormalities; thymus gland abnormality; and parathyroid

hormone deficiency. In some cases, death has occurred with other retinoids with certain of the abnormalities previously noted.

7.4 Efficacy Assessments

Subjects who began non-flare-up based treatment during Amendment 1 will continue this visit schedule, and will receive non-flare-up based treatment for up to an additional 48 months.

Therefore, these subjects may undergo non-flare-up based treatment for up to 72 months over the entire study. Subjects who will start non-flare-up based treatment will receive non-flare-up based treatment for up to 48 months.

7.4.1 Low-Dose Whole Body Computed Tomography

For subjects from Amendment 1 continuing non-flare-up based treatment, a low-dose WBCT scan (excluding head) will be performed during annual site visits at Months 12, 24, 36, 48, 60 and 72.

For subjects from Amendment 1 starting non-flare-up based treatment, a low-dose WBCT scan (excluding head) will be performed at Amendment 3 Screening and during annual site visits at Months 12, 24, 36 and 48.

For subjects in Part D, a low-dose WBCT scan (excluding head) will be performed during annual site visits at Y1 and Y2 post last dose of study treatment.

Interpretation of the CT scan will document the absence or presence of HO across various body regions, volume of total body HO, and presence and volume of new HO at follow-up visits. All images will be interpreted by a central imaging core laboratory using standardized procedures detailed in an imaging charter.

7.4.2 FOP-Physical Function Questionnaire

On clinic days when multiple assessments are to be performed, the age-appropriate FOP-PFQ and the age-appropriate PROMIS Global Health Scale should be completed (in that order) by the subject/parent before any other procedures are completed on those visit days.

For subjects from Amendment 1 continuing non-flare-up based treatment, age-appropriate forms of the FOP-PFQ will be administered every 6 months (Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72).

For subjects from Amendment 1 starting non-flare-up based treatment, age-appropriate forms of the FOP-PFQ will be administered at Amendment 3 Screening and every 6 months (Months 6, 12, 18, 24, 30, 36, 42 and 48).

Study personnel will be trained on the administration of the instruments and subjects (and parents of subjects under the age of 15 years) will be provided specific instructions on how to complete the instrument independently.

To evaluate the effect of palovarotene on physical function, age-appropriate forms of the FOP-PFQ will be administered. The adult form of the FOP-PFQ will be completed by subjects 15 years of age and older (see Appendix 2A). Two Pediatric FOP-PFQ (FOP-PFQ-P) forms will be utilized in subjects under the age of 15 years: a self-completed form developed for 8- to 14-year-olds and a proxy-completed form developed for 5- to 14-year-olds (see Appendix 2B and Appendix 2C, respectively).

Study personnel will be trained on the administration of the instruments and subjects (and parents of subjects under the age of 15 years) will be provided specific instructions on how to complete the instrument independently.

7.4.3 PROMIS Global Health Scale

For subjects from Amendment 1 continuing non-flare-up based treatment, age-appropriate forms of the PROMIS Global Health Scale will be administered every 6 months (Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, and 72).

For subjects from Amendment 1 starting non-flare-up based treatment, age-appropriate forms of the PROMIS Global Health Scale will be administered at Amendment 3 Screening and every 6 months (Months 6, 12, 18, 24, 30, 36, 42 and 48).

To evaluate the effect of palovarotene on physical and mental health in subjects ≥15 years of age and mental health in subjects <15 years, age-appropriate forms of the PROMIS Global Health Scales will be administered. The adult form of the PROMIS Global Health Scale will be administered to subjects 15 years of age and older (see Appendix 7A). Two PROMIS Pediatric Global Health Scale forms will be utilized in subjects under the age of 15 years: a self-completed form developed for 8- to 14-year-olds and a proxy-completed form developed for subjects under the age of 15 years (see Appendix 7B and Appendix 7C, respectively).

Study personnel will be trained on the administration of the instruments and subjects (and parents of subjects under the age of 15 years) will be provided specific instructions on how to complete the instrument independently.

7.4.4 Cumulative Analogue Joint Involvement Scale

For subjects from Amendment 1 continuing non-flare-up based treatment, CAJIS will be administered every 6 months (Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72).

For subjects from Amendment 1 starting non-flare-up based treatment, CAJIS will be administered at Amendment 3 Screening and every 6 months (Months 6, 12, 18, 24, 30, 36, 42 and 48).

Range of motion will be assessed by the Investigator using CAJIS (see Appendix 1). The CAJIS should be assessed by the same Investigator at each time point. The CAJIS assessment may be performed remotely or by videoconferencing.

7.5 Pharmacokinetics

The pharmacokinetics of palovarotene dosing will be assessed in all subjects during non-flare-up and flare-up-based treatments.

During non-flare-up palovarotene treatment, pharmacokinetic blood samples will be collected at the first 3-month safety assessment. If blood samples cannot be obtained during the first 3-month safety assessment, or if the subject is on flare-up-based treatment, then the non-flare-up treatment pharmacokinetic blood sample can be obtained during any subsequent 3-month safety visit.

Pharmacokinetics of palovarotene dosing will also be assessed twice during flare-up based treatment: once during the 20-mg regimen at any time between Study Days 4 to 28, and once during the 10-mg regimen at any time between Study Days 32 to 84, for the first treated flare-up only. If this is not possible for the first treated flare-up, pharmacokinetic blood samples can be obtained during any subsequent flare-up dosing cycle.

Pharmacokinetic blood samples will be collected at pre-dose and 3, 6, 10, and 24 hours post-dose. Subjects who underwent a prior flare-up dosing pharmacokinetic assessment will not require a repeat assessment of flare-up dosing pharmacokinetics. However, these subjects will require a pharmacokinetic assessment for non-flare-up palovarotene dosing at a 3-month safety visit.

The determination of palovarotene plasma concentrations will be performed using a validated LC-MS/MS method, and exploration of any relationships with palovarotene exposure will be performed. The time of sample collection as it relates to the time of dosing on the pharmacokinetic blood sampling days will be recorded.

Detailed instructions for collection, storage, labeling, and shipment of all samples will be provided in the Laboratory Manual.

7.6 Data Monitoring Committee

A DMC will review safety information periodically and on an ad hoc basis as outlined in the DMC Charter, which is maintained separately from the study protocol. The DMC can recommend temporary or permanent stopping of the study at any time if there are significant safety concerns. The DMC Charter includes recommended safety stopping rules. The DMC will also review the results of pre-planned interim analyses (see Section 8.6). In addition to the Investigator, the DMC will make recommendations for potential dose modifications in the event of treatment-related adverse bone effects as described in the Bone Safety Management Plan.

The DMC will include members with relevant clinical expertise, including a good understanding of the safety of retinoids. The methodology and the operating procedures for the safety reviews will be developed by the Chairperson in collaboration with the sponsor and will be documented in the DMC Charter.

7.7 Temporary Measures (Procedures Related to COVID-19 Pandemic)

Procedures related to COVID-19 pandemic

Temporary measures put in place for the conduct of Study PVO-1A-204 during the COVID-19 pandemic and until such time as the situation resolves, at which point the protocol assessments will return to those specified. Investigators will determine the feasibility of dosing on a subject-by-subject basis, depending on the ability to conduct safety monitoring and providing subjects an adequate supply of study drug, in accordance with local requirements. These recommendations will remain in place for as long as the COVID-19 pandemic warnings are in effect in territories participating in the trial. The timing of when the pandemic is declared over may vary on a country-by-country basis as well as between sites in the same country, and as such the temporary measures may remain in place for differing periods of time per country/site.

The study visits and assessments to be conducted during this period are listed below:

Study Visits and Assessments

(1) **For subjects aged under 14 years that are still participating in the study but not currently receiving palovarotene treatment as per the global partial clinical hold or for any other reason,** they will complete Part C EOT/EOS and be invited to participate in Part D and undergo assessments outlined in Table 4.

(2) **For subjects aged 14 years and older who are being considered for re-starting palovarotene treatment but have NOT yet re-started,** the following minimum assessments are to be done via remote monitoring (video conference/phone calls) by the Investigator (or delegated study staff):

(a) Non-flare-up-based visits every 3-6 months (per protocol): assess for childbearing status (females only) and pregnancy prevention measures, CAJIS, ConMeds, adverse events, review subject diary, PROMIS Global Health Scale*, FOP-PFQ* (*assessments that can occur remotely but not required as these are not essential to ensure subjects' safety).

(b) For females of childbearing status: if pregnancy testing did not continue monthly per protocol post the study medication interruption then at a minimum a self-administered urine pregnancy test is to be done within 4 weeks before re-starting palovarotene treatment.

(c) All subjects should have laboratory assessments (hematology, biochemistry, urinalysis) within 4 weeks before re-starting palovarotene treatment.

(d) All subjects who were skeletally immature at the last assessment will have a hand-wrist and knee radiographs within 12 weeks before re-starting palovarotene treatment. For on-treatment subjects who have not reached at least 90% skeletal maturity radiograph assessments should continue per protocol either on site or remotely.

Site staff will also assess the subject's ability to restart remotely.

(3) **For subjects 14 years and over that plan to reinitiate dosing, once dosing is reinitiated following the required approvals for restart (Ethics Committee and Competent Authority),** the following minimum assessments that cannot be performed via remote monitoring must be performed either at the clinical site, at the subject's home (by Symphony nursing) or at a local medical facility in order for the Investigator to adequately monitor the safety of subjects:

(a) Via remote monitoring (telephone or video conferencing) by Investigator (or delegated study staff):

i. Non-flare-up-based visits (per protocol schedule every 3 and/or 6 months): C-SSRS, assess for childbearing status (females only) and pregnancy prevention measures, CAJIS, ConMeds, adverse events, PROMIS Global Health Scale*, FOP PFQ* (*assessments that can occur remotely but are not required as these are not essential to ensure subjects' safety), study drug dispensing

ii. Flare up visits (per protocol schedule): C-SSRS, ConMeds, adverse events, study drug dispensing

(b) Via home visit by Symphony nursing/local assessment

i. Non-flare-up-based visits per protocol schedule (every 3 and/or every 6 months): body weight, vital signs, hematology, biochemistry, urinalysis, self-administered pregnancy test (monthly), ConMeds, adverse events, review subject diary

ii. Flare up visits (per protocol schedule): vital signs, body weight, hematology, biochemistry, urinalysis, self-administered pregnancy testing, ConMeds, adverse events, review subject diary

(4) **Based on the known safety profile of palovarotene to date in FOP patients, the following assessments can be postponed as determined by the Sponsor and individual site Investigators, as they do not constitute assessments where a safety concern has been raised.** The below assessments were also deemed acceptable to postpone by the DMC chair.

(a) To date low dose whole-body CT has not indicated a safety concern of avascular necrosis of the hip. Any concerns for avascular necrosis of the hip based on clinical assessment should be followed up;

(b) For subjects who have reached at least 90% skeletal maturity radiograph assessments may be postponed given the low risk of early growth plate closure as well as growth plate abnormalities;

(c) Linear height and knee height (Subjects 14 years and older are at or near adult height indicated by skeletal maturity of at least 90%);

(d) ECG (FOP patients can have ECG abnormalities, ECG changes noted in subjects on Palovarotene were similar to those seen in the untreated subjects in the Natural History Study. Clinical concerns of abnormal ECG findings should continue to be followed);

(e) Hearing evaluation (As a class, retinoids can cause abnormal hearing. Evaluation should be performed if there is clinical concern);

(f) Physical exam (Palovarotene has been shown to cause retinoid skin reactions which can be assessed remotely).

Individual subjects may require assessments if there is a clinical concern as identified by the Investigator. Protocol deviations that have an impact on subject safety should be notified immediately to CRO/Sponsor as it may necessitate an urgent safety measure notification to competent authorities and ethics committees in some countries.

(5) **End of Treatment/End of Study Assessments:**

(a) The following assessments should be performed via remote monitoring (telephone or video conferencing) by Investigator (or delegated study staff):

i. C-SSRS, assess for childbearing status (females only) and pregnancy prevention measures, CAJIS, Con-Meds, adverse events, PROMIS Global Health Scale, FOP PFQ

(b) The following assessments should be performed at the subject's home (by Symphony nursing) or at a local medical facility: Body weight, vital signs, hematology, biochemistry, urinalysis, pregnancy test (monthly), ConMeds, adverse events, review subject diary

(6) **Once on-site visits resume, the following assessments should be performed on site as well as any assessment that was not obtained via remote monitoring or Symphony nurse:**

(a) X-rays, Whole-Body CT, Linear and Knee Height, Physical Exam, ECG.

(7) **Informed Consent/Subject Communication:** In consultation with their site IRB/EC, Investigators are required to inform subjects of the temporary changes (during the COVID-19 global pandemic) to the study conduct and monitoring plans that could impact them and their willingness to continue participation in the trial. The method of communication to subjects (e.g., email, phone call, information letter) and documentation of subject/caregiver acknowledgement is to be performed and documented in accordance with local regulations/EC requests and guidance. All contacts with subjects must be filed in the source records.

A risk mitigation assessment will be performed for each subject at the site in order to determine how their participation may be impacted. Sites must ensure that appropriate measures are taken to ensure the safety of FOP subjects in light of the ongoing COVID-19 pandemic, taking into consideration local Ethics Committee and Competent Authority guidance, as well as the ability of individual Investigators and sites to adequately monitor subject safety.

8 STATISTICAL AND ANALYTICAL PLANS

This study is intended to assess whether a non-flare-up based dosing regimen, combined with higher doses during times of flare-ups, will result in a lower incidence of new HO formation. As this is an open-label study with no comparator arm, use of subject data from Study PVO-1A-001 (Natural History Study [NHS]) will form the basis for a control arm. Additional analysis of the flare-up-based treatment regimen will be described in the Statistical Analysis Plan (SAP).

A summary of the general methods and strategies for analysis is provided in the sections below. A more comprehensive SAP will be written that will describe the manner in which the analysis will be performed.

References to Parts B/C/D are to PVO-1A-202 Parts B/C/D which corresponds to PVO-1A-204, ongoing in France.

8.1 General Methods

For purposes of assessing the efficacy of the non-flare-up based dosing regimen, low-dose WBCT imaging data obtained under the original protocol and all amendments will be combined.

8.2 Sample Size

The new HO volume data as assessed by low dose WBCT scan, excluding head, from the original protocol and all amendments will be combined. The sample size was fixed by the number of subjects enrolled in the original protocol and Amendment 1 and was not based on power calculations.

8.3 Study Populations

The following populations will be analyzed under Amendment 3 (and all subsequent amendments):

- The Full Analysis Set (FAS) includes all enrolled subjects having a baseline
- HO volume measurement and at least one post-baseline HO volume measurement. For efficacy comparisons to the NHS, the FAS will also include subjects enrolled in the NHS with available baseline and at least one post-baseline HO volume measurements.

- The Per-Protocol Set (PPS) is a subset of the FAS including subjects with no major protocol deviations that are expected to interfere with assessments of the primary endpoint, and with at least 80% compliance to the study drug regimen. For efficacy comparisons to the NHS, the PPS will also include subjects in the NHS with available baseline and at least one post-baseline HO volume measurements and with no major protocol deviations that are expected to interfere with assessments of the primary endpoint.
- The Safety Analysis Set (SAS) includes all enrolled subjects receiving at least one dose of palovarotene during Amendment 2. For safety comparisons to the NHS, the SAS will also include subjects enrolled in the NHS with available post-baseline follow-up.
- The Pharmacokinetic Analysis Set (PAS) is a subset of the SAS including subjects with evaluable pharmacokinetics data.

8.4 Baseline and Disease Characteristics (including Medical History)

Baseline and disease characteristics will be tabulated descriptively (eg, number and percentage of subjects for each category for categorical parameters, and the number, mean, standard deviation, and range for continuous parameters).

8.5 Subject Disposition

Subject disposition will be listed and summarized.

8.6 Extent of Exposure

The extent (duration) of exposure will be determined from the date of first dose of study drug through the date of last dose of study drug. For times during which subjects are receiving flare-up based treatment, tabulation of the number of days at the higher dose(s) will be presented. An assessment of the proportion of subjects who are able to tolerate the higher doses will be performed.

8.7 Efficacy

8.7.1 Primary Efficacy

The primary efficacy endpoint is the annualized change in new HO volume (as assessed by low-dose WBCT scan, excluding head). The primary efficacy analysis comparing the annualized change in new HO volume between subjects treated with palovarotene and untreated subjects from the NHS will be conducted using a weighted linear mixed effects (wLME) model. A subject-level random effect will be used to account for the correlation among repeated measures on the same subject as subjects may contribute follow-up from the NHS and the current trial.

Baseline HO volume divided by age will be the only covariate included in the model. As HO volume is non-decreasing, the LME model will be fit using only a subject's observations associated with the longest follow-up in the NHS and the current study with weights used to account for the different lengths of observed subject follow-up.

The estimated difference in the annualized change in new HO volume between subjects treated with palovarotene and untreated subjects and its associated Wald statistic will be used for hypothesis testing. Hypothesis testing will be performed using a two-sided, type I error rate of 5%.

8.7.2 Secondary Efficacy

Secondary efficacy variables for non-flare-up based treatment will include the following: percent of subjects with new HO, change from baseline in ROM as assessed by CAJIS, change from baseline in physical function using age-appropriate forms of the FOP-PFQ, and change from baseline in physical and mental function for subjects ≥15 years old and mental function for subjects <15 years old using age-appropriate forms of the PROMIS Global Health Scale.

The secondary efficacy endpoints will be summarized by visit and, where applicable, compared to the relevant time point from the NHS.

8.8 Safety

The safety analysis will be descriptive in nature. Safety evaluations will include AE and SAE reporting, ECGs (for subjects receiving treatment), vital signs (temperature, respiratory rate, blood pressure, and heart rate), physical examination, body weight and height, laboratory parameters (hematology, biochemistry, and urinalysis), urine pregnancy tests for FOCBP, and concomitant medication reporting.

Evaluation of subjects with open epiphyseal growth plates at the most recent assessment will include knee (A/P) and hand/wrist radiographs (P/A view) for assessment of epiphyseal growth plate; and standardized stadiometry and knee height (in triplicate) for assessment of linear growth.

Any limb/joint AEs reported by these subjects will be evaluated by clinical and radiographic assessments as deemed appropriate by the Investigator.

All safety data collected and captured in the eCRF will be included in data listings sorted by domain, subject, and time point, or as appropriate. Mean changes from pre-treatment to on-treatment will generally be tabulated by protocol-specified time points, while the number of subjects with potentially clinically significant values at pre-treatment and at each endpoint will be presented. The last non-missing baseline value will be used as the pre-treatment value for that parameter.

8.8.1 Adverse Events

Adverse events will be classified using the MedDRA coding dictionary. Adverse event severity will be assessed and reported according to criteria defined in the protocol (mild, moderate, severe).

Adverse events known to be associated with retinoids (eg, mucocutaneous events) will be further graded according to CTCAE, Version 4.03, 14 June 2010.

Tabulations will include an overall incidence of at least one AE, incidence within body system, and incidence by preferred term. Each subject may only contribute once (ie, first occurrence) to each of the incidence rates, regardless of the number of occurrences. Incidences (denominators and percentages) for selected gender-specific AEs will be adjusted by the number of males or females, as appropriate.

8.8.2 Suicide Ideation

The number of subjects who report any type 4 or 5 suicide ideations in the C-SSRS or any suicide behavior during the study will be presented (see Appendix 5).

8.8.3 Clinical Laboratory Findings

Change in clinical laboratory findings, vital signs, and other continuous safety parameters will be assessed descriptively, with pre-treatment, on-treatment, and change from pre-treatment values calculated. For purposes of this analysis, pre-treatment will be the last values prior to initiation of non-flare-up based dosing.

Group-mean plots (mean and standard error) over time will be provided.

The number and percentage of subjects with potentially clinically significant (PCS) values will be summarized. A focus will be on new-onset PCS values, ie, subjects with pre-existing PCS values at pre-treatment will not be considered to have new-onset values on-treatment.

8.9 Pharmacokinetics

Plasma palovarotene concentrations will be summarized for the PAS by descriptive statistics of n, arithmetic mean, standard deviation (SD), coefficient of variance, geometric mean, median, minimum, and maximum.

8.10 Pharmacodynamics

Exploratory analyses will be performed to assess potential exposure/biomarker relationships.

9 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

9.1 Adverse Event and Serious Adverse Event Documentation, Severity Grading, and Reporting

9.1.1 Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product during the course of a study and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal product.

Disease, signs, symptoms, and/or laboratory abnormalities already existing prior to the use of the product are not considered AEs after administration of the study product unless they reoccur after the subject has recovered from the pre-existing condition or they represent an exacerbation in intensity or frequency.

Only a clinically significant laboratory test abnormality, physical examination finding, or other objective finding should be reported as an AE, whether it represents an exacerbation or a new abnormality.

9.1.2 Serious Adverse Event or Adverse Drug Reaction

An SAE (experience) or reaction is any untoward medical occurrence that results in any of the following outcomes and at any dose:

- Death.

- Life threatening situation (the subject was at risk of death at the time of the event). It does not refer to the hypothetical risk of death if the AE was more severe or was to progress.
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant disability/incapacity.
- Congenital anomaly/birth defect (any structural abnormality in subject offspring that occurs after intrauterine exposure to treatment).
- Other medically important event (important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon medical judgment, they may jeopardize the subject or may require intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse).

9.1.3 Adverse Event Documentation

Adverse event or SAE reports will be completed for all AEs. Signs and symptoms of each AE should be described in detail: nature, date of onset, end date, severity, relationship to study drug, and action taken and outcome.

9.1.4 Severity of Adverse Events

The term severity is used to describe the intensity of a specific event. The severity of AEs will be categorized as follows:

- Mild: events that are easily tolerated with no disruption of normal daily activity.
- Moderate: events that cause sufficient discomfort to interfere with daily activity and/or require a simple dose medication.
- Severe: events that incapacitate and prevent usual activity or require systemic drug therapy or other treatment.

Adverse events known to be associated with retinoids (eg, mucocutaneous) will be further graded according to CTCAE, Version 4.03, 14 June 2010. The site will be provided with specific criteria for the coding of AEs.

9.1.5 Causality Assessment

Causality assessment by the Investigator in terms of relationship to study drug is required for purposes of reporting AEs. To promote consistency, the following definitions should be taken into consideration along with good clinical and scientific judgment when determining the relationship of study drug to an AE:

- Definitely Related: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to the study drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study drug (dechallenge) should be clinically plausible.
- Probable: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to the study drug administration, and which is unlikely to be explained

by concurrent disease or other drugs or chemicals. The response to withdrawal of the study drug (dechallenge) should be clinically plausible.

- Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the study drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on the study drug withdrawal (dechallenge) may be lacking or unclear.
- Not related: A clinical event that has no temporal relationship to the study drug or has a much more likely alternative etiology.

9.1.6 Action Taken With Study Drug

The action taken to remedy the reported/observed AEs will be defined as follows:

(1) None

(2) Study drug dosage modified

(3) Study drug dosage interrupted

(4) Study drug permanently discontinued

9.1.7 Outcome of Adverse Event

The outcome of the AEs will be recorded as follows:

(1) Event resolved with no sequelae

(2) Event resolved with sequelae

(3) Event ongoing

(4) Death

9.1.8 Reporting of Serious Adverse Event

All SAEs must be reported within 24 hours to the Medpace Clinical Safety Group:

Medpace SAE hotline – USA:
Tel: PPD
Fax: PPD
E-mail: PPD

Medpace SAE hotline – Europe:
Tel: PPD
Fax: PPD
E-mail: PPD

The Investigator will be requested to complete and transmit to the sponsor or designee the SAE information using the electronic reporting form, or a paper form should the electronic system not be available.

The Investigator will inform the sponsor or designee within 24 hours of any findings with the use of the study drug that may suggest significant hazards, contraindications, SAEs, and precautions pertinent to the safety of the study drug.

The sponsor or designee will notify the regulatory authorities within the required time frames for all SAEs subject to expedited reporting, either due to their nature ("serious") or due to the significant, unexpected information they provide.

The Investigator will notify the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of SAEs occurring during the trial likely to affect the safety of trial subjects or the conduct of the trial.

9.1.9 Pregnancy

If any female subject or partner of a male subject becomes or is found to be pregnant during their participation in the study, the site will submit this information on a Pregnancy Reporting Form to the sponsor or designee. The subject will be followed up through their pregnancy and the health status of the baby will be verified. The study site will record the pregnancy on the AE and the pregnancy reporting forms.

9.1.10 Follow-Up of Adverse Events and Serious Adverse Events

The AE, SAE and death reporting period for the non-flare-up based treatment and the flare-up-based treatment begins at the time of informed consent and continues through study completion, including Part D + 30 days. References to Parts B/C/D are to PVO-1A-202 Parts B/C/D which corresponds to PVO-1A-204, ongoing in France.

Adverse events will be assessed at every site and remote visit. The Investigator will follow-up on all AEs observed or reported by the subject up to the end of the reporting period or until follow-up is no longer necessary. The Investigator will follow-up on SAEs until they are considered resolved or the outcome is known. Limb/joint AEs reported by subjects with open epiphyses will be evaluated by clinical and radiographic assessments deemed appropriate by the Investigator.

9.2 Administrative Requirements

9.2.1 Informed Consent Form

It should be noted that the word "parents" is used throughout this protocol to denote the legally authorized representatives (eg, parents, caregivers, or legal guardians) of subjects under the age of 18 years.

Prior to participation in the clinical study, the Investigator and/or delegate must fully explain to the subjects/parents all aspects of the study that are relevant to the decision of participation in the trial. The Informed Consent Form (ICF) is documented by means of a written, signed, and dated subject/parent consent form (or age-appropriate assent form) per local requirements, prior to the start of the study. Age-appropriate assent forms will be completed for all subjects under the age of 18 years. The ICF will be written in a language and in a form understandable to the subjects/parents. The Investigator and/or delegate will also sign the ICF. Any modifications to the ICF required by the Investigator prior to submission to the IRB/IEC or requested by the IRB/IEC must be submitted to the sponsor or designee for approval prior to the implementation of the ICF.

One signed and dated copy of the ICF will be given to the subject/parent and one signed and dated original copy will be maintained by the Investigator in the study file until the end of the study.

The Investigator should clearly indicate the subject's participation in a clinical trial in his/her medical chart.

Institutions, the Investigator, contract research organizations (CROs), etc., under this protocol shall abide by all requirements applicable to the use and disclosure of subjects' protected health information (such as the requirements provided for under the Health Insurance Portability and Accountability Act in the United States, the Personal Information and Electronics Document Act in Canada, the European Union (EU) Directive on Data Protection, and any other similar regulations or legislation).

9.2.2 Ethical Conduct of the Study

The clinical study will be conducted in accordance with the protocol, in addition to the ethical principles that have their origin in the Declaration of Helsinki (see Appendix 8), inclusive of any subsequent amendment(s), and that are consistent with the ICH GCP, EU Directive 2001/20/EC, US FDA Code of Federal Regulations and other applicable local regulatory requirements, which ever affords the greater subject protection.

9.2.3 Ethics Board Approval

The IRB/IEC will be in compliance with the ICH GCP and local regulatory requirements. It will consist of at least five qualified and experienced members with varying backgrounds, including at least one member whose primary interest is in a non-scientific area and one member who is independent from the institution/site. The committee will review the science, medical aspects, and ethics of the clinical study.

The following documents will be submitted to and reviewed by the IRB/IEC:

- Final study protocol/amendment(s)
- Investigator's Brochure
- Written ICF and consent/assent form updates
- Written information to be provided to subject/parent
- Subject recruitment procedures
- Information about payments and compensation available to subjects
- Investigator's curriculum vitae and/or other documentation evidencing qualifications

Any other documents that the IRB/IEC may need to fulfill its responsibilities will be provided to the committee.

The study protocol and informed consent/assent documents to be used in the clinical study must be approved by the IRB/IEC, prior to initiation of the study. The IRB/IEC will notify the Investigator and/or the sponsor in writing, clearly identifying the study, the documents reviewed and the date of approval. The committee will also provide a list of the members, their qualifications and affiliations. The IRB/IEC will conduct continuing review of the ongoing study at an appropriate interval.

The Investigator will be responsible for ensuring the initial approval of the clinical study protocol, written ICF, consent form updates, subject recruitment, and other documents. The Investigator and/or the sponsor is also responsible to promptly report to the IRB/IEC all changes in the research activities and all SAEs likely to affect the safety of the subjects, or the conduct of the study. The Investigator will not make any changes in the research without approval from the sponsor and without submitting for review and approval by the IRB/IEC, except where necessary to eliminate apparent immediate hazards to subjects.

9.2.4 Subject Confidentiality

Any research information obtained about the subject in this study will be kept confidential in accordance with all relevant national and international laws governing data privacy and security. The subject's name or any other identifying information will not appear in any reports published as a result of this study.

However, information obtained from individual subject's participation in the study may be disclosed with his/her express written consent to the health care providers for the purpose of obtaining appropriate medical care. The subject's medical records/charts and tests with his/her name on them may be made available to the appropriate CRO, the sponsor, its potential eventual partners, and any other regulatory authorities. This is for the purpose of verifying information obtained for this study. Confidentiality will be maintained throughout the study within the limits of the law.

A subject's name will not be given to anyone except the researchers conducting the study, who have pledged an oath of confidentiality. All identifying information will be kept behind locked doors, under the supervision of the study Investigator and will not be transferred outside of the investigator site.

A subject may take away his/her permission to collect, use, and share information about him/her at any time. If this situation occurs, the subject will not be able to remain in the study. No new information that identifies the subject will be gathered after that date. However, the information about the subject that has already been gathered and transferred may still be used and given to others as described above in order to preserve the scientific integrity and quality of the study.

9.2.5 Amendments to the Protocol

Modifications to the protocol are only possible by approved protocol amendments authorized by the study sponsor. All protocol amendments will be approved by the appropriate regulatory authorities as well as each IRB prior to implementation. The Investigator must not implement any deviations from, or changes to the protocol, except where it is necessary to eliminate an immediate hazard to the study subject.

9.2.6 Protocol Deviations

The protocol must be read thoroughly and the instructions followed exactly. Any major deviation to the protocol has to be reported as soon as possible to the sponsor. The governing reporting guidelines for protocol deviations must be adhered to by the Investigator.

9.2.7 Study Termination

This study may be prematurely terminated, if in the opinion of the Investigator or the sponsor, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the Investigator or the sponsor by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

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

Should the study be closed prematurely, all study materials must be returned to the sponsor. If the study is closed prematurely due to safety concerns, all subjects exposed to the investigational drug will be followed for safety with the length of follow-up determined based on the safety risk.

9.2.8 Retention of Subject Records and Study Files

To enable evaluations and/or audits from the regulatory authorities, the appropriate CRO, or the sponsor, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eCRFs, and hospital records), all original signed ICFs, copies of all eCRFs, source documents, and detailed records of treatment disposition. The Investigator should retain these records according to federal and local regulations or as specified in the Clinical Trial Agreement, whichever is longer.

If the Investigator relocates, retires, or for any reason withdraws from the study, then the sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the sponsor. The Investigator must obtain written permission from the sponsor before disposing of any records.

9.3 Data Quality Assurance

As per GCP guidelines, the sponsor or designee will be responsible for implementing and maintaining quality assurance and quality control systems for this study.

The participating site, the study database, and study documentation including subject medical records may be subject to a quality assurance audit during the course of the study. In addition, inspections may be conducted by regulatory bodies at their discretion.

If the site receives a request for an inspection or written or oral inquiries regarding any aspect of the institution's or Investigator's activities related to this study from a regulatory authority, the Investigator must immediately notify the sponsor and the appropriate CRO of the request.

Following this inspection and/or audit, the Investigator must notify the sponsor of any violation or deficiency noted by the regulatory authority.

9.4 Monitoring

The sponsor or their representative will monitor the study for compliance with GCP. The monitors will verify that the rights and well-being of subjects are respected, that the reported trial data are accurate, complete, as well as verifiable from source documents, and finally that the conduct of the trial is in accordance with the current approved protocol/amendments, GCP, and regulatory requirements.

Original subject records must be made available for reviews conducted by the sponsor or their representative.

9.5 Data Capture and Management

The sponsor or designee will provide the study site with an electronic case report system.

Electronic CRFs will be completed for each subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data entered in each subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and document the dates and details of study procedures, AEs, and subject status.

The Investigator, or designated representative, should complete the eCRF as soon as possible after information is collected, preferably on the same day that a subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be entered immediately after the final examination. An explanation should be given for all missing data.

9.6 Liability and Insurance

The sponsor has subscribed to an insurance policy covering, in its terms and conditions, its legal liability for certain injuries to participating persons arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

9.7 Publication and Clinical Data Reporting

All information regarding palovarotene supplied by the sponsor to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without written consent from the sponsor. It is understood that there is an obligation to provide the sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of palovarotene and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. A Publications Committee, comprised of the Investigator participating in the study and representatives from the sponsor, as appropriate, will be formed to oversee the publication of the study results, which will reflect the experience of the participating study center. Subsequently, the individual Investigator may publish results from the study in compliance with their agreement with the sponsor.

9.8 Coordinating Investigator

The Coordinating Investigator will be designated by the Sponsor prior to database lock. The Coordinating Investigator will approve the final clinical study report for Study PVO-1A-204.

10 INVESTIGATOR AGREEMENT

I have read Protocol PVO-1A-204 (France-Specific) Amendment 6, dated 18 December 2020:

A Phase 2, Open-Label, Efficacy and Safety Study of an RARγ-Specific Agonist (Palovarotene) to Prevent Heterotopic Ossification in Subjects with Fibrodysplasia Ossificans Progressiva (FOP).

I agree to conduct the study as detailed herein and in compliance with ICH Guidelines for Good Clinical Practices and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator (printed name)

_____ _____

Investigator signature Date

_____

_____

_____

Investigational site or name of institution and location (printed)

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