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25 February 2021

Global Addendum to Protocol PVO-1A-301, Amendment #5 dated 30 October 2020

Study Title and Number: A Phase 3, Efficacy and Safety Study of Oral Palovarotene for the Treatment of Fibrodysplasia Ossificans Progressiva (FOP); Protocol No. PVO-1A-301; Amendment #5 dated 30 October 2020.

Purpose: Administrative change.

This administrative addendum serves as a clarification associated with the conduct of Study PVO-1A-301.

The Parexel Informatics Strategic Business Unit separated from Parexel International on 11-Jan-2021; the resultant independent company is Calyx. All activities, addresses, phone numbers and relevant contacts remain the same with the exception of the change in the company name and e-mail address. The e-mail address of the Project Manager is now PI .

This study should be conducted in accordance with the current IRB/EC approved protocol, along with the clarification noted above.

_____

PI , MD
PI
Clementia Pharmaceuticals Inc.

I acknowledge the receipt of this addendum and will conduct the study as detailed above.

_____

Investigator (printed name)

_____ _____

Investigator signature Date

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Clementia Pharmaceuticals Inc.

Clinical Study Protocol

MOVE Trial

A Phase 3, Efficacy and Safety Study of Oral Palovarotene for the Treatment of Fibrodysplasia Ossificans Progressiva (FOP)

Study Number: PVO-1A-301
EudraCT: 2017-002541-29

Original Protocol: 10 July 2017
Amendment 1: 8 March 2018
Amendment 2: 19 February 2019
Amendment 3: 29 October 2019
Amendment 4: 4 February 2020
Amendment 5: 30 October 2020

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Protocol Signature Page

A Phase 3, Efficacy and Safety Study of Oral Palovarotene for the Treatment of Fibrodysplasia Ossificans Progressiva (FOP)

Protocol Number: PVO-1A-301

Signature of Approval for Protocol PVO-1A-301
(Amendment 5: 30 October 2020)

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

NAME: PI

SIGNATURE: _____ **DATE:** _____

Protocol Amendment 5 Summary of Changes

This fifth amendment to the protocol for Study PVO-1A-301 was finalized on 30 October 2020.

Location/Section Number	Change	Rationale
Major changes that affected the clinical conduct of the study:		
Protocol Synopsis Table 1, Table 3 Section 1.1.3.2.2 Palovarotene Phase 2 Interventional Studies Section 2.4 Secondary Objectives for Part C Section 3.1 Overview of Study Design Section 3.2 Study Rationale Section 5.3 Subject Withdrawal or Early Termination from Study Section 7.1 Screening, Recruitment, and Informed Consent Section 7.2.2 Physical Examination Section 7.2.3 Body Weight and Linear Growth Section 7.2.4 Vital Signs 7.2.8 Adverse Events Section 7.2.9 Concomitant Medications Section 7.3.2 Knee and Hand-wrist Radiographs Section 7.3.5 Serum Lipids Section 7.3.6 Liver Enzymes Section 7.3.7 Lipase/Amylase Section 7.3.8 Central Nervous System through 7.3.9 Hearing and Visual Disturbances Section 7.4.1 Low-dose Whole Body Computed Tomography Section 7.8 Temporary Measure (Procedures Related to COVID-19 Pandemic) Section 8.5.3 Safety Section 9.1.10 Follow-up of Adverse Events and Serious Adverse Events	Part C was added for skeletally immature subjects who stopped taking study medication for any reason before completion of Part A/B. Part C includes yearly visits for up to a 2-year follow-up period following last dose. No dosing will occur during Part C. Assessments obtained in Part C 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 C will continue only as long as subjects remain skeletally immature. The up to 2-year period for Part C would begin the last day the subject stopped receiving study drug in Part A/B. However, the maximum participation in the trial will not be extended beyond 48 months for Parts A, B, and C in total. Secondary objective added for Part C to monitor off treatment longer-term safety in skeletally immature subjects off treatment. Safety will be summarized for Part C.	To implement safety measures based on DMC recommendations given the serious identified risk of premature physeal closure. Part C 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 medication for any reason before completion of Part A/B. A 2 year follow up is an adequate timeframe to assess growth and physeal changes off palovarotene treatment.

Location/Section Number	Change	Rationale
Synopsis Section 3.1 Overview of the Study Design Section 3.2 Study Rationale Section 5.1 Study Population	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 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 C 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 Section 7.4.1 Low-dose, Whole Body Computed Tomography	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 FOP subjects.
Section 3.1 Overview of Study Design Section 7.1 Screening, Recruitment, and Informed Consent Section 7.8 Temporary Measures (Procedures Related to COVID)	Integrated protocol amendment 4 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 (who were skeletally immature at their last assessment) as part of the minimal safety procedures prior to re-initiation of palovarotene.	To integrate protocol amendment 4 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.
Other changes that did not affect the clinical conduct of the study:		
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 SAE (including) death reports.
Table 1	Corrected table 1 header.	Integration of administrative change from protocol amendment 4 addendum.
Groups responsible for study conduct	Revised the vendor contact information.	To ensure that contact information is up-to-date.

Location/Section Number	Change	Rationale
Section 7.3.5 Lipid Profile Section 7.3.6 Liver Enzymes Section 7.3.7 Lipase/Amylase	Added to text that assessments during flare-up-based treatment in Parts A/B (complete lipid, liver enzyme, and lipase/amylase profiles) will be performed as part of the biochemistry testing at 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.	To align text with Table 2
General	Corrected minor errors and formatting irregularities. Added clarifications. Renumbered tables as required.	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	PI Pharmaceutical Product Development Inc. (PPD) PPD Data Management Lead Email: PI PPD 3900 Paramount Parkway Morrisville, NC 27560 Tel: PI PI PPD Study Manager Email: PI PPD PI PI Tel: PI
Electronic Data Capture System	PI Medidata Project Manager Email: PI Medidata PI PI Tel: PI
Clinical Monitoring	PI PPD Clinical Team Manager (Global) Email: PI PPD PI . PI Greece Tel: PI Cell: PI
Medical Monitoring	PI PPD PI PPD PI PI 24-Hour Safety Hotline: 1.800.201.8725 Safety Fax: 1.888.488.9697 Safety Email: wilsafety@ppd.com ePIP.ppd.com

Task	Vendor or Responsible Group
Central Laboratory	PI PPD Project Manager Email: PI PPD Laboratories PI PI , PI Tel: PI
Central Electrocardiogram Laboratory	PI BioTelemetry Project Manager Email: PI BioTelemetry Research PI PI Tel: PI
Clinical Trial Material Logistics	PI Marken Project Manager Email:PI Marken PI PI Tel: PI Cell: PI
Imaging Core Laboratory	PI PAREXEL Project Manager Email: PI PAREXEL International PI PI USA, PI Tel: PI
Statistical Analysis Support	PI Cytel PI , Biostatistics, Email: PI Cytel Inc. PI PI PI Tel: PI
Bioanalytical Laboratory	PI BS Q^2 Solutions Project Manager Email: PI Q^2 Solutions PI PI Tel: PI

Task	Vendor or Responsible Group
Genetics Laboratory	PI Genetic Diagnostic Laboratory, Laboratory Manager University of Pennsylvania PI PI PI PI Tel: PI

Protocol Synopsis

Title	**MOVE Trial:** A Phase 3, Efficacy and Safety Study of Oral Palovarotene for the Treatment of Fibrodysplasia Ossificans Progressiva (FOP)
Sponsor	Clementia Pharmaceuticals Inc.
Objectives	Primary Objectives • To evaluate the efficacy of palovarotene in decreasing heterotopic ossification (HO) in adult and pediatric subjects with FOP as assessed by low-dose, whole body computed tomography (WBCT), excluding head, as compared to untreated subjects from Clementia's FOP natural history study over 24 months. • To evaluate the safety of palovarotene in adult and pediatric subjects with FOP. Secondary Objectives • To evaluate the effect of palovarotene on flare-up rate and proportion of subjects reporting at least one flare-up. • To evaluate the effect of palovarotene on range of motion (ROM) as assessed by the Cumulative Analogue Joint Involvement Scale for FOP (CAJIS). • To evaluate the effect of palovarotene on physical function using age-appropriate forms of the FOP-Physical Function Questionnaire (FOP-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 B) • To continue to provide palovarotene to adult and pediatric subjects with FOP and to monitor longer-term safety. Secondary Objective (Part C) • 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 3, multicenter, open-label study in adult and pediatric subjects with FOP will be conducted in three parts: Part A, the main part of the study; Part B, the 24-month extension; and Part C, the up-to-2-year post last dose of study treatment follow-up for skeletally immature subjects. Sources of subjects eligible for enrollment in Part A of the MOVE Trial will include: (1) subjects from Study PVO-1A-001 (the natural history study [NHS]); (2) additional subjects clinically diagnosed with FOP with the R206H ACVR1 mutation or other FOP variants reported to be associated with progressive HO (who have not previously participated in any Clementia-sponsored study); and (3) Phase 2 Study PVO-1A-202 or Study PVO-1A-204 subjects who cannot receive the chronic/flare-up regimen due to country of residence or those traveling long distances to participate in the Phase 2 trial. Up to a maximum of 110 subjects will be enrolled into the MOVE Trial (up to 99 with the R206H mutation and no previous exposure to palovarotene, and up to 11 with other mutations or previous participation in the Phase 2 trials), and receive chronic dosing for up to 24 months and undergo flare-up-based treatment should they experience an eligible flare-up or traumatic event as confirmed by the Investigator.

Protocol Synopsis

	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. The efficacy of palovarotene treatment in the MOVE Trial Part A, as measured by the change in new HO volume, will be compared to that observed in untreated subjects who participated in the NHS.
Study Design (cont.)	In Part B, the study will be extended for an additional 24 months in order to provide the chronic/flare-up palovarotene dosing regimen to all subjects until commercial availability and to obtain longer-term safety data. No new subjects will be enrolled into Part B. **Chronic Treatment: Part A** Subjects will receive orally administered 5 mg palovarotene once daily (weight-adjusted for skeletally immature subjects [ie, subjects under the age of 18 years with less than 90% skeletal maturity on hand-wrist radiography at Screening]) as chronic dosing for up to 48 months. 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 at Study Months 6, 12, 18, and 24) will continue until these subjects achieve 100% closure of the growth plate at both locations. Additional radiographic assessments will be performed at Study Months 3, 9, 15, or 21 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% skeletally maturity on their last radiographic assessment. All subjects will undergo the procedures and assessments specified in the Schedule of Assessments in Table 1, including low-dose, WBCT (excluding head) at Screening and at site visits at Months 6, 12, 18, and 24. In order to ensure consistent interpretation of the acquired images, a central imaging laboratory will perform blinded reads of all images obtained in this study as well as those obtained from the natural history study (control group) using standardized procedures as documented in the Image Acquisition Guidelines and Independent Review Charter. Remote visits (eg, at home, at a local medical facility, or via video-conference or telephone contact from clinical site personnel) will occur at Week 6 and at Study Months 3, 9, 15, and 21 unless the Investigator deems that a site visit is necessary; urine pregnancy tests will be performed each month for females of childbearing potential (FOCBP). **Chronic Treatment: Part B** The assessments conducted in Part A will continue into Part B except that WBCT imaging will be performed annually thereafter at Months 36 and 48. **Flare-up-Based Treatment: Parts A and B** 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 begin flare-up-based treatment. 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.

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	• Palovarotene 20 mg for 4 weeks (28 days) once daily. The first dose will be taken upon flare-up or traumatic event confirmation by the Investigator (Flare-up Day 1). To be followed by: • Palovarotene 10 mg for 8 weeks (56 days) once daily. For a total flare-up treatment duration of 12 weeks (84 days).
Study Design (cont.)	If the Investigator deems it necessary, the subject can be evaluated at the clinical site to confirm the presence of a flare-up. 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 the 4-week extension treatment has been completed. 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. 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. Should a subject experience an intercurrent flare-up (defined as a new flare-up location or marked worsening of original flare-up), or 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 equivalents]). 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 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 undergo the procedures and assessments specified in the Schedule of Assessments in Table 2. 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 chronic treatment with 5 mg palovarotene once daily (weight-adjusted doses for skeletally immature subjects). Subjects currently receiving flare-up-based treatment in Study PVO-1A-202 or Study PVO-1A-204 will not enroll into Study PVO-1A-301 until flare-up treatment is complete and at least 4 weeks have elapsed since the last flare-up symptom. **Off-treatment Part C:** No study drug will be administered in Part C. For skeletally immature subjects in Part C, 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 C will end. The

Protocol Synopsis

	total duration of participation, on and off treatment, is a maximum of 4 years (±1 month).
Number of Subjects	Up to a maximum of 110 subjects will be enrolled; up to 99 of the enrolled subjects will have the R206H mutation and will not have been previously treated with palovarotene.
Total Number of Sites	Approximately 20 international investigational sites.
Study Population	Inclusion Criteria Subjects must meet all of the following criteria to be eligible for enrollment: 1. Written, signed, and dated informed subject/parent consent; and for subjects who are minors, age-appropriate assent (performed according to local regulations). 2. Male or female at least 4 years of age. 3. Previous participation in the NHS; or clinically diagnosed with FOP, with the R206H ACVR1 mutation or other FOP variants reported to be associated with progressive HO (who have not previously participated in any Clementia-sponsored study); or participants in Study PVO-1A-202 or Study PVO-1A-204 who cannot currently receive the chronic/flare-up regimen due to country of residence or those traveling long distances to participate in the Phase 2 trial. 4. No flare-up symptoms within the past 4 weeks, including at the time of enrollment. 5. 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. 6. Must be accessible for treatment and follow-up, and be able to undergo all study procedures. 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. Subjects must be able to undergo low-dose, WBCT (excluding head) without sedation. Exclusion Criteria Subjects meeting any of the following criteria are not eligible for enrollment: 1. Weight <10 kg. 2. 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.

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Study Population (cont.)

3. Exposure to synthetic oral retinoids other than palovarotene within 4 weeks prior to screening.
4. Concurrent treatment with tetracycline or any tetracycline derivatives due to the potential increased risk of pseudotumor cerebri.
5. History of allergy or hypersensitivity to retinoids, gelatin, or lactose (note that lactose intolerance is not exclusionary).
6. Concomitant medications that are strong inhibitors or inducers of cytochrome P450 (CYP450) 3A4 activity; or kinase inhibitors such as imatinib (see Section 5.2.1).
7. Amylase or lipase >2x above the upper limit of normal (ULN) or with a history of chronic pancreatitis.
8. Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5x ULN.
9. Fasting triglycerides >400 mg/dL with or without therapy.
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 Columbia-Suicide Severity Rating Scale (C-SSRS).
13. Simultaneous participation in another interventional clinical research study (other than palovarotene studies) within 4 weeks prior to Screening; or within five half-lives of the investigational agent, whichever is longer.
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.

Investigational Product

Palovarotene supplied as powder-filled hard gelatin capsules. The capsules may be swallowed whole or opened and the contents added onto specific foods as specified in the dosing instructions.

Dose/Route/Regimen for Chronic Dosing

Palovarotene: 5 mg daily or weight-based equivalents for those subjects who are skeletally immature (<90%) at entry into the study / taken orally with food / at approximately the same time each day. For 5 mg palovarotene, weight equivalent doses for <20 kg, 20 to <40 kg, 40 to <60 kg, and ≥60 kg will be 2.5 mg, 3 mg, 4 mg, and 5 mg, respectively.

Dose/Route/Regimen for Flare-Up Dosing

Palovarotene initiated at the start of an eligible flare-up: 20 mg for 4 weeks (28 days), 10 mg for 8 weeks (56 days) 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 for skeletally immature subjects and dose de-escalation for flare-up and chronic 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 kg	10 mg	7.5 mg	5 mg	3 mg	2.5 mg	1 mg
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 equivalents, respectively.

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Comparator	In this single-arm treatment study, the control reference group will be the untreated subjects who participated in the NHS.
Assessments of Efficacy	Primary Endpoint: The annualized change in new HO volume as assessed by low-dose, WBCT (excluding head) compared to untreated subjects from the NHS over 24 months. Secondary Endpoints assessed in Parts A and B: 1. The proportion of subjects (key secondary endpoint) with any new HO. 2. The change from baseline in the number of body regions with new HO. 3. The proportion of subjects reporting flare-ups. 4. The flare-up rate per subject-month exposure.
Assessments of Efficacy (cont.)	Exploratory Endpoints assessed in Parts A and B: 1. Change from baseline in ROM assessed by CAJIS. 2. Change from baseline in physical function using age appropriate forms of the FOP-PFQ. 3. 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.
Assessments of Safety	Safety evaluations will include adverse event (AE) and serious AE (SAE) reporting, electrocardiograms, 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 enrolled with open epiphyses will include knee (anterior/posterior [AP] view) and hand-wrist radiographs (posterior/anterior [PA] view) for assessment of epiphyseal growth plate and distal femoral angle; tibial and femoral long bone lengths; and standardized stadiometry and knee height for assessments of linear growth (in triplicate). 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 consult with the sponsor and the DMC. In addition, bilateral hand-wrist and knee growth plate morphology will be assessed by WBCT scan safety read (performed every 6 months up to Month 24 in Part A, and annually thereafter in Parts B and C). 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.

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	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 treatment-related adverse bone effects. The DMC Charter includes recommended safety stopping rules (see Section 7.7).
Clinical Genotyping	On Screening/Study Day 1, a blood sample will be collected and the ACVR1 gene-coding region will be sequenced to assess for the presence of an FOP-associated mutation of the ACVR1 gene for new subjects or for subjects who have not undergone previous genotyping as part of Study PVO-1A-001. Subjects enrolling from Study PVO-1A-202 or Study PVO-1A-204 do not need to undergo repeat genotyping. Any subject enrolled who does not have an ACVR1 mutation known to be associated with FOP will be discontinued. If the Investigator has any reason to believe a subject does not possess an FOP mutation, enrollment may be delayed until the genotype is confirmed.
Pharmacokinetics	Pharmacokinetics of palovarotene will be assessed at the first 3-month safety assessments during chronic-based treatment; if samples cannot be obtained during the first 3-month safety assessment, then they can be obtained during any subsequent 3-month safety visit in Part A (ie, up to Month 24). 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, pharmacokinetic blood samples can be obtained during any subsequent flare-up dosing cycle. Pharmacokinetic blood samples will be collected at predose and 3, 6, 10, and 24 hours post-dose for the three time points listed above. The following palovarotene pharmacokinetic parameters will be determined where possible by model independent analysis using WinNonlin™: $C_{max,ss}$, $C_{min,ss}$, $T_{max,ss}$, $AUC_{0\text{-}24ss}$, λ_z, $t_{½z}$, and CL/F.
Statistical Analysis	**Analysis Populations** The **Principal Enrolled Population (Principal EP)** includes all subjects with the R206H ACVR1 mutation who have not previously been treated with palovarotene and who sign the informed consent form and meet all eligibility criteria of the MOVE Trial. The **Principal Full Analysis Set (Principal FAS)** includes all enrolled subjects in the Principal EP who have a baseline HO volume measurement and at least one post-baseline HO volume measurement in the MOVE Trial. For efficacy comparisons to the NHS, the Principal FAS will also include subjects enrolled in the NHS with available baseline and at least one post-baseline HO volume measurements. The **Principal Per-Protocol Set (Principal PPS)** is a subset of the Principal 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, assessed over the first 24 months of participation in Part A. For efficacy comparisons to the NHS, the Principal PPS will also include subjects in the NHS with available baseline and at least one post-baseline HO volume

Protocol Synopsis

	measurement and with no major protocol deviations over 24 months that are expected to interfere with assessments of the primary endpoint. The **Principal Safety Set (Principal SS)** includes all enrolled subjects receiving at least one dose of palovarotene in the MOVE Trial. For safety comparisons to the NHS, the Principal SS will also include subjects enrolled in the NHS with available post-baseline follow-up. The **Principal Pharmacokinetic Set (Principal PS)** includes all enrolled subjects receiving at least one dose of palovarotene and providing evaluable pharmacokinetics data in the MOVE Trial.
Statistical Analysis (cont.)	Subjects who do not have the R206H ACVR1 mutation or who have received previous treatment with palovarotene in PVO-1A-202 or PVO-1A-204 will comprise the **Supplementary EP**, the **Supplementary FAS**, the **Supplementary PPS**, the **Supplementary SS**, and the **Supplementary PS**, with these populations defined analogously as above for the subjects with the R206H ACVR1 mutation. **Primary Efficacy Analysis** The primary efficacy endpoint is the annualized change in new HO volume (as assessed by low-dose WBCT, excluding head) over 24 months in Part A. The primary efficacy analysis comparing the annualized change in new HO volume between subjects treated with palovarotene and untreated subjects will be conducted using a Bayesian compound Poisson distribution in the Principal FAS. The Principal FAS is used to match the NHS population which was restricted to subjects with the R206H mutation and no previous palovarotene exposure. Hypothesis testing will be performed using random samples generated via Gibbs sampling from the posterior distribution of the treatment effect variables. The primary efficacy endpoint will be summarized for the Supplementary FAS. There will be three early interim efficacy analyses and one final analysis. The first interim analysis will occur when 35 subjects complete 1-year of follow-up; the second and third interim analyses will occur when all subjects enrolled in the Principal EP have completed (ie, have WBCT data) 12 months and then 18 months of follow-up, respectively. The interim analyses will include the Month 6 WBCT results when that is the only observation available from a subject in the current study. An O'Brien-Fleming alpha spending function will be used to specify the alpha level threshold for determination of treatment effect significance at each interim analysis and the final analysis. Using the percentage of patient years of follow-up as an approximation to the statistical information available at each analysis and assuming a one-sided, overall type I error rate of 2.5%, the one-sided significance thresholds are 0.0058, 0.0103, 0.0156, and 0.0190 for the first, second and third interim analyses, and the final analysis, respectively. Study success will be declared if the posterior probability that palovarotene reduces the annualized change in new HO volume is greater than 1 minus the one-sided significance threshold. For example, the posterior probability that palovarotene reduces the annualized change in new HO volume must be greater than 0.9810 to declare study success at the final analysis. A futility analysis was conducted for the second interim analysis based on the pre-specified criteria using square-root transformation and on additional analyses without the square-root transformation. Based on feedback received by the DMC following the second interim analysis, the futility analysis conducted at the third analyses will use the predefined model with and without square-root transformation to assess whether the study shows insufficient evidence of efficacy. If the efficacy criteria have not been met by the final analysis of Part A the study may be terminated.

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	Efficacy will be described for Parts A and B together.
	Sample Size Determination The sample size was determined via simulation based on the available WBCT HO volumes from the NHS, and the observed efficacy of palovarotene treatment in the Phase 2 studies. With the NHS contributing untreated follow-up information on approximately 90 subjects, and 80 subjects originally planned for enrollment into the current study in the Principal FAS population (including approximately 45 from the NHS), the probability of declaring statistical significance is 0.51, 0.79, 0.89 at the first, second, and third interim analyses, respectively, if palovarotene treatment reduces the mean number of body regions with new HO in 1 year by 30%, and reduces the new HO volume conditional on new HO in a body region by 50% compared to the NHS control group. The overall power of the study is 0.92. The increase in the number of enrolled subjects will not substantially change the power of the trial or have a significant impact on the primary or secondary statistical analyses.

Table 1. Schedule of Assessments for Chronic Treatment

	Part A (Main Study)					Part B (Extension)			Parts A & B
Assessment/Procedure	**Screening/ Study Day 1[1] Site Visit (-1 month)**	**Every Month Remote Visit[2] (±1 week)**	**Week 6 Telephone Contact (±1 week)**	**Months 3, 9, 15, 21 Remote Visit[2] (±2 weeks)**	**Months 6, 12, 18, 24 Site Visit[3] (±1 month)**	**Every Month Remote Visit[2] (±1 week)**	**Months 27, 33, 39, 45 Remote Visit[2] (±2 weeks)**	**Months 30, 36, 42, 48 Site Visit[3] (±1 month)**	**EOT/EOS Site Visit[3] (±1 month)**
Informed consent/assent[4,5]	X								
Inclusion/exclusion	X								
Knee and hand-wrist radiographs[6]	X			X[7]	X		X[7]	X	X
Linear and knee height growth assessments (<18 years)[6]	X				X			X	X
Medical history (including FOP history)	X								
Physical examination	X				X			X	X
Hearing test	X[8]				Months 12, 24 only			Months 36, 48 only	X
Linear height (subjects ≥18 years)	X								
Body weight	X			X	X		X	X	X
Electrocardiogram	X				X			X	X
Dispense study drug[9]	X		As needed from Study Day 1 through Month 48						
Study drug treatment		Continuous from Study Day 1 through Month 48							
Dispense/review subject diary		Dispense diary as needed and review at every subject contact[10]							
Subject diary assessment for onset of flare-up symptoms		From Study Day 1 through Month 48							
Vital signs	X			X	X		X	X	X
C-SSRS (age-appropriate)[11]	X			X	X		X	X	X
Assess for child-bearing status (females only) and pregnancy prevention measures (females and males)	X			X	X		X	X	X
Hematology	X[4]				X			X	X
Biochemistry (includes lipids, serum pregnancy test)	X[4]				X			X	X
Urinalysis[12]	X[4]				X			X	X
Pregnancy test[13]		X				X			X
FOP-PFQ (age-appropriate)	X				X			X	X
PROMIS Global Health Scale	X				X			X	X

Table 1. Schedule of Assessments for Chronic Treatment

	Part A (Main Study)					Part B (Extension)			Parts A & B
Assessment/Procedure	**Screening/ Study Day 1[1] Site Visit (-1 month)**	**Every Month Remote Visit[2] (±1 week)**	**Week 6 Telephone Contact (±1 week)**	**Months 3, 9, 15, 21 Remote Visit[2] (±2 weeks)**	**Months 6, 12, 18, 24 Site Visit[3] (±1 month)**	**Every Month Remote Visit[2] (±1 week)**	**Months 27, 33, 39, 45 Remote Visit[2] (±2 weeks)**	**Months 30, 36, 42, 48 Site Visit[3] (±1 month)**	**EOT/EOS Site Visit[3] (±1 month)**
CAJIS	X				X			X	X
Low-dose, WBCT scan (excluding head)[14]	X				X			Months 36, 48 only	X
Prior/concomitant medications		At every subject contact[10]							
Adverse events[15]		At every subject contact[10]							
Pharmacokinetic blood sample[16]				Month 3 only					
Genotyping[17]	X								

1 The first day that study drug is administered will be defined as Study Day 1.

2 Assessments other than knee and hand-wrist radiographs will be performed remotely (eg, at the subject's home by qualified study personnel, at a local medical facility, or via video-conference or telephone contact from clinical site personnel) unless the Investigator deems that a site visit is necessary. Monthly remote visits will only be conducted for FOCBP subjects.

3 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 C. 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 C.

4 May be obtained remotely.

5 Subjects currently receiving flare-up-based treatment in Study PVO-1A-202 or Study PVO-1A-204 will not enroll into Study PVO-1A-301 until flare-up treatment is complete and at least 4 weeks have elapsed since the last flare-up symptom.

6 At Screening, subjects under the age of 18 years will undergo knee (AP view) and hand-wrist radiographs (PA view, preferable on the left side) to determine whether they have open epiphyseal growth plates and to assess the distal femoral angle; they will also undergo standardized measurements of linear and knee height. (Subjects enrolling from the NHS or the Phase 2 studies that underwent knee and hand-wrist radiographs within 1 month of Screening will not need to have radiographs repeated at Screening.) Those subjects found to be skeletally immature will continue knee and hand-wrist radiographs, and linear and knee height measurements (all in triplicate) at Months 6, 12, 18, 24, 30, 36, 42, and 48. 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. 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.

7 Knee and hand-wrist radiograph assessments will be performed at Months 3, 9, 15, 21, 27, 33, 39, or 45 (±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% skeletally maturity on their last assessment. These radiographic 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.

Table 1. Schedule of Assessments for Chronic Treatment

	Part A (Main Study)					Part B (Extension)			Parts A & B
Assessment/Procedure	Screening/ Study Day 1[1] Site Visit (-1 month)	Every Month Remote Visit[2] (±1 week)	Week 6 Telephone Contact (±1 week)	Months 3, 9, 15, 21 Remote Visit[2] (±2 weeks)	Months 6, 12, 18, 24 Site Visit[3] (±1 month)	Every Month Remote Visit[2] (±1 week)	Months 27, 33, 39, 45 Remote Visit[2] (±2 weeks)	Months 30, 36, 42, 48 Site Visit[3] (±1 month)	EOT/EOS Site Visit[3] (±1 month)

[8] The initial hearing test may be obtained at Month 6 (or at the next possible visit) if it was not performed at Screening.

[9] Except at EOT/EOS/Month 48.

[10] Includes telephone contact by clinical site personnel at Week 6.

[11] C-SSRS will be used for subjects 8 years of age and older. The adult form will be used for subjects 12 years and older; the pediatric form will be used for subjects 8 to 11 years old.

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

[13] 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.

[14] The last low-dose, WBCT scan (excluding head) from the NHS will be used as the baseline assessment for those subjects enrolling from the NHS as long as the scans were performed within 1 month of Screening/Study Day 1. The last low-dose, WBCT scan (excluding head) from Study PVO-1A-202 or Study PVO-1A-204 will be used as the baseline assessment for those subjects on chronic treatment enrolling from the Phase 2 study, as long as the scans were performed within 6 months of Study Day 1. All other subjects (ie, subjects who will start chronic treatment during Study PVO-1A-301) will undergo a low-dose, WBCT scan (excluding head) at Screening/Study Day 1.

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

[16] Blood samples for pharmacokinetic assessment will be collected during 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, then they can be obtained during any subsequent 3-month safety visit up to Month 24.

[17] Blood samples may be obtained remotely for new subjects or for subjects who have not undergone previous genotyping as part of Study PVO-1A-001. Subjects enrolling from Study PVO-1A-202 or Study PVO-1A-204 do not need to undergo repeat genotyping.

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

Table 2. Schedule of Assessments for Flare-up-based Treatment (Subjects with a Flare-Up in Parts A and B)

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

Treatment/Assessment/Procedure	FLARE-UP TREATMENT AND PHARMACOKINETICS[8]			
	Flare-up Day 1[4,11,12]	High Dose Treatment	Low Dose Treatment	
Flare-up treatment (first flare-up or restart for intercurrent flare-up)[10,11]	X	Week 1 to 4 (4 weeks)	Weeks 4 to 12 (8 weeks)	4-Week Extension (if applicable)
Flare-up(s) status/end date confirmation[10]	X		End of Week 12	End of Each 4-Week Extension
Pharmacokinetic blood sample[13]		X	X	

1 All visit windows are ±4 days.

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 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 chronic 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 the study. Note that the Flare-up Cycle Safety assessments will also be applicable to any treated high-risk traumatic event likely to lead to a flare-up.

4 Subjects with normal or non-clinically significant abnormal laboratory results observed within 1 month of starting flare-up-based treatment will not need to have Flare-up Cycle Safety Day 1 laboratory tests repeated. 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 treatment of the last flare-up or traumatic event is completed. 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.

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

6 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.

[7] Subjects will be provided with the appropriate dose of study drug to be used to initiate treatment when a flare-up or traumatic event is confirmed by the Investigator. Flare-up-based treatment can begin immediately after the Investigator confirms the presence of an eligible flare-up or traumatic 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).

[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, followed by 8 weeks (56 days) of 10 mg palovarotene (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 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 equivalents]). This may occur more than once during a Flare-up Cycle.

[10] Flare-up status will be assessed at Flare-up Day 1 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 (after confirmation by the Investigator).

[12] Flare-ups 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.

[13] Pharmacokinetics of palovarotene dosing will be assessed twice: once during the 20-mg regimen at any time between Study Days 4 and 28 and once during the 10-mg regimen at any time between Study Days 32 and 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 up to Month 24. Blood samples will be collected at predose and 3, 6, 10, and 24 hours post-dose.

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

Table 3. Schedule of Assessments for Part C

Assessment/Procedure	Y1 and Y2/SC 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)	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[6]	At every subject contact

1 Year 1 (Y1), Year 2 (Y2 visits following the last dose of study medication will be done within the 4-year total study duration from enrolment in Part A.
Y1 to be completed in the window of ≥6 - <18 months post last dose of study medication. If Part A or B EOS date is within the Y1 window then the EOS will serve as the Y1 visit. If Part A or B EOS date is prior to Y1 window then Y1 should be scheduled ≥ 6 months from Part A or B EOS date but still within the Y1 window. If Y1 is completed within 6 months of when Month 48 (Part B) is to occur, then Y1 will serve as the Part C study completion (SC) visit.
Y2 to be completed ≥18 – 24 months post last dose of study medication and will serve as the Part C study completion (SC) visit. If Part A or B EOS date is within the Y2 window then the EOS will serve as the Y2 visit (Y2 not required) as well as the Part C study completion (SC) visit. If Part A or B EOS date or Y1 date (if applicable) is prior to Y2 window then Y2 should be scheduled ≥ 6 months from the Part A or B 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 or B EOS more than 2 years prior to their consent for Part C, then these subjects will complete Y2 following their consent for Part C and no later than 48 months (+1 month) from Study Day 1 (first day that study drug is administered). This will serve as their Part C study completion (SC) visit and will conclude their participation in the study.

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 C informed consent is required prior to conducting Part C 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 C 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.

EOS = end of study, SC = study completion

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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
BMP	bone morphogenetic protein
CAJIS	Cumulative Analogue Joint Involvement Scale for FOP
CI	confidence interval
CL/F	apparent total clearance after oral administration
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
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end-of-study
EOT	end-of-treatment
EP	Enrolled Population
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FOCBP	female of child-bearing potential (who is a pre-menopausal female [≥12 years old or at onset of menses, whichever is earlier]) capable of becoming pregnant
FOP	Fibrodysplasia Ossificans Progressiva
FOP-PFQ	FOP-Physical Function Questionnaire
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

Abbreviation	Definition
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDL	low-density lipoprotein
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
PCS	potentially clinically significant
PO	per os
PPS	Per Protocol Set
PROMIS	Patient Reported Outcomes Measurement Information System
PS	Pharmacokinetic Set
RAR	retinoic acid receptor
RARγ	retinoic acid receptor gamma
ROM	range of motion
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SS	Safety Set
$t_{½}$	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 9%) 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. 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) without clinical symptoms.

The majority of patients with FOP are confined to a wheelchair by the third decade of life, and require caregiver assistance to perform daily living activities. Respiratory insufficiency leads to a markedly shortened survival (Kaplan-Meier survival = 56 years) with cardiorespiratory failure and pneumonia the most common causes of death.[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.[Error! Reference source not found.] 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.[Error! Reference source not found.] 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 in-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[Error! Reference source not found.] and that unliganded RAR transcriptional repressor activity is needed for chondrogenic differentiation.[14,15] Inhibition of HO with non-selective retinoids or RARα receptor agonists has also been achieved but to a lesser degree.[Error! Reference source not found.]

RARγ is expressed in chondrogenic cells and chondrocytes[Error! Reference source not found.] where it also operates as an unliganded transcriptional repressor.[Error! Reference source not found.] 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 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.[18,19]

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.**Error! Reference source not found.**

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.**Error! Reference source not found.** 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); 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), 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 4weeks (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 flare-up 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.

- 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.

Preliminary data from the Phase 2 program and the NHS is based on 150 prospectively assessed flare-ups. Administration of the 20/10 mg palovarotene flare-up regimen resulted in a 72% reduction in new HO volume relative to untreated flare-ups. The results were similar with the 10/5 mg flare-up regimen (75% reduction). There was a 48% reduction in new HO volume in flare-ups treated with the 20/10 mg chronic/flare-up regimen. The proportion of flare-ups with any new HO was lowest with the 20/10 mg chronic/flare-up regimen (21%) versus the other regimens (untreated: 34%, 10/5 flare-up: 29%, 20/10 flare-up: 41%); the 20/10 mg chronic/flare-up regimen also had the lowest incidence of flare-ups with baseline edema.

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 adverse events 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 metaphysical 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 Objectives

The primary objectives are:

- To evaluate the efficacy of palovarotene in decreasing heterotopic ossification (HO) in adult and pediatric subjects with FOP as assessed by low-dose, whole body computed tomography (WBCT), excluding head, as compared to untreated subjects from Clementia's FOP natural history study over 24 months.
- To evaluate the safety of palovarotene in adult and pediatric subjects with FOP.

2.2 Secondary Objectives

- To evaluate the effect of palovarotene on flare-up rate and proportion of subjects reporting at least one flare-up.
- To evaluate the effect of palovarotene on range of motion (ROM) as assessed by the Cumulative Analogue Joint Involvement Scale for FOP (CAJIS).

- To evaluate the effect of palovarotene on physical function using age-appropriate forms of the FOP-Physical Function Questionnaire (FOP-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 B)

- To continue to provide palovarotene to adult and pediatric subjects with FOP and to monitor longer-term safety

2.4 Secondary Objective (Part C)

- 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

A Phase 3, multicenter, open-label study in adult and pediatric subjects with FOP will be conducted in three parts: Part A, the main part of the study; Part B, the 24-month extension and Part C, the up-to-2-year post-treatment period for skeletally immature subjects. Sources of subjects eligible for enrollment in the MOVE Trial will include: (1) subjects from Study PVO-1A-001 (the natural history study [NHS]); (2) additional subjects clinically diagnosed with FOP with the R206H ACVR1 mutation or other FOP variants reported to be associated with progressive HO (who have not previously participated in any Clementia-sponsored trials); and (3) Study PVO-1A-202 or Study PVO-1A-204 subjects who cannot receive the chronic/flare-up regimen due to country of residence or those traveling long distances to participate in the Phase 2 trial. Up to a maximum of 110 subjects will be enrolled into the MOVE Trial (up to 99 with the R206H mutation and no previous exposure to palovarotene, and up to 11 with other mutations or previous participation in the Phase 2 trials). In Part A, qualified subjects will receive chronic dosing with palovarotene for up to 24 months and undergo flare-up-based treatment should they experience an eligible flare-up or traumatic events.

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.

The efficacy of palovarotene treatment in Part A of the MOVE Trial, as measured by the change in new HO volume over 24 months, will be compared to that observed in untreated subjects who participated in the NHS.

In Part B, the study will be extended for an additional 24 months in order to provide the chronic/flare-up palovarotene dosing regimen to all subjects until commercial availability; and to obtain longer-term safety data. No new subjects will be enrolled into Part B.

Subjects will follow all assessments as outlined in Table 1 and Table 2.

In Part C, 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 C. Subjects will follow assessments as outlined in Table 3 for as long as they are not 100% skeletally mature.

Adverse events will be assessed at every site and remote visit during chronic and flare-up-based treatment as well as annually for up to 2 years post last dose of study 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. The end of Study PVO-1A-301 will occur when the last subject has completed the last study visit (ie, last subject last visit).

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.

A global addendum (dated 15Apr2020) to Study PVO-1A-301 Amendment 4 detailed temporary procedural measures related to the COVID-19 pandemic. The temporary measures were to be followed during the COVID-19 pandemic and until such time as the situation resolves, at which point the protocol assessments were to return to those specified in the current approved protocol effective at that time. Investigators were to 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 were to 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 global addendum (dated 15Apr2020) to Study PVO-1A-301 Amendment 4 was provided to study sites to ensure the safety of trial participants, maintain compliance with good clinical practice, minimize risks to trial integrity, and ensure compliance with local policies. Sites were to use the addendum as a basis to create a study-specific risk management plan that addressed the impact of COVID-19 on Study PVO-1A-301. In addition, a risk mitigation assessment was to be performed for each subject at the site in order to determine how their participation might be impacted. Sites were to ensure that appropriate measures were 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. Notwithstanding this temporary addendum subject visit assessments that could not be done per protocol were to be reported as deviations.

Chronic Treatment: Part A

Subjects will receive orally administered 5 mg palovarotene once daily (weight-adjusted for skeletally immature subjects [ie, subjects under the age of 18 years with less than 90% skeletal maturity on hand-wrist radiography at Screening]; see Table 4) for chronic dosing for up to 48 months. 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 at Months 6, 12, 18, and 24) will continue until these subjects achieve 100% closure of the growth plate at both locations. Additional radiographic assessments will be performed at Study Months 3, 9, 15, or 21 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% skeletally maturity on their last radiographic assessment. For 5 mg palovarotene, weight equivalent doses for <20 kg, 20 to <40 kg, 40 to <60 kg, and ≥60 kg will be 2.5 mg, 3 mg, 4 mg, and 5 mg, respectively. All subjects will undergo the procedures and assessments specified in the Schedule of Assessments in Table 1, including low-dose, WBCT (excluding head) at Screening and at site visits at Months 6, 12, 18, and 24.

In order to ensure consistent interpretation of the acquired images, a central imaging laboratory will perform blinded reads of all images obtained in this study as well as those obtained from the natural history study (control group) using standardized procedures as documented in the Image Acquisition Guidelines and Independent Review Charter. Remote visits (eg, at home, at a local medical facility, or via video-conference or telephone contact from clinical site personnel) will occur at Week 6 and at Study Months 3, 9, 15, and 21 unless the Investigator deems that a site visit is necessary; urine pregnancy tests will be performed each month for females of childbearing potential (FOCBP).

Chronic Treatment: Part B

The assessments and procedures conducted in Part A will continue into Part B except that WBCT imaging will be performed annually at Months 36 and 48.

Flare-up-based Treatment: Parts A and B

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 begin flare-up-based treatment.

- Palovarotene 20 mg for 4 weeks (28 days) once daily. The first dose will be taken upon flare-up or traumatic event confirmation by the Investigator (Flare-up Day 1).

  To be followed by:

- Palovarotene 10 mg for 8 weeks (56 days) once daily. For a total flare-up treatment duration of 12 weeks (84 days).

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.

If the Investigator deems it necessary, the subject can be evaluated at the clinical site to confirm the presence of a flare-up. 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 the 4-week extension treatment has been completed.

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.

All dosing, be it chronic or flare-up, 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 4).

Table 4. Weight-Adjusted Palovarotene Doses for Skeletally Immature (<90%) Subjects and Dose De-escalation Dosing for All Subjects

Weight Range Category	20-mg Equivalent	15-mg Equivalent*	10-mg Equivalent	7.5-mg Equivalent*	5-mg Equivalent	2.5-mg Equivalent*
<20 kg	10 mg	7.5 mg	5 mg	3 mg	2.5 mg	1 mg
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 equivalents, respectively.

If the subject experiences intolerable side effects, the dose may be reduced to the next lower dose as shown in Table 4; 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 location or marked worsening of an 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 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 equivalents]). 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 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 undergo the procedures and assessments specified in the Schedule of Assessments in Table 2. 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 chronic treatment with 5 mg palovarotene once daily (weight-adjusted doses for skeletally immature subjects).

Subjects currently receiving flare-up-based treatment in Study PVO-1A-202 or Study PVO-1A-204 will not enroll into Study PVO-1A-301 until flare-up treatment is complete and at least 4 weeks have elapsed since the last flare-up symptom.

Up to 2-year follow-up Part C:

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. 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.

No new subjects will be enrolled into Part C. Subjects who were enrolled in Parts A or B who have discontinued the study will be invited back to participate in the off-treatment Part C safety follow-up.

3.2 Study Rationale

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.

FOP 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 the original protocol, subjects from the NHS and new subjects clinically diagnosed with FOP with the R206H ACVR1 mutation (who had not previously participated in any Clementia study) were eligible for enrollment. In addition to these subjects, this study (under Amendment 1) will allow for the enrollment of new subjects with other FOP mutations. This will enable these subjects, who also experience progressive HO, to receive treatment with palovarotene. Amendment 1 will also allow for the enrollment of Study PVO-1A-202 or Study PVO-1A-204 subjects who cannot currently receive the chronic/flare-up regimen due to country of residence or those traveling long distances to participate in the Phase 2 trial. This will provide for optimal palovarotene treatment and reduced travel burden for these subjects.

The primary analysis of the MOVE study will be restricted to palovarotene-naïve subjects with the R206H ACVR1 mutation, compared to untreated subjects from the NHS. As the MOVE study control is data from the NHS, the subject populations should match as closely as possible between the two studies. Subjects with FOP mutations other than R206H will not be included in the primary analysis due to the limited number of patients with these mutations (estimated as 3% of the world's known FOP population of approximately 800 individuals – or approximately 24 subjects) and because the NHS only enrolled subjects with the R206H ACVR1 mutation. Subjects who previously participated in the palovarotene Phase 2 program will also not be included in the primary analysis due to their previous episodic exposure to palovarotene prior to the initiation of the MOVE study dosing regimen. However, these two groups of subjects are being allowed to participate in the MOVE study in order to provide the palovarotene dosing regimen that has demonstrated the best efficacy results to date, allowing collection of efficacy and safety data within the context of a clinical trial that will be summarized descriptively, while also reducing subject burden.

The study was extended in Part B for an additional 24 months in order to provide the chronic/flare-up palovarotene dosing regimen to all subjects until commercial availability; and to obtain longer-term safety data.

As of 04Dec2019, 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.

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

3.3 Dose Justification

FOP 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 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 immunization; mandibular blocks for dental work; muscle fatigue; blunt muscle trauma from bumps, bruises, or 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.**Error! Reference source not found.** 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 Phase 2 and current 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 Phase 2 study and in the current study. Therefore, careful safety monitoring and dose modification procedures for intolerable side effects will be employed in the current study.

3.4 Appropriateness of Measures

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,**Error! Reference source not found.** magnetic resonance imaging (MRI),**Error! Reference source not found.** and radionuclide bone scan.**Error! Reference source not found.** 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.**Error! Reference source not found.**

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 whole body CT scan (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, whole body CT scan (excluding head).

In order to ensure consistency and standardization, interpretation of the acquired hand-wrist and knee radiographs for subjects under the age of 18 years and WBCT scans for the assessment of HO from the MOVE Trial, as well as from the NHS comparator, will be performed in a blinded fashion by a central imaging laboratory by two independent radiologists using standardized procedures as documented in the Image Acquisition Guidelines and Independent Review Charter. The maximal possible radiation exposure for imaging procedures conducted during Study PVO-1A-301 is 28.9 mSv over 48 months or approximately 10.2 mSv annually for the first 2 years in Part A; and 4.1 mSv annually for the last 2 years in Part B or C. These estimates are much lower than those discussed in the 21 March 2017 American Association of Physicists in Medicine Position Statement on Radiation Risks from Medical Imaging Procedures, stating there is no convincing epidemiological evidence of increased cancer incidence or mortality from radiation doses below 100 mSv.**Error! Reference source not found.**

3.4.2 Measures of Functional Disability and General Health

Two key measures of functional disability include:

- The Cumulative Analogue Joint Involvement Scale (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-Physical Function Questionnaire (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.

The baseline data from the Natural History Study (PVO-1A-001) demonstrated clear correlations of these endpoints with age, but minimal to no change over 12 months.**Error! Reference source not found.** As it is anticipated that change in untreated comparator subjects over 48 months may be minimal, these questionnaires are being evaluated as exploratory endpoints only.

4 Study Endpoints

4.1 Primary Endpoint

The primary endpoint is the annualized change in new HO volume as assessed by low-dose, WBCT (excluding head) compared to untreated subjects from the NHS over 24 months.

4.2 Secondary Endpoints

The following secondary endpoints will be assessed in Parts A and B:

1. The proportion of subjects (key secondary endpoint) with any new HO.
2. The change from baseline in the number of body regions with new HO.
3. The proportion of subjects reporting flare-ups.
4. The flare-up rate per subject-month exposure.

4.3 Exploratory Endpoints

The following exploratory endpoints will be assessed in Parts A and B:

1. Change from baseline in ROM assessed by CAJIS.
2. Change from baseline in physical function using age-appropriate forms of the FOP-PFQ.
3. 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.

5 Selection of Study Population

The target study population consists of adult and pediatric subjects with FOP. Sources of subjects eligible for enrollment in the MOVE Trial will include: (1) subjects from Study PVO-1A-001 (the natural history study [NHS]), (2) additional subjects clinically diagnosed with FOP with the R206H ACVR1 mutation or other FOP mutations reported to be associated with progressive HO (who have not previously participated in any Clementia-sponsored trials), and (3) Study PVO 1A-202 or Study PVO-1A-204 subjects who cannot currently receive the chronic/flare-up regimen due to country of residence or those traveling long distances to participate in the Phase 2 trial.

5.1 Study Population

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.

5.1.1 Inclusion Criteria

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

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

2. Male or female at least 4 years of age.

3. Previous participation in the NHS; or clinically diagnosed with FOP, with the R206H ACVR1 mutation or other FOP variants reported to be associated with progressive HO (who have not previously participated in any Clementia-sponsored study); or participants in Study PVO-1A-202 or Study PVO-1A-204 who cannot currently receive the chronic/flare-up regimen due to country of residence or those traveling long distances to participate in the Phase 2 trial.

4. No flare-up symptoms within the past 4 weeks, including at the time of enrollment.

5. 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.

6. Must be accessible for treatment and follow-up, and be able to undergo all study procedures. 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. Subjects must be able to undergo low-dose, WBCT (excluding head) without sedation.

5.1.2 Exclusion Criteria

Subjects with any of the following exclusion criteria will not be eligible for enrollment:

1. Weight <10 kg.

2. 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.

3. Exposure to synthetic oral retinoids other than palovarotene within 4 weeks prior to screening.

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

5. History of allergy or hypersensitivity to retinoids, gelatin, or lactose (note that lactose intolerance is not exclusionary).

6. Concomitant medications that are strong inhibitors or inducers of cytochrome P450 (CYP450) 3A4 activity; or kinase inhibitors such as imatinib (see Section 5.2.1).

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

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

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

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 Columbia-Suicide Severity Rating Scale (C-SSRS).

13. Simultaneous participation in another interventional clinical research study (other than palovarotene studies) within 4 weeks prior to Screening; or within five half-lives of the investigational agent, whichever is longer.

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.

5.2 Prior and Concomitant Medications and Other Study Restrictions

5.2.1 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.**Error! Reference source not found.** 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 (chronic or flare-up-based treatment):

- 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) 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.

- Kinase inhibitors such as imatinib, and other drugs used off-label as potential treatments for FOP such as rapamycin, as reported in the literature.[28,29] A washout period of 5 half-lives is required prior to enrollment into the study.

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.

5.2.2 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.

It is well recognized that retinoids are teratogens with a high risk of fetal abnormalities should women become pregnant during treatment with such agents. The risk of pregnancy will be carefully described and acknowledgement of the need to remain abstinent or use two effective methods of birth control will be explicitly elicited in the informed consent. In addition, pregnancy tests (urine or blood) will be conducted as specified in Table 1 and Table 2.

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.

5.3 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 subjects' safety is at risk. Additional details regarding study drug dose modification are provided in Section 6.5.

If any subject enrolled in Part C chooses to enroll in another clinical trial, all reasonable efforts should be made by the study personnel to have the subject continue on Study PVO-1A-301 until their final study completion 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.

5.4 Replacement of Subjects

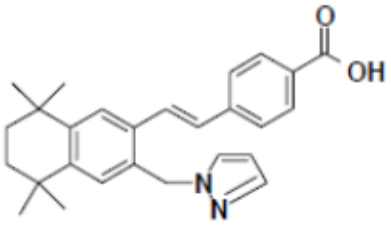
Subjects may be replaced at the discretion of the sponsor.

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, 1.5, and 1 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 study drug blinding.

6.4 Administration

Subjects will receive orally administered 5 mg palovarotene daily (or weight-adjusted for skeletally immature subjects, Table 4) for chronic dosing for up to 48 months. The first day that study drug is administered for chronic treatment will be defined as Study Day 1. Details for handling, preparing, storing, and discarding study drug will be provided to subjects.

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) followed by palovarotene 10 mg for 8 weeks (56 days), 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 (Table 4). 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 an 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 equivalents]).

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

The dose of study drug taken each day during chronic and flare-up-based treatment and a daily assessment of whether a subject is experiencing the onset of flare-up symptoms will be documented in the subject dosing diary. Subjects who experience the onset of flare-up symptoms during chronic treatment or flare-up symptoms at a different site other than the one being treated during flare-up-based treatment should contact the site as soon as possible.

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 4 (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 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.

7 Study Procedures and Assessments

7.1 Screening, Recruitment, and Informed Consent

Individuals with FOP will learn about this Phase 3, open-label study through their participation in Studies PVO-1A-001 (NHS), PVO-1A-202, and PVO-1A-204, and through the FOP community (physicians, patient support groups, and other contacts). A maximum of up to 110 subjects will be enrolled into the MOVE Trial (up to 99 with the R206H mutation and no previous exposure to palovarotene, and 11 with other mutations or previous participation in the Phase 2 trials), and receive chronic dosing for up to 24 months in Part A and up to an additional 24 months in Part B; and undergo flare-up-based treatment should they experience an eligible flare-up confirmed by the Investigator.

Part C was added for skeletally immature subjects who stopped taking study medication for any reason before completion of Part A/B. Part C includes yearly visits for up to a 2-year follow-up period following last dose with a total subject participation of no more than 4 years. Maximum length of study participation is 48 months (+1 month). No dosing will occur during Part C.

Due to the burden of travel, subjects may undergo an 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-301 Amendment 4, 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, and Table 3 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

A medical history, including FOP history, is to be documented at Screening for each subject.

For subjects receiving flare-up-based treatment, the flare-up assessment will include current flare-up location, symptoms, and probable cause documented on Flare-up Day 1.

7.2.2 Physical Examination

A physical examination of all body systems is to be documented at Screening and every 6 months in Part A (Months 6, 12, 18, and 24) and Part B (Months 30, 36, 42, and 48), Part A or B EOT/EOS and Part C (Years 1 and 2 or SC post last dose of study treatment) for each subject.

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 adverse events.

7.2.3 Body Weight and Linear Growth Assessments

All subjects will have body weight assessed at Screening and every 3 months in Part A (Months 3, 6, 9, 12, 15, 18, 21, and 24) and Part B (Months 27, 30, 33, 36, 39, 42, 45, and 48), Part A or B EOT/EOS and Part C (Years 1 and 2 or SC post last dose of study treatment).

For subjects receiving flare-up-based treatment in Parts A and B, body weight will also 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 18 years of age and older will have linear growth assessed by stadiometer at Screening in Part A. Subjects under the age of 18 years enrolled with open epiphyseal growth plates will

have linear growth assessments (in triplicate) by stadiometer and knee height measurements (in triplicate) at Screening and every 6 months (Months 6, 12, 18, and 24). Once a subject is 18 years old, triplicate linear growth and knee height assessments will no longer be required. The 6-month assessments of linear growth in subjects under the age of 18 years will continue in Part B (Months 30, 36, 42, and 48), Part A or B EOT/EOS and Part C (Years 1 and 2 or SC post last dose of study treatment)

Linear growth measurements will be performed by trained and qualified study personnel at the same time of day for each assessment, if possible. 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.

In addition, the length of bilateral tibia and femur will be assessed by WBCT scan every 6 months up to Month 24 in Part A; and annually up to Month 48 in Part B; and annually in the NHS.

7.2.4 Vital Signs

Vital signs (temperature, respiratory rate, blood pressure, and heart rate) will be assessed at Screening and every 3 months in Part A (Months 3, 6, 9, 12, 15, 18, 21, and 24) and Part B (Months 27, 30, 33, 36, 39, 42, 45, and 48), Part A or B EOT/EOS and Part C (Years 1 and 2 or SC post last dose of study treatment) for each subject.

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

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. To minimize the potential for a flare-up at the cuff site when measuring blood pressure, pump the cuff slowly to a maximum of 140 mm Hg. DO NOT measure blood pressure on an arm with a flare-up.

7.2.5 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at Screening and every 6 months in Part A (Months 6, 12, 18, and 24), Part B (Months 30, 36, 42, and 48), and Part A or B EOT/EOS for each subject.

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 at Screening and every 6 months in Part A (Months 6, 12, 18, and 24), Part B (Months 30, 36, 42, and 48), and Part A or B EOT/EOS for each subject.

For subjects receiving flare-up-based treatment in Parts A and B, 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 laboratory results observed within 1 month of starting flare-up-based treatment will not need to have Flare-up Day 1 laboratory tests repeated. 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 always be performed monthly during chronic 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 results are needed promptly (eg, Screening for eligibility), testing can be completed at a local, qualified laboratory. If urinalysis results are abnormal, a microscopic evaluation will be completed.

The total blood volume drawn from a subject over the course of the entire study (48 months) will range from approximately 66 mL (in the case of no flare-ups) to 182 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 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.

Table 5 presents the clinical laboratory parameters that will be assessed in this study.

Table 5. 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
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 and Part A or B EOT/EOS. 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 and given counsel on pregnancy prevention and birth control methods as appropriate.

7.2.8 Adverse Events

Adverse event monitoring will be conducted throughout the study for all subjects. The AE, SAE and death reporting period begins at the time of informed consent and continues through Part A/B EOS +30 days (for subjects not participating in Part C) or Part C SC + 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. 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.

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

Prior/concomitant medications will be assessed at every site and remote visit during chronic treatment, flare-up-based treatment, Part A or B EOT/EOS and Part C (Years 1 and 2 or SC post last dose of study treatment).

See Section 5.2 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 using the C-SSRS (see Appendix 5A) at Screening and every 3 months in Part A (Months 6, 9, 12, 15, 18, 21, and 24); in Part B (Months 27, 30, 33, 36, 39, 42, 45, and 48) and Part A or B EOT/EOS and as part of every Flare-Up Cycle Safety Assessment in Parts A and B.

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 (see Appendix 5B). Study personnel administering the questionnaire will receive formal training to ensure accuracy and consistency in application of the instrument.

Any subject reporting a type 4 or 5 suicidal ideation or any suicidal behavior within 1 month prior to 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, subjects under the age of 18 years at the time of enrollment (Screening) with open epiphyses will have follow-up knee (AP view) and hand-wrist radiographs (PA view, preferable on the left side) every 6 months in Part A (Months 6, 12, 18, and 24), Part B (Months 30, 36, 42, and 48) and Part A or B EOT/EOS. Subjects who are skeletally immature at the time of study drug discontinuation and entering Part C (Y1 and Y2 or SC post last dose of study treatment) will have follow-up knee (AP view) and hand-wrist radiographs (PA view, preferable on the left side) every year. Additional radiographic assessments will be performed every 3 months in Parts A and B 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% skeletally maturity on their last radiographic assessment.

Subjects enrolling from the NHS and Phase 2 studies that underwent knee and hand-wrist radiographs within 1 month of Screening will not need to have radiographs repeated at Screening. At the Screening/Study Day 1 visit, in order to obtain a more rapid assessment of the subject's skeletal maturity so that dosing can be determined while the subject is on site, sites may have the subject's bone age also assessed by qualified physician staff.

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.

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 above in Section 7.3.2, WBCT scans acquired from subjects under the age of 18 years in both Study PVO-1A-301 and the NHS 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 at Screening and every 6 months in Part A (Months 6, 12, 18, and 24), Part B (Months 30, 36, 42, and 48), and Part A or B EOT/EOS (excepting Part C) for all subjects. During flare-up-based treatment in Parts A/B, a complete lipid profile will be performed as part of the biochemistry testing at 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, 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 at Screening and every 6 months in Part A (Months 6, 12, 18, and 24), Part B (Months 30, 36, 42, and 48), and Part A or B EOT/EOS (excepting Part C) for all subjects. During flare-up-based treatment in Parts A/B, a liver enzyme profile will be performed as part of the biochemistry testing at 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.

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)* (Appendix 7).

7.3.7 Lipase/Amylase

Amylase and lipase will be monitored as part of the biochemistry testing at Screening and every 6 months in Part A (Months 6, 12, 18, and 24), Part B (Months 30, 36, 42, and 48), and Part A or B EOT/EOS (excepting Part C) for all subjects. During flare-up-based treatment in Parts A/B, a lipase/amylase profile will be performed as part of the biochemistry testing at 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.

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

Hearing loss is a common finding in individuals with FOP. In Study PVO-1A-001 (NHS), 42% of subjects (48 of 114) reported hearing loss at baseline. However, impaired hearing also has been reported in subjects taking retinoids. Thus, hearing tests will occur at baseline (or at

Month 6, or the next possible visit, if they were not obtained at screening) and at Months 12 and 24 in Part A, Months 36, and 48 in Part B, and Part A or B EOT/EOS (excepting Part C).

Hearing will be assessed with age-appropriate audiometry behavior testing. The assessments will determine auditory thresholds in response to speech and frequency-specific stimuli presented through earphones. In addition, 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) should be discontinued from treatment, based on a benefit-risk assessment.

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

7.4.1 Low-Dose, Whole Body Computed Tomography

All subjects will undergo a low-dose, WBCT scan (excluding head) every 6 months in Part A (Months 6, 12, 18, and 24) and annually in Part B (Months 36 and 48), Part A or B EOT/EOS and Part C (Y1 and Y2 or SC post last dose of study treatment). Of note, the last low-dose, WBCT scan (excluding head) from the NHS will be used as the baseline assessment for those subjects enrolling from the NHS as long as the scans were performed within 1 month of Screening/Study Day 1. The last low-dose, WBCT scan (excluding head) from Study PVO-1A-202 or Study PVO-1A-204 will be used as the baseline assessment for those subjects on chronic treatment enrolling from Phase 2, as long as the scans were performed within 6 months of Study Day 1. All other subjects (ie, subjects who will start chronic treatment during Study PVO-1A-301) will undergo a low-dose, WBCT scan (excluding head) at Screening/Study Day 1.

Interpretation of the CT scan will document the absence or presence of HO across various body regions, volume of total body HO, presence and volume of new HO at follow-up visits, and spinal health. 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.

To evaluate the effect of palovarotene on physical function, age-appropriate forms of the FOP-PFQ will be administered at Screening and every 6 months in Part A (Months 6, 12, 18, and 24), Part B (Months 30, 36, 42, and 48), and Part A or B EOT/EOS for each subject.

The adult form of the FOP-PFQ will be completed by subjects 15 years of age and older (see Appendix 2A). Three 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 (see Appendix 2B), a proxy-completed form developed for 5- to 14-year-olds (see Appendix 2C), and a proxy-completed form developed for 2- to 4-year-olds (see Appendix 2D).

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

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 at Screening and every 6 months in Part A (Months 6, 12, 18, and 24), Part B (Months 30, 36, 42, and 48), and Part A or B EOT/EOS for each subject.

The adult form of the PROMIS Global Health Scale will be administered to subjects 15 years of age and older (see Appendix 8A). 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 8B and Appendix 8C, 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

Range of motion will be assessed by the Investigator using CAJIS (see Appendix 1) at Screening and every 6 months in Part A (Months 6, 12, 18, 24), Part B (Months 30, 36, 42, and 48) and Part A or B EOT/EOS for each subject. The CAJIS should be assessed by the same Investigator at each time point. All Investigators will be trained to administer the CAJIS prior to subject enrollment.

7.5 Pharmacokinetics

Pharmacokinetics of palovarotene dosing will be assessed at the first 3-month safety assessment during chronic-based treatment; if samples cannot be obtained during the first 3-month safety assessment, then they can be obtained during any subsequent 3-month safety visit in the first 24 months (ie, in Part A).

Pharmacokinetics will also be assessed twice during flare-up dosing: 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 and 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 in the first 24 months (ie, in Part A). Pharmacokinetic blood samples will be collected at predose and 3, 6, 10, and 24 hours post-dose.

The following parameters will be determined where possible by model independent analysis using WinNonlin™: $C_{max,ss}$, $C_{min,ss}$, $T_{max,ss}$, $AUC_{0\text{-}24ss}$, λ_z, $t_{½z}$, and CL/F.

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 days will be recorded.

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

7.6 Genotyping

On Screening/Study Day 1, a blood sample will be collected and the ACVR1 gene-coding region will be sequenced by a central genotyping laboratory to assess for the presence of an FOP-associated mutation of the ACVR1 gene for new subjects or for subjects who have not undergone previous genotyping as part of Study PVO-1A-001. Subjects enrolling from Study

PVO-1A-202 or Study PVO-1A-204 do not need to undergo repeat genotyping. Any subject enrolled who does not have an ACVR1 mutation known to be associated with FOP will be discontinued. If the Investigator has any reason to believe a subject does not possess an FOP mutation, enrollment may be delayed until the genotype is confirmed.

7.7 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established to 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.

7.8 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-301 (MOVE study) during the COVID-19 pandemic will continue 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 A or B EOT/EOS and be invited to participate in Part C and undergo assessments outlined in Table 3.
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 are 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. 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, Hearing Test, 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 Considerations

8.1 General Considerations

This study is intended to assess whether a chronic dosing regimen, combined with higher doses during times of flare-ups, will reduce new HO formation. As this is an open-label study with no randomized control group, use of subject data from Study PVO-1A-001 (Natural History Study [NHS]) over 24 months will form the basis for a control arm. Therefore, the primary comparison of outcomes from this study will be made to data collected from the NHS in order to determine whether the chronic/flare-up regimen provides benefit over the untreated condition (data from the NHS). In addition, the primary efficacy analysis will be restricted to MOVE subjects who have the R206H mutation and who have not previously been treated with palovarotene. These restrictions increase the validity of the comparison to the NHS historical control which only enrolled subjects with the R206H mutation and no previous palovarotene exposure.

This section contains a brief overview of the statistical analyses planned for this study. Details of all planned analyses will be provided in the formal statistical analysis plan (SAP).

8.2 Sample Size Determination

The sample size required for this Phase 3 study was determined via simulation based on the available WBCT HO volumes from the NHS and the observed efficacy of palovarotene treatment in the Phase 2 studies. The NHS will serve as the external control group, with the expectation that 45 subjects will have baseline, 1-year, and 1.5-year WBCT HO volumes and 45 subjects will have baseline, 1-year, and 2-year WBCT HO volumes. It is also anticipated that approximately 50% of these 90 subjects will enter the Phase 3 study to begin palovarotene treatment.

There are three interim efficacy analyses and a final analysis planned. Assuming a one-sided, overall type I error rate of 2.5%, the Lan-DeMets alpha-spending function with O'Brien-Fleming parameterization was used to determine stopping boundaries (see Section 8.5.2 for additional details). The simulated power is summarized in Table 6, given the specified testing sequence and 80 subjects originally planned for enrollment into the current study with the R206H mutation and no previous palovarotene experience (including approximately 45 subjects from the NHS). Note that the increase in the number of enrolled subjects will not substantially change the power of the trial or have a significant impact on the primary or secondary statistical analyses.

Table 6. Power of MOVE Study Primary Efficacy Analysis Assuming 80 Subjects Enrolled with the R206H Mutation and No Previous Palovarotene Exposure

Scenario		Cumulative Prob. of Success			
% Reduction HO Volume Conditional on New HO in a Body Region	% Reduction in Number of Regions with New HO	Interim #1	Interim #2	Interim # 3	Final
0%	0%	0.006	0.010	0.013	0.021
50%	30%	0.507	0.789	0.886	0.922

HO=heterotopic ossification.

The primary efficacy analysis comparing the annualized change in new HO volume between subjects treated with palovarotene and untreated subjects has an overall probability of study success of 0.92 if palovarotene treatment reduces the number of regions with new HO by 30% and reduces the new HO volume conditional on new HO in a per body region by 50%. With this treatment effect, the probability of declaring study success is 0.51, 0.79, and 0.89 at the first, second, and third interim analyses, respectively. Table 6 shows that the type I error rate is maintained under the null hypothesis of no palovarotene treatment effect.

8.3 Disposition of Subjects

Screened subjects will be defined as any subject who has signed the informed consent form. Screened subjects who complete screening and met all eligibility criteria will be eligible for palovarotene treatment.

8.4 Analysis Populations

In Part A, the MOVE subjects will be grouped into the following populations for analysis:

- The Principal Enrolled Population (Principal EP) includes all subjects with the R206H ACVR1 mutation who have not previously been treated with palovarotene and who sign the informed consent form and meet all eligibility criteria of the MOVE Trial.

- The Principal Full Analysis Set (Principal FAS) includes all enrolled subjects in the Principal EP who have a baseline HO volume measurement and at least one post-baseline HO volume measurement in the MOVE trial. For efficacy comparisons to the NHS, the Principal FAS will also include subjects enrolled in the NHS with available baseline and at least one post-baseline HO volume measurements.

- The Principal Per-Protocol Set (Principal PPS) is a subset of the Principal 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, over the first 24 months of participation in the study. For efficacy comparisons to the NHS, the Principal 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 over 24 months that are expected to interfere with assessments of the primary endpoint.

- The Principal Safety Set (Principal SS): includes all enrolled subjects receiving at least one dose of palovarotene in the current study. For safety comparisons to the NHS, the Principal SS will also include subjects enrolled in the NHS with available post-baseline follow-up.

- The Principal Pharmacokinetic Set (Principal PS) includes all enrolled subjects receiving at least one dose of palovarotene and providing evaluable pharmacokinetics data in the current study.

Subjects who do not have the R206H ACVR1 mutation or who have received previous treatment with palovarotene will comprise the Supplementary EP, the Supplementary FAS, the Supplementary PPS, the Supplementary SS, and the Supplementary PS, with these populations defined analogously as above for the subjects with the R206H ACVR1 mutation.

8.5 Statistical Methods

8.5.1 Extent of Exposure

The extent of study treatment will be assessed, and summary statistics will be presented for the SS populations.

8.5.2 Analyses of Efficacy Endpoints

8.5.2.1 Primary Efficacy Analysis

The primary efficacy endpoint is the annualized change in new HO volume (as assessed by low-dose WBCT) over 24 months in Part A. The change in new HO volume is calculated by summing the increase in HO volume across all body regions for which new HO has occurred, where the increase in HO volume per region is defined as the square root of the volumetric increase in that region. The change in new HO volume is modeled using a Bayesian compound Poisson distribution. The Bayesian compound Poisson distribution assumes that the change in new HO volume can be modeled as a compound distribution of the number of body regions with new HO, K, and the new HO volume per region where new HO has occurred. The number of body regions with new HO in subject i for WBCT scan j with duration w_{ij} (the time between scan j and the previous scan) is distributed as

$$K_{ij} \sim Pois\left(\lambda_i * w_{ij} * \theta_{1,t(ij)}\right).$$

The subject-level rate λ_i follows a gamma distribution and $t(ij)$ is an indicator function equal to 1 if the subject was on treatment at the time of the jth WBCT scan and 0 if the subject was not on treatment. Letting $\theta_{1,0} = 1$, the variable $\theta_{1,1}$ is the multiplicative effect of palovarotene treatment on the mean number of body regions with new HO. The new HO volume in region r where new HO has occurred for subject i in scan j is assumed to be distributed as

$$Z_{ijr} \sim N\left(\alpha * \alpha_r * \theta_{2,t(ij)}, \frac{\alpha_r^2}{\tau_{t(ij)}}\right).$$

Letting $\theta_{2,0} = 1$, the variable $\theta_{2,1}$ is the multiplicative effect of palovarotene treatment on the new HO volume conditional on new HO occurring.

The primary efficacy analysis comparing the annualized change in new HO volume between subjects treated with palovarotene and untreated subjects is performed by calculating the ratio of the annual mean change in HO volume in palovarotene treated subjects to untreated subjects using the Principal FAS and assuming missing at random. Using the Bayesian compound Poisson model described above, this ratio is calculated as the treatment effect on the rate of body regions with new HO, $\theta_{1,1}$, multiplied by the treatment effect on new HO volume conditional on new HO occurring, $\theta_{2,1}$, expressed as $\gamma = \theta_{1,1} * \theta_{2,1}$. Random samples generated via Gibbs sampling from the posterior distribution of $\theta_{1,1}$ and $\theta_{2,1}$ will be used to compute the posterior probability that $\gamma < 1$ to determine statistical significance. The primary efficacy analysis described above will be repeated without the square-root transformation. Additional supportive analyses including the weighted mixed linear effect (wLME) analysis with and without the square-root transformation will also be performed.

Approximately 80 palovarotene-naïve subjects with the R206H ACVR1 mutation will be enrolled into the current study and will be followed for 2 years in Part A. There will be three early interim efficacy analyses and one final analysis in Part A. The first interim analysis will occur when 35 subjects complete 1 year of follow-up; the second and third interim analyses will occur when all subjects enrolled in the Principal EP have completed (ie, have WBCT data) 12 months and then 18 months of follow-up, respectively. The interim analyses will include the Month 6 WBCT results when that is the only observation available from a subject in the current study. While study success may be declared after one of the interim analyses or at the final analysis in Part A, all subjects will continue until completing 48 months of treatment.

Accrual of 80 palovarotene-naïve subjects with the R206H ACVR1 mutation is expected to take place in approximately 10 months to 1 year and it is assumed that the full NHS dataset will be available at the first interim. The amount of statistical information at each interim analysis can be approximated by the sum of the follow-up in each study divided by the total expected. The total follow-up expected across the NHS and the MOVE Trial is 317.5 years (NHS: 45∗1.5 years + 45∗2.0 years; MOVE: 80∗2.0 years). Assuming eight subjects enrolled in the MOVE study per month, the percentage of patient follow-up for each analysis is 66%, 80%, and 92% at the first, second, and third interim analysis, respectively. Using these percentages, the alpha level threshold used to determine treatment effect significance at each analysis was derived using the Lan-DeMets alpha-spending function with O'Brien-Fleming parameterization and assuming a one-sided, overall type I error rate of 2.5%. The one-sided significance thresholds are 0.0058, 0.0103, 0.0156, and 0.0190 for the first, second, and third interim analyses, and the final analysis, respectively. Study success will be declared if the posterior probability that palovarotene reduces the annualized change in new HO volume is greater than 1 minus the one-sided significance threshold. For example, the posterior probability that palovarotene reduces the annualized change in new HO volume must be greater than 0.9810 to declare study success at the final analysis. A futility analysis was conducted for the second interim analysis based on the

pre-specified criteria using square-root transformation and additional analyses without the square-root transformation. Based on feedback received by the DMC following the second interim analysis, the futility analysis conducted at the third analyses will use the predefined model with and without square-root transformation to assess whether the study shows insufficient evidence of efficacy. If the efficacy criteria have not been met by the final analysis of Part A the study may be terminated. Stopping the study for futility will be considered if the posterior probability that $\gamma < 0.7$ (at least a 30% reduction in annualized new HO volume on the square-root scale) is less than 5%. and taking into consideration additional analyses performed without the square-root transformation.

The primary efficacy analysis will be repeated using the Principal PPS. Further details regarding primary analysis and the planned sensitivity analyses are provided in the Statistical Analysis Plan. The primary efficacy endpoint will be summarized for the Supplementary FAS and PPS.

8.5.2.2 Secondary Efficacy Analysis

The secondary efficacy endpoints will be analyzed using the Principal FAS and PPS populations. Treatment effect estimates will be generated for Part A, and overall for data obtained in Parts A and B.

The proportion of subjects with any new HO and the change in the number of body regions with any new HO will be analyzed using the Bayesian compound Poisson distribution used for the primary efficacy analysis. The variables in that model can be used to construct the hypothesis test for both of these secondary efficacy endpoints.

The proportion of subjects with any flare-ups and the flare-up rate per subject-month exposure will be analyzed using a Bayesian Poisson distribution.

The secondary efficacy endpoints will be summarized for the Supplementary FAS and PPS.

8.5.3 Safety

Safety evaluations will include AE and SAE reporting, ECGs, 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. Safety analyses will use the Principal SS, and separately, the Supplementary SS. Safety will be summarized for Part A and overall for data obtained in Parts A, B and C. Where appropriate, comparisons to safety information from the NHS will be made.

Safety evaluations will include AE and SAE reporting, vital signs (temperature, respiratory rate, blood pressure, and heart rate), physical examination, body weight and height, and concomitant medication reporting. Safety will be summarized for Part C.

Evaluation of subjects under the age of 18 enrolled with open epiphyseal growth plates will include knee (AP view) and hand-wrist radiographs (PA view) for assessment of epiphyseal growth plate and distal femoral angle, WBCT scans for growth plate assessments of the bilateral hand-wrist and knee, tibial and femoral long bone lengths, and stadiometry and knee height (in

triplicate) for assessment of linear growth. Safety will be summarized for Part A and overall for data obtained in Parts A, B and C In addition, bilateral assessments of hip growth plate morphology for AVN will be performed in all subjects.

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.

8.5.3.1 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, 14June2010.

Tabulations will include an overall incidence of at least one AE, incidence within body system, and incidence by preferred term (including by severity and relationship to study drug). 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.

8.5.4 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 in listings (see Appendix 5A and Appendix 5B).

8.5.5 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 chronic 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.

8.6 Pharmacodynamics

Exploratory analyses will be performed to assess potential exposure relationships.

8.7 Interim Analyses

Interim efficacy analyses will be conducted under the auspices of the DMC to assess whether efficacy is sufficiently demonstrated prior to the completion of the study. The study will not stop early if an interim efficacy analysis meets the efficacy criteria (pre-specified to trigger potential early submission for marketing authorization); subjects will continue treatment until completion of 48 months of palovarotene treatment. The pre-specified significance thresholds to declare study success at each interim efficacy analysis is described in Section 8.5.2.1.

A futility analysis was conducted for the second interim analysis based on the pre-specified criteria using square-root transformation and additional analyses without the square-root transformation. Based on feedback received by the DMC following the second interim analysis, the futility analysis conducted at the third analyses will use the predefined model with and without square-root transformation to assess whether the study shows insufficient evidence of efficacy. If the efficacy criteria have not been met by the final analysis of Part A the study may be terminated. Stopping the study for futility will be considered if the posterior probability that $\gamma < 0.7$ (at least a 30% reduction in annualized new HO volume on the square-root scale) is less than 5% and taking into consideration additional analysis performed without the square-root transformation.

Additional supportive analyses including the primary analysis without the square-root transformation of the data and the wLME analysis will be performed.

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:

- None
- Study drug dosage modified
- Study drug dosage interrupted
- Study drug permanently discontinued

9.1.7 Outcome of Adverse Event

The outcome of the AEs will be recorded as follows:

- Event resolved with no sequelae
- Event resolved with sequelae
- Event ongoing
- Death

9.1.8 Reporting of Serious Adverse Event

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

North America
SAE hotline:
Tel: 1.888.483.7729
Fax: 1.888.529.3580 **or** 1.919.654.3836
E-mail: RTPSafety@ppd.com

Latin America
SAE hotline:
Tel: +55.11.4504.4801
Fax: +55.11.3958.0983
E-mail: LATSafety@ppd.com

EMEA/APAC
SAE hotline:
Tel: +44.1223.374.240
Fax: +44.1223.374.102
E-mail: EMEAASIASafetyCentral.SM@ppd.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 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 begins at the time of informed consent and continues through Part A/B EOS +30 days (for subjects not participating in Part C) or Part C SC + 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 until follow-up is no longer necessary. 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 9), 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.

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 participating study Investigators by the Sponsor prior to database lock. The Coordinating Investigator will approve the final clinical study report for Study PVO-1A-301.

10 Investigator Agreement

I have read Protocol PVO-1A-301 Amendment 5, dated 30 October 2020:

MOVE Trial: A Phase 3, Efficacy and Safety Study of Oral Palovarotene for the Treatment of 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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Appendices

Appendix 1. Cumulative Analogue Joint Involvement Scale for FOP

CUMULATIVE ANALOGUE JOINT INVOLVEMENT 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. **Protocol: PVO-1A-301**
Version: 06-Feb-2014

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 2D. Pediatric FOP-Physical Function Questionnaire (Proxy-Completed for Subjects Ages 2 to 4 Years)

Pediatric Fibrodysplasia Ossificans Progressiva Physical Function Questionnaire (FOP-PFQ-P) Proxy-Completed for Ages 2 to 4
[Proxy 2-4 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.

*[If your child has difficulty doing a certain activity or is unable to do it because he/she is too young but **not because he/she is** RESTRICTED BY FOP, please mark the box labeled "Not Applicable".]*

	With no trouble	With a little trouble	With some trouble	With a lot of trouble	Not able to do	Not Applicable
1. My child can button his/her shirt or pants…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
2. My child can dry his/her back with a towel…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
3. My child can go up one step…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
4. My child can walk outdoors or on flat ground…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
5. My child can get in and out of bed or stand up in a crib…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
6. My child can pull a shirt on over his/her head…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
7. My child can zip up his/her clothes…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
8. My child can put on his/her clothes…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
9. My child can put on his/her socks...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
10. My child can get up from a regular toilet or potty chair…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
11. My child can get up from the floor...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
12. My child can get in and out of a car or toy car…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
13. My child can walk up stairs without holding on to anything...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

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	Not Applicable
14. My child can put on his/her shoes…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
15. My child can lift a cup to drink...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
16. My child can brush his/her teeth...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
17. My child can bend over to pick something up…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
18. My child can get down on his/her knees without holding on to something…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
19. My child can turn his/her head all the way to the side…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
20. My child can wash his/her hair…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
21. My child can reach a shelf above his/her head…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
22. My child can write or scribble with a pen or pencil...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
23. My child can wipe himself/herself after using the toilet…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
24. My child can chew his/her food…	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

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

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

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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
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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?*** 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 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 <u>some intent to act on such thoughts</u>, 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). ***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: **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** ☐ ▪ ☐
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 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.

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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	____

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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* _____

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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.

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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** ☐
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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 _____
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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* _____

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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
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Appendix 7. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation

Guidance for Industry

Drug-Induced Liver Injury: Premarketing Clinical Evaluation

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2009
Drug Safety

Guidance for Industry

Drug-Induced Liver Injury: Premarketing Clinical Evaluation

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
Tel: 301-796-3400; Fax: 301-847-8714; E-mail: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

or

Office of Communication, Outreach, and Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
Tel: 800-835-4709 or 301-827-1800
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2009
Drug Safety

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Contains Nonbinding Recommendations

Guidance for Industry[1] Drug-Induced Liver Injury: Premarketing Clinical Evaluation

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist the pharmaceutical industry and other investigators who are conducting new drug development in assessing the potential for a drug[2] to cause ***severe*** liver injury (i.e., irreversible liver failure that is fatal or requires liver transplantation). In particular, the guidance addresses how laboratory measurements that signal the potential for such drug-induced liver injury (DILI) can be obtained and evaluated during drug development. This evaluation is important because most drugs that cause severe DILI do so infrequently; typical drug development databases with up to a few thousand subjects exposed to a new drug will not show any cases. Databases may, however, show evidence or signals of a drug's *potential* for severe DILI if the clinical and laboratory data are properly evaluated for evidence of lesser injury that may not be severe, but may predict the ability to cause more severe injuries. This guidance describes an approach that can be used to distinguish signals of DILI that identify drugs likely to cause severe liver injury from signals that do not suggest such a potential. This guidance does not address issues of preclinical evaluation for signals of DILI, nor the detection and assessment of DILI after drug approval and marketing.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

[1] This guidance has been prepared by the Division of Gastroenterology Products in the Office of New Drugs, the Office of Medical Policy, and the Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA).

[2] This guidance uses the term *drug* or *product* to refer to all products, except whole blood and blood components, regulated by CDER and CBER, including vaccines, and uses the term *approval* to refer to both drug approval and biologic licensure.

Contains Nonbinding Recommendations

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND: DILI

DILI has been the most frequent single cause of safety-related drug marketing withdrawals for the past 50 years (e.g., iproniazid), continuing to the present (e.g., ticrynafen, benoxaprofen, bromfenac, troglitazone, nefazodone). Hepatotoxicity discovered after approval for marketing also has limited the use of many drugs, including isoniazid, labetalol, trovafloxacin, tolcapone, and felbamate (Temple 2001). Several drugs have not been approved in the United States because European marketing experience revealed their hepatotoxicity (e.g., ibufenac, perhexiline, alpidem). Finally, some drugs were not approved in the United States because premarketing experience provided evidence of the potential for severe DILI (e.g., dilevalol, tasosartan, ximelagatran). Although most significant hepatotoxins have caused predominantly hepatocellular injury, indicated by leakage of aminotransferase (AT) enzymes from injured liver cells without prominent evidence of hepatobiliary obstruction or intrahepatic cholestasis, the pattern of injury can vary. Many drugs cause cholestasis, but in general this condition is reversible after administration of the offending drug has stopped. Cholestatic injuries are less likely to lead to death or transplant, although there have been exceptions.

Drugs cause liver injuries by many different mechanisms. These injuries resemble almost all known liver diseases and there are no pathognomonic findings, even upon liver biopsy, that make diagnosis of DILI certain. Therefore, when possible DILI is suspected, it is essential to gather additional clinical and laboratory information necessary for differential diagnosis of the cause. It is important to observe the time course of the injury, and to seek alternative causes of the liver injury, such as acute viral hepatitis A, B, or C; concomitant use of a hepatotoxic drug or exposure to hepatotoxins; autoimmune or alcoholic hepatitis; biliary tract disorders; and circulatory problems of hypotension or right heart congestive failure that may cause ischemic or hypoxic hepatopathy. It is also prudent to assess the subject for previously existing liver disease, such as chronic hepatitis C or nonalcoholic steatohepatitis (NASH), that may or may not have been recognized before exposure to the experimental drug. It should be recognized that DILI may occur also in persons with preexisting liver disease as a superimposed problem.

Only the most overt hepatotoxins can be expected to show cases of severe DILI in the 1,000 to 3,000 subjects typically studied and described in a new drug application (NDA). Overtly hepatotoxic agents (e.g., carbon tetrachloride, chloroform, methylene chloride) are toxic to anyone receiving a large enough dose, and drugs that cause such predictable and dose-related injury generally are discovered and rejected in preclinical testing. More difficult to detect is toxicity that is not predictable or clearly dose-related that occurs at doses well tolerated by most people, but seems to depend on individual susceptibilities that have not as yet been characterized. Most of the drugs withdrawn from the market for hepatotoxicity have caused death or transplantation at frequencies in the range of ≤1 per 10,000, so that a single case of such an event rarely would be found even if several thousand subjects were studied. Severe DILI cases rarely have been seen in drug development programs of significantly hepatotoxic drugs.

Contains Nonbinding Recommendations

What are often seen during drug development are mild elevations of serum aminotransferases, usually without any symptoms. The problem is that these types of signals can be generated by drugs that are capable of causing severe DILI as well as by drugs that have a low potential for causing severe injury (e.g., aspirin, tacrine, heparin, hydroxyl-methylglutaryl coenzyme A-reductase inhibitors (*statins*)). Therefore, an approach is needed that can distinguish drugs likely to cause severe DILI from drugs unlikely to do so.

In general, the type of liver injury that leads to severe DILI is a predominantly hepatocellular injury. Hepatocellular injury is indicated by rises in AT activities in serum reflecting release of alanine or aspartate aminotransferase (ALT or AST) from injured liver cells. The ability to cause some hepatocellular injury, however, is not a reliable predictor of a drug's potential for severe DILI. Many drugs that cause transient rises in serum AT activity do not cause progressive or severe DILI, even if drug administration is continued. It is only those drugs that can cause hepatocellular injury extensive enough to reduce the liver's functional ability to clear bilirubin from the plasma or to synthesize prothrombin and other coagulation factors that cause severe DILI. It is important to identify those drugs as early as possible.

The drugs that have caused severe DILI in humans have not shown clear hepatotoxicity in animals, generally have not shown dose-related toxicity, and, as noted, generally have caused low rates of severe injury in humans (1 in 5,000 to 10,000 or less). One of the few exceptions to these findings is acetaminophen, whose toxicity can be shown in animal models and whose toxicity is clearly dose-related. These reactions thus appear to reflect host factors and individual susceptibility. Consequently, they have been termed *idiosyncratic*, meaning dependent upon the individual person's particular constitution. Whether they are the result of genetic and/or acquired differences has not yet been established, and to date no genetic, metabolic, or other characteristic has been found to reliably predict severe DILI in an individual.

Some severe DILI examples have presented differently from the more commonly seen hepatocellular idiosyncratic type. Perhexiline, an anti-anginal drug marketed in Europe, produced toxicity within months of starting the drug that had the histological appearance of alcoholic cirrhosis (Pessayre and Biachara et al. 1979). Fialuridine caused modest acute liver injury, but most strikingly led to severe metabolic acidosis and multiorgan failure as mitochondrial oxidative capacity was obliterated over a period of months (Kleiner and Gaffey et al. 1997; Semino-Mora and Leon-Monzon et al. 1997). Valproic acid causes hyperammonemic encephalopathy even without notable rises in serum AT activities. Benoxaprofen (Oraflex) induced intrahepatic cholestasis that over many months led to significant, sometimes fatal, liver injury, especially in elderly patients (Taggart and Alderdice 1982).

Past experience indicates that appropriate testing and analysis in premarketing trials can detect drugs that can cause severe hepatocellular injury.

III. SIGNALS OF DILI AND HY'S LAW

Hepatocellular injury (usually detected by serum AT elevations) can be caused by drugs that rarely, if ever, cause severe DILI (e.g., aspirin, tacrine, statins, and heparin) as well as by drugs

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that do cause such injury. Evidence of hepatocellular injury is thus a necessary, but not sufficient, signal of the potential to cause severe DILI (note, however, that the drugs causing hepatic injury through mitochondrial toxicity may not cause early hepatotoxicity). The frequency of serum AT elevations also is not a good indicator of a potential for severe DILI, because drugs such as tacrine (not a cause of severe DILI) can cause AT elevations in as many as 50 percent of patients. Very high levels of observed ATs may be a somewhat better indicator of potential for severe DILI, but the most specific indicator is evidence of altered liver *function* accompanying or promptly following evidence of hepatocellular injury (see below).

As noted, a typical NDA or biologics license application (BLA) database usually will not show any cases of severe DILI, even for a drug that can cause such injury, because the rate of severe injury is usually relatively low (1/10,000 or less). Many drugs, however, including both significant hepatotoxins and drugs that do not cause severe liver injury, cause laboratory evidence of mild, transient hepatic injury, with leakage of liver enzymes and the appearance in serum of elevations in AT activities to levels of 3, 5, and sometimes greater than 5 times the upper limits of normal (ULN). Generally, ALT is considered a somewhat more liver-specific aminotransferase enzyme than AST, although it also occurs in many tissues (Green and Flamm 2002). The finding of a higher rate of such elevations in drug-treated subjects than in a control group is a sensitive signal of a potential to cause severe DILI, but it is not a specific signal.

A more specific signal of such potential is a higher rate of more marked peak AT elevations (10x-, 15xULN), with cases of increases to >1,000 U/L causing increased concern. The single clearest (most specific) predictor found to date of a drug's potential for severe hepatotoxicity, however, is the occurrence of a small number of cases of hepatocellular injury (aminotransferase elevation) accompanied by increased serum total bilirubin (TBL), not explained by any other cause, such as viral hepatitis or exposure to other hepatotoxins, and without evidence of cholestasis, together with an increased incidence of AT elevations in the overall trial population compared to control. Increased plasma prothrombin time, or its international normalized ratio (INR), a consequence of reduced hepatic production of Vitamin K-dependent clotting factors, is another potentially useful measure of liver function that might suggest the potential for severe liver injury.

Recognition of the importance of altered liver function, in addition to liver injury, began with Zimmerman's observation that drug-induced hepatocellular injury (i.e., aminotransferase elevation) accompanied by jaundice had a poor prognosis, with a 10 to 50 percent mortality from acute liver failure (in pretransplantation days) (Zimmerman 1978, 1999). The reason for this now seems clear. Because the liver has a large excess of bilirubin-excreting capacity, injury to hepatocytes sufficient to cause jaundice or even mild hyperbilirubinemia (i.e., a bilirubin >2xULN) represents an extent of liver injury so great that recovery may not be possible in some patients. Zimmerman's observation that hepatocellular injury sufficient to impair bilirubin excretion was ominous has been used at the Food and Drug Administration (FDA) over the years to identify drugs likely to be capable of causing severe liver injury. The observation of the critical importance of altered liver function has been referred to informally as *Hy's Law* (Temple 2001; Reuben 2004).

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Hy's Law is essentially a translation of Zimmerman's observation that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. Thus, a finding of ALT elevation, usually substantial, seen concurrently with bilirubin >2xULN, identifies a drug likely to cause severe DILI (fatal or requiring transplant) at a rate roughly 1/10 the rate of Hy's Law cases. It is critical to rule out other causes of injury (e.g., other drugs or viral hepatitis) and to rule out an obstructive basis for the elevated bilirubin, so that alkaline phosphatase (ALP) should not be substantially elevated. In all cases to date, the small number of Hy's Law cases has arisen on a background of an increased incidence of more modest signs of hepatocellular injury (e.g., greater incidence of 3xULN elevations in AT than seen in a control group).

Briefly, Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo
2. Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

Finding one Hy's Law case in the clinical trial database is worrisome; finding two is considered highly predictive that the drug has the potential to cause severe DILI when given to a larger population. Clinical trials of the beta blocker dilevalol (enantiomer of labetalol, a diastereoisomeric mixture) showed two such cases in about 1,000 exposures. The drug was not approved in the United States, and examination of a postmarketing study in Portugal revealed fatal liver injury. Clinical trials of tasosartan, an angiotensin II blocking agent, showed a single Hy's Law case. This led to a request for a much larger premarketing database and the drug was abandoned.

Severe DILI can be estimated to occur at a rate of at least one-tenth the rate of the so-called Hy's Law cases (Temple 2001). This observation was recently confirmed in large studies of DILI in Spain (Andrade and Lucena et al. 2005) and in Sweden (Björnsson and Olsson 2005) in which approximately 10 percent of subjects with hyperbilirubinemia or jaundice died or needed liver transplants.

Recent examples of some drugs causing idiosyncratic hepatotoxicity (e.g., bromfenac, troglitazone, ximelagatran) further illustrate the predictive value of Hy's Law, where findings during clinical trials were noted and severe DILI occurred after marketing. These examples are described in detail in Appendix A.

Hy's Law cases represent one end of a spectrum of laboratory abnormalities that indicate liver injury. Each of these cases has different sensitivity and specificity as a predictor for the potential for severe liver injury. Although it is not possible to provide precise specificity and sensitivity

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estimates for the various signals, guidance can be provided on use of these major indicators of a potential for severe DILI, as follows:

- **An excess of AT elevations to >3xULN compared to a control group**

  AT elevations to >3xULN are relatively common and may be seen in all groups, but an excess of these elevations compared to a control group is nearly always seen for drugs that ultimately prove severely hepatotoxic at relatively high rates (1/10,000). Therefore, the sensitivity of a significantly increased incidence compared to control (e.g., of >3xULN AT elevations) as an indicator of a potential for liver injury is high. But many drugs show this signal without conferring a risk of severe injury (e.g., tacrine, statins, aspirin, heparin), indicating low specificity for an excess of AT elevations alone. There are no good data to predict how great this excess incidence of AT elevations should be compared to controls to suggest an increased risk of DILI. Such an excess may not be apparent for drugs with a potential to cause idiosyncratic DILI that are used for short treatment courses, such as many antibiotics.

- **Marked elevations of AT to 5x-, 10x-, or 20xULN in modest numbers of subjects in the test drug group and not seen (or seen much less frequently) in the control group**

  Many, but not all, severely hepatotoxic drugs show such elevations, indicating high sensitivity for predicting severe DILI; again, however, some drugs, such as tacrine and others that are not severely hepatotoxic, also can cause AT elevations to this degree, so that specificity of this finding is suboptimal.

- **One or more cases of newly elevated total serum bilirubin to >2xULN in a setting of pure hepatocellular injury (no evidence of obstruction, such as elevated ALP typical of gall bladder or bile duct disease, or malignancy, or impaired glucuronidation capacity caused by genetic (Gilbert syndrome) or pharmacologic (treatment with atazanavir or other drugs) factors), with no other explanation (viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs), accompanied by an overall increased incidence of AT elevations >3xULN in the test drug group compared to placebo**[3]

  The sensitivity of this observation appears high for any given incidence rate of severe DILI if enough people are exposed to the drug. For example, if the true incidence of severe injury is 1/10,000, and the rate of Hy's Law cases is 1/1,000, about 3,000 exposed subjects (*Rule of 3*) would be needed to have a 95 percent probability of observing at least one Hy's Law case in the treated population (Rosner 1995).[4] The specificity of this

[3] This constellation of findings is the hallmark of a Hy's Law case. The predictive value of these three findings for a drug's potential to cause DILI may be different if these findings are identified in patients with preexisting liver disease, fatty liver disease such as NASH, chronic hepatitis C or B, or bilirubin metabolism abnormalities (Gilbert syndrome), or in patients on drugs that treat liver disease or that inhibit bilirubin glucuronidation, such as indinavir or atazanavir (Zhang and Chando et al. 2005).

[4] The Rule of 3 is derived from simple binomial calculation. There will be at least a 95 percent chance of seeing one or more cases of DILI in 3n trial subjects if its true incidence is 1 in **n** subjects, and the group is well observed.

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finding appears very high if two or more cases are seen (e.g., dilevalol, bromfenac, troglitazone, ximelagatran). We are not aware of the occurrence of false positive Hy's Law findings for a drug that was subsequently found not to cause severe DILI in a larger treatment population. Therefore, the finding of two Hy's Law cases, and probably even one, is a strong predictor of a significant risk of severe liver injury. Failure to find a case, however, does not imply that a drug with AT elevations is free of a risk of severe DILI. The degree of assurance depends on the population exposed for a long enough time, the discontinuation rules used in the protocols, and the true incidence rate of severe DILI.

IV. CLINICAL EVALUATION OF DILI

A. General Considerations

For most drugs in development that reach phase 3 testing, the chances of encountering severe DILI are low. An increased incidence of mild hepatotoxicity (AT elevations) in early trials usually results in heightened screening to detect and evaluate liver injury during phase 3 testing. It is critical, however, to determine whether mild hepatotoxicity reflects a potential for severe DILI or reflects a capacity for only limited injury. To make this distinction, it is important to detect any cases of more severe injury and to examine such cases closely, observing the course and outcome of the injury, and seeking additional information that might identify other causes. The following general recommendations for evaluating and monitoring potential drug-induced hepatotoxicity may not be suitable for all situations and should be modified for special populations, such as people with preexisting liver disease or malignancies, and in light of accumulating data. In addition, clinical trials of cellular and gene therapies and of vaccines pose specific challenges related to trial size and design, biodistribution and persistence of vectors, the function and anatomic location of cellular products, and other factors. Applicants are encouraged to discuss these issues with the relevant review division.

1. Patients with Liver Abnormalities or Disease

Patients are sometimes excluded from clinical trials because of baseline liver test abnormalities or a history of liver disease, but there is no well-established reason to do this, except perhaps to avoid confusion between the previous disease and an effect of the test drug. Patients with acute viral, autoimmune, alcoholic, or other types of hepatitis are unstable and generally not appropriate subjects for clinical trials other than trials of treatments for their acute illness. Patients with stable underlying liver disease can be included cautiously in late-stage clinical trials, but probably not if bilirubin excretory or protein synthetic functions are impaired, unless there is a strong need that they be treated. This implies that diagnostic screening for liver test abnormalities should be conducted before enrolling subjects into trials. Patients with stable liver disease generally should be included in at least some phase 3 trials if they are likely to be treated with the drug if it is marketed. Preexisting liver disease has not been thought to make patients more susceptible to DILI (Zimmerman 1978, 1999), but it may be that a diminished *liver reserve* or the ability to recover could make the consequences of injury worse. This appears to be the case with highly active antiretroviral therapy in patients with chronic viral hepatitis. If the drug

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is intended to be prescribed or marketed to such patients after approval, they should be enrolled in controlled trials.

2. *Detection of DILI*

Depending on the mechanism underlying DILI, different drugs can be associated with different treatment time/hazard profiles. In many cases, there is a delay of at least a few weeks between initiation of treatment and onset of liver injury. However, for some drugs, rapid onset of injury may occur, sometimes in the presence of a systemic hypersensitivity reaction that can be associated with multi-organ involvement, fever, eosinophilia, and/or rash. In general, early trials of a drug in trial subjects with presumably normal liver function should involve obtaining liver enzyme (ALT, AST, ALP) and bilirubin tests every 2 to 4 weeks, at least for a few months. For drugs being studied with short treatment courses, both baseline and post-treatment liver enzyme testing should be performed, since there may be a gap between the end of treatment and the onset of liver injury. In circumstances when there is a high likelihood that such a drug will be chronically used in an off-label fashion, long-term treatment trials to measure risk for DILI may be warranted.

It is uncertain whether early and nonspecific symptoms (e.g., anorexia, nausea, fatigue, right upper abdominal discomfort, vomiting) precede or follow the first laboratory signs of hepatic injury (rising ALT, AST, or ALP), and the pattern of clinical and laboratory changes may vary with different drugs and recipients. In most cases, however, the first evidence of a problem is the discovery of elevated AT or ALP during routine serial measurements. In longer trials, if there is no sign of liver injury after a reasonable length of exposure (e.g., 3 months), the monitoring interval can be increased to once every 2 to 3 months. Later trials also can use less frequent liver chemistry monitoring if there is no indication of hepatotoxicity in earlier trials.

As previously noted, if symptoms compatible with DILI precede knowledge of serum chemical test abnormalities, liver enzyme measurements should be made immediately, regardless of when the next visit or monitoring interval is scheduled. In some cases, symptoms may be an early sign of injury and although typically less sensitive than serum enzyme elevations, they may indicate a need for prompt serum testing. Reliance on early symptoms, rather than serum enzyme monitoring, has become the standard for monitoring isoniazid therapy for prophylaxis of tuberculosis and seems to prevent severe liver injury if acted upon promptly by discontinuation of isoniazid (Nolan and Goldberg et al. 1999). Attention to symptoms does not supplant routine periodic assessment of AT, TBL, and ALP in trials of investigational drugs.

3. *Confirmation*

In general, an increase of serum AT to >3xULN should be followed by repeat testing within 48 to 72 hours of all four of the usual serum measures (ALT, AST, ALP, and TBL) to confirm the abnormalities and to determine if they are increasing or decreasing. There also should be inquiry made about symptoms. Serum AT may rise and fall quite rapidly, and waiting a week or two before obtaining confirmation of elevations may lead to a false conclusion that the initially observed abnormality was spurious. Of greater concern, delay in retesting may allow progression to severe worsening if the initial abnormality was the herald of a severe reaction to

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follow. The need for prompt repeat testing is especially great if AT is much greater than 3xULN and/or TBL is greater than 2xULN. For outpatient trials, or trials in which subjects are far away from the trial site, it may be difficult for the subjects to return to the trial site promptly. In this case, the subjects should be retested locally, but normal laboratory ranges should be recorded, results should be made available to trial investigators immediately, and the data should be included in the case reports. If symptoms persist or repeat testing shows AT >3xULN for subjects with normal baseline measures or 2-fold increases above baseline values for subjects with elevated values before drug exposure, it is appropriate to initiate close observation to determine whether the abnormalities are improving or worsening (see below). If close monitoring is not possible, the drug should be discontinued.

4. Close Observation

It is critical to initiate close observation immediately upon detection and confirmation of early signals of possible DILI, and not to wait until the next scheduled visit or monitoring interval. A threshold of aminotransferase levels greater than 3xULN seems reasonable, as lesser elevations are common and nonspecific. If additional testing, beyond that specified in the trial protocol, is carried out, it is important that the subject's information be added to the case report forms and database.

Close observation includes:

- Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.

5. Decision to Stop Drug Administration

It has been observed that *dechallenge* (stopping drug administration) does not always result in immediate improvement in abnormal lab values. Abnormal test values and symptoms may progress for several days or even weeks after discontinuation of the drug that caused the abnormality. For example, rising TBL usually follows serum AT increases by a few days to weeks. The primary goal of close observation is to determine as quickly as possible whether observed abnormal findings are transient and will resolve spontaneously or will progress. For most DILI, no specific antidotes are available (except N-acetylcysteine for acute acetaminophen

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overdose if given promptly, and, possibly, intravenous carnitine for valproic acid hepatotoxicity). Promptly stopping the offending drug usually is the only potentially effective therapy.

A difficult question is when should the investigational drug be stopped? Because transient fluctuations of ALT or AST are common, and progression to severe DILI or acute liver failure is uncommon, automatic discontinuation of trial drug upon finding a greater than 3xULN elevation of ALT or AST may be unnecessary. For most people, the liver appears capable of adapting to injury by foreign chemical substances, which may render a person tolerant to the drug despite continued exposure. Stopping a drug at the first hint of mild injury does not permit learning whether adaptation will occur, as it does for drugs such as tacrine, which cause liver injury but do not cause severe DILI. On the other hand, continuing drug appears unacceptably dangerous if there is marked serum aminotransferase elevation or evidence of *functional* impairment, as indicated by rising bilirubin or INR, which represent substantial liver injury. Although there is no published consensus on exactly when to stop a drug in the face of laboratory abnormalities and the decision will be affected by information on related drugs, the accumulating clinical experience, the clinical status of the patient, and many other factors, the following can be considered a basic guide. Discontinuation of treatment should be considered if:

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN **and** (TBL >2xULN **or** INR >1.5)
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

It should be noted that although these guidelines have not been evaluated systematically in a prospective fashion, they represent an approach that is similar to current practice.

6. Evaluating Data for Alternative Causes

An important purpose of close observation is to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, such as one of the following common causes:

- **Acute viral hepatitis.** The usual onset of hepatocellular DILI is indistinguishable from acute viral hepatitis A or B. Hepatitis C is much less often acute in its onset and tends to be insidious, but it sometimes can resemble acute DILI. The presence of acute viral hepatitis A, B, and C should be evaluated by serological markers. Viral hepatitis D (requires concomitant hepatitis B infection) and E are relatively rare in the United States. Hepatitis E is more common in developing countries, including Southeast Asia, and should be considered in recent travelers to those countries and in patients in trials conducted in those countries. Also rare are hepatocellular liver injuries caused by Epstein-Barr virus, cytomegalovirus, herpes simplex virus, toxoplasmosis, varicella, and parvovirus, although these infections are seen more typically in immuno-suppressed individuals. Adolescent and young adult patients with possible DILI should be tested for Epstein-Barr virus. Hepatitis is common among transplant patients with cytomegalovirus disease.

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- **Alcoholic and autoimmune hepatitis.** Acute alcoholic hepatitis usually is recurrent, with a history of binging exposure to alcohol preceding episodes, and it has some characteristic features, such as associated fever, leukocytosis, right upper quadrant pain and tenderness, hepatomegaly, and AST >ALT, that may help distinguish it from other causes of liver injury. Other features of the physical examination may include the presence of stigmata of cirrhosis, such as spider nevi, palmar erythema, estrogenic changes in males, and Dupuytren's contractures. Alcoholic and autoimmune hepatitis should be assessed by history, physical examination, and laboratory testing, including serologic testing (e.g., antinuclear or other antibodies).

- **Hepatobiliary disorders.** Biliary tract disease, such as migration of gallstones or intrahepatic lesions, more often causes cholestatic injury initially and should be investigated with gall bladder and ductal imaging studies, especially if ALP is increased. Malignant interruption of the biliary tract also should be considered.

- **NASH.** NASH may be seen in obese, hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels, and hepatic and sometimes splenic enlargement. It is sometimes associated with cirrhosis and portal hypertension.

- **Cardiovascular causes.** Cardiovascular disease, especially right heart failure and hypotension or any cause of impaired oxygenation of the liver, may cause acute centrilobular hypoxic cell necrosis (*ischemic hepatitis*) with rapid and sometimes spectacular increases of serum AT (e.g., AT >10,000 U/L). Cardiovascular dysfunction or impaired liver oxygenation, including hypotension or right heart failure, should be assessed by physical examination and history.

- **Concomitant treatments.** It is critical to discover concomitant treatments, including exposure to nonprescription and dietary supplement products that might be responsible for injury. Many people take multiple drugs, perhaps less often in controlled clinical trials because of exclusion criteria, but subjects may not report taking disallowed drugs or other agents. The possible exposure to potentially toxic herbal or dietary supplement mixtures (sometimes of unknown composition), nonprescription medications such as acetaminophen, or to occupational chemical agents may not be volunteered unless subjects are specifically questioned.

7. Follow-Up to Resolution

All trial subjects showing possible DILI should be followed until all abnormalities return to normal or to the baseline state. DILI may develop or progress even after the causative drug has been stopped. Results should be recorded on the case report form and in the database. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be DILI, indicating that liver injury was related to underlying liver disease.

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8. Rechallenge

Whether or not to rechallenge a subject who showed mild DILI is a difficult decision. Reexposure may initiate a sometimes explosive and more severe reaction, as was observed with halothane several decades ago. Some cases of DILI show indicators of immunological reaction such as eosinophilia, rash, fever, or other symptoms or findings, and it is possible that such cases are more prone to recur with reexposure. Rechallenge may not be considered *negative* unless the subject is exposed to and tolerates the same dose and treatment duration that preceded the original reaction. A *negative rechallenge* does not necessarily allow a conclusion that the drug did not cause the injury. Most people can adapt to xenobiotic substances, including new drugs, and develop tolerance for them. This has been observed even for drugs that can cause severe injury, such as isoniazid. The large majority of people showing hepatocellular injury while taking isoniazid recover fully or recover while continuing to take the drug, and some, but not all, can resume or continue taking the drug without further adverse consequence. If such tolerance has developed, the use of rechallenge to verify drug causation would give a false negative result.

Generally, rechallenge of subjects with significant AT elevations (>5xULN) should not be attempted. If such subjects are rechallenged, they should be followed closely. Rechallenge can be considered if the subject has shown important benefit from the drug and other options are not available or if substantial accumulated data with the test drug do not show a potential for severe injury. The subject should be made aware of the potential risk, and consent to the rechallenge, and the institutional review board consulted.

B. Research Opportunities

It is not known why only a few people show severe DILI in response to a hepatotoxic drug while others show nothing or seem to adapt. The current thinking is that both genetic and acquired factors may be important in determining the susceptibility to injury. Close observation provides a major opportunity to gather and store serial samples of blood and urine, to investigate characteristics of subjects who show evidence of mild or severe DILI, and to see how they differ from each other and from people who do not show any effects despite being similar in age, sex, and drug exposure. These serial samples can be studied by genomic, proteomic, and metabolomic methods to determine how subjects differ, and to seek biomarkers that identify the susceptible persons.

As part of the Critical Path Initiative,[5] the FDA is working with industry, academia, and other experts to broaden its understanding of the biochemical and genetic bases of DILI. It is hoped that predictive bioassays and biomarkers can be identified through analysis of systematically collected biospecimens that will help determine which patients are most likely to suffer liver injury from specific compounds. If tests that identify people susceptible to severe DILI can be developed, a drug that is hepatotoxic to them could remain available to other people who are not susceptible to severe DILI.

In addition, identification of common genotypic characteristics among patients experiencing DILI in response to one or more class-related hepatotoxic drugs might permit the development of

[5] See http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm.

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in vitro or ex vivo tests or genetically altered animal strains that can be used to better predict serious hepatotoxic potential, or the lack thereof, of new drugs belonging to the same or closely related classes.

C. Case Report Forms

Because DILI has resulted in the marketing withdrawal or cessation of development of many drugs, every clinical trial should include case report form pages specifically designed to capture information pertinent to the evaluation of treatment-emergent liver abnormalities. In addition to collecting information on laboratory abnormalities, clinical symptoms, and the potential cause of any hepatic illness, case report forms and narratives should include the following information for cases in which liver injury is found (including control subjects with such injury):

- Time and date from start of drug administration to start of illness.
- Time and date of cessation of drug, or interruption of drug administration.
- Complete description of the injury, including systemic symptoms, other organ involvement, rash, fever, and eosinophilia.
- Outcomes such as death, liver transplant, hospitalization, recovery, and treatment for DILI.
- Free text describing the course of illness, including pertinent physical examination findings, such as hepatomegaly, splenomegaly, right-upper quadrant tenderness, the time course of abnormalities of aminotransferases, ALP, TBL with dates of testing, normal ranges, and results for tests done in addition to those specified in the original protocol, and tests done during any unscheduled visits. These additional laboratory test results, including reference ranges, should also become part of the overall database. Supportive tabular and/or graphical display of serial laboratory data is often desirable in addition to narrative information. Pre-study AT values should be sought, which may suggest chronic liver disease and/or an acute process that may have preceded exposure to the investigational drug.
- Risk factors, especially history of alcohol use; risk factors for NASH such as diabetes, obesity, and hypertriglyceridemia, which may prompt ultrasound examination of the liver to detect steatosis.
- All concomitant drugs (dose, start and stop dates, whether they are known to be hepatotoxic, information on rechallenge or dechallenge with drugs with the same or similar structure).
- Evaluation of nondrug causes: recent hepatitis A, B, and C serology; evidence for biliary obstruction; imaging study results; acute alcoholic hepatitis (recent drinking and AST >2xALT are supportive); recent history of severe hypotension or congestive heart failure; other underlying viral disease.
- All supplemental information, including consultation reports, narrative information, and special studies.

Any potential Hy's Law case should be handled as a serious unexpected adverse event associated with the use of the drug and reported to the FDA promptly (i.e., even before all other possible causes of liver injury have been excluded). It should be promptly reported to the FDA before fully working up the patient to rule out other etiologies. Reporting should include all available

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information, especially that needed for evaluating the severity and likelihood that the drug caused the reaction, and should initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

D. Interpretation of Signals of DILI or Acute Liver Failure

1. Frequency and Magnitude of Liver AT Abnormalities

The presence of even a single case of severe liver injury resulting from treatment in the premarketing clinical trials database is a signal of a high level of hepatotoxic risk. More commonly, however, there will be no identifiable cases of severe liver injury, but rather varying degrees of serum AT abnormalities that need to be interpreted. As previously noted, slight abnormalities of this kind (to <3xULN) are common in untreated and placebo-treated subjects and are not informative about the potential for the development of severe DILI. Subjects with such abnormalities should be watched.

Therefore, it has become standard practice to look at greater deviations, such as AT values ≥3x-, 5x-, or 10xULN. Because these abnormalities are often associated with other causes, such as NASH or hepatitis C, they can occur in placebo-treated groups, and it is important to compare their incidence in drug-exposed subject groups to that observed in control groups (i.e., placebo or treatment with products that do not cause elevation of aminotransferases). A significantly increased incidence of AT abnormalities >3xULN is a signal of a potential for severe DILI, but, even though it has high sensitivity, it is not specific. Abnormalities of greater magnitude (e.g., ≥10xULN) are rarely seen spontaneously in placebo arms of clinical trials in most settings. Therefore, greater magnitude AT elevations can be examined in the entire clinical trials database, not just in the controlled trials. Serum AT activity is a relatively volatile measurement, often rising and falling within days. It cannot be concluded from one measurement that a peak value has been seen, so detection of an abnormal rise calls for serial measures to determine which way the abnormality is moving, whether increasing or decreasing.

A number of factors may confound interpretation of AT abnormalities seen in NDA or BLA databases. Although the more extreme AT elevations may be better predictors of toxicity than smaller elevations, close monitoring can affect the magnitude of abnormalities seen if it leads to earlier cessation of drug treatment. In addition, the contribution of drug treatment to an exacerbation of preexisting liver disease or the effects of concomitant hepatotoxic drugs may be difficult to determine. Finally, normalization of abnormalities on continued treatment is not proof that the abnormality was not drug-caused, as it can result from liver adaptation to the drug.

2. Combined Elevations of Aminotransferases and Bilirubin

When AT abnormalities indicating hepatocellular injury are accompanied by evidence of impaired hepatic function (bilirubin elevation >2xULN), in the absence of evidence of biliary obstruction (i.e., significant elevation of ALP) or some other explanation of the injury (e.g., viral hepatitis, alcohol hepatitis), the combined finding (i.e., Hy's Law cases) represents a signal of a potential for the drug to cause severe DILI. Experience has indicated that the occurrence of even

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one or two well-documented cases of this combination is ominous, indicating a likelihood that the drug will cause severe liver injury.

The absence of Hy's Law cases in an NDA or BLA database may allow an estimate of an upper limit of the rate for severe DILI, using the Rule of 3 derived from simple binomial calculation. There will be at least a 95 percent chance of seeing one or more cases of DILI in 3n trial subjects if its true incidence is 1 in **n** subjects, and the group is well observed. Thus, if no cases of AT and bilirubin elevations are seen in 3,000 well-observed subjects, it can be concluded with 95 percent confidence that the true rate of such occurrences is not more than 1 per 1,000. This calculation would then suggest a rate of expected severe liver injury ≤1 per 10,000 exposed patients, assuming that the rate of severe injury among patients with concomitant AT and TBL elevations is about 10 percent (Andrade and Lucena et al. 2005; Björnsson and Olsson 2005).

E. Analysis of Signals of DILI

Based on the FDA's experience, the following analyses related to liver injury potential should be carried out and included in an NDA or BLA, or included in an investigational new drug application when DILI is suspected and being evaluated.

1. Assessment of Drug Metabolism

The metabolism of a drug can markedly affect the safety profile of the drug. A drug may be metabolized to a hepatotoxic metabolite (e.g., acetaminophen, halothane, isoniazid). Most hepatotoxic drugs have been oxidatively metabolized by the CYP450 system.

2. Assessment of Liver-Related Adverse Events in Controlled Trials

Applicants should provide an analysis of the incidence of abnormalities in AT, bilirubin, and ALP levels seen in subjects in controlled trials with at least one dose of drug exposure. Generally, the analysis should be for pooled data, although trial-to-trial differences may be of interest. Incidence can be given as the number of events per number of subjects exposed, or can incorporate treatment exposure, as the number of events per subject-years of exposure, preferably both. Changes in mean values for groups are not informative. For many drugs, it appears that a minimum duration of exposure is needed before DILI occurs. Therefore, it is useful to describe liver-related adverse events for subjects who have had the minimum duration of exposure (e.g., subjects with at least 1-month exposure). For some drugs, patterns of early injury after initiation of treatment may occur, and for these patients testing intervals should be modified appropriately. Incidences for pooled data should include, but are not limited to:

- 3x-, 5x-, 10x-, and 20xULN elevations of AST, ALT, and either ALT or AST.
- Any elevations of bilirubin; elevated TBL to >2xULN.
- Any elevations of ALP >1.5xULN.
- Elevation of AT (>3xULN) accompanied by elevated bilirubin (>1.5xULN, >2xULN).
- Elevation of AT in temporal association with nausea, vomiting, anorexia, abdominal pain, or fatigue.

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- Possibly liver-related deaths and liver-related treatment discontinuations. These cases should be described and time-to-event analyses should be performed. Follow-up status also should be provided. There should be a description of any histologic and rechallenge data.

All incidences should be calculated separately for drug-, placebo-, and active-controlled groups. Normal ranges for all tests should be provided. Time-to-event analyses for events occurring with increased incidence should be provided (e.g., elevated AT, bilirubin). The contribution of sex, age, risk factors, and drug dose or regimen to the abnormalities seen should be explored.

3. Assessment of Liver-Related Adverse Events in the Entire Clinical Trials Database

Applicants should provide an analysis of the incidence of abnormalities in AT, bilirubin, and ALP levels for the entire clinical trials database, including subjects with exposure of at least one dose of trial drug in phase 1 or phase 2 trials, or in uncontrolled, open label, extension trials. We recommend the same evaluation as for the controlled trials database discussed in section IV.D.2. Time-to-event analyses of events occurring at increased incidence, and rates of death and trial withdrawal in subjects with abnormalities, should be provided. The contribution of sex, age, drug dose or regimen, use of concomitant drugs, and underlying disease to the abnormalities seen should be explored.

4. Assessment of Hy's Law Cases in the Clinical Trials Database

NDA and BLA submissions should include a listing of possible Hy's Law cases identified by treatment group (e.g., subjects with any elevated AT of >3xULN, ALP <2xULN, and associated with an increase in bilirubin ≥2xULN). A narrative summary for each Hy's Law case should be provided. Narrative summaries should not only provide, in text format, the data that are already presented in the case report tabulation, but also should provide a complete synthesis of all available clinical data and an informed discussion of the case, allowing for a better understanding of what the subject experienced. For a narrative summary to be useful, it should contain the following information:

- Subject's age, sex, weight, and height
- Discussion of signs and symptoms related to hepatotoxicity: type and timing to exposure
- Relationship of exposure duration and dose to the development of the liver injury
- Pertinent medical history
- Concomitant drugs with dates and doses
- Pertinent physical exam findings
- Test results (e.g., laboratory data, biopsy data and reports, with dates and normal ranges)
- Time course of serum enzyme and bilirubin elevations (consider tabular and/or graphical display of serial laboratory data)
- A summary of all available clinical information including, if known:
  - Prior or current history of ethanol use
  - Presence of risk factors for NASH (e.g., obesity, diabetes, marked hypertriglyceridemia)

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  - Evidence for pre- or co-existing viral hepatitis, or other forms of liver disease, pre-study AT values, if available
  - Symptoms and clinical course including follow-up to resolution
  - Special studies (i.e., ultrasound, radiologic examinations, liver biopsy results)
  - Presence or absence of possible confounders, including concomitant illness, use of concomitant drugs that are known hepatotoxins, such as acetaminophen
- Discussion of hepatotoxicity as supported by available clinical data and overall assessment of the treating physician, consultants, and applicants as to the likelihood of DILI
- Treatment provided
- Dechallenge and rechallenge results, if done
- Outcomes and follow-up information
- Copies of hospital discharge summaries, pathology and autopsy reports

The availability of liver biopsy, explant, or autopsy slides for pathology review by review staff or external expert consultants has been helpful in the FDA's assessment of Hy's Law cases. Reports of external consultant opinions solicited by the applicant should be provided to the FDA.

Applicants also should provide complete narrative summaries that include the components previously listed for all subjects who died of hepatic illness, or who discontinued trial drugs for hepatotoxicity, including subjects with abnormalities consistent with protocol-specific stopping rules.

In some cases, a drug under consideration in the United States will have been marketed in other countries. In these cases it is important for the applicant to provide a synopsis of the global safety experience and level of usage and to describe in detail all cases of hepatotoxicity observed or suspected.

5. Overall Assessment of a Drug's Potential to Cause DILI

The overall assessment should characterize a drug's potential for DILI and should consider at least the following questions:

- Was liver monitoring sufficiently frequent and thorough to characterize DILI risk?
- Were there any cases of probable severe DILI?
- Were there signals of a potential for DILI (e.g., AT elevations, Hy's Law cases) and how were these signals assessed?
- What doses and durations of exposure were associated with hepatotoxicity signals?
- What approximate incidence of mild, moderate, and severe DILI can be expected postmarketing?
- Is the trial information sufficient to inform an overall risk-benefit assessment?
- Was there sufficient drug exposure (i.e., number of trial subjects and duration of treatment of each trial subject) and adequate liver test monitoring to reliably set an upper boundary for risk of severe DILI after marketing?

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- What rate of severe injury (assuming Hy's Law cases occur at about 10 times the rate of severe injury) has been suggested or has been ruled out (e.g., no Hy's Law cases in 3,000 subjects implies a rate of such cases of <1/1,000 and thus a rate of severe DILI of <1/10,000)? This consideration should reflect the presence or absence of other signals, such as marked elevations of AT.
- Will some form of monitoring, by symptoms or serum testing, be needed? Usually, this would be considered only if there was evidence of severe liver injury or the potential for it. If so, effectiveness of monitoring, whether by symptoms or laboratory tests, and at what intervals should be discussed, and whether the results justify a monitoring recommendation in product labeling at the time of marketing approval.

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APPENDIX A: ILLUSTRATIVE EXAMPLES OF DILI

Duract (bromfenac)

Bromfenac was a nonsteroidal anti-inflammatory drug (NSAID) studied for both short-term analgesia and long-term arthritis treatment. There was little evidence of hepatotoxicity in the short-term analgesic trials, but during longer term clinical trials in arthritis, ALT elevations >3xULN were seen in 2.8 percent of patients on bromfenac, compared to none in placebo group. Among 1,195 exposed patients, there were two cases in which there was elevated TBL as well as AT elevation in the clinical trial data submitted for review in the NDA. Concerns about possible liver toxicity led to the approval of bromfenac in July 1997 for short-term use only and not for osteoarthritis or rheumatoid arthritis. As an NSAID, however, it was prescribed long-term off-label in arthritic patients, and severe hepatotoxicity emerged. Within 6 months of approval, reports of severe hepatic failure, including two cases requiring liver transplant, were received. All severe cases involved the use of bromfenac for more than 10 days, the maximum duration of treatment recommended in the labeling.

In response, the FDA and the manufacturer strengthened the warnings in the package insert with a boxed warning, and issued a Dear Health Care Professional Letter. Despite these efforts, the manufacturer and the FDA continued to receive reports of severe injuries, including reports of death or need for liver transplantation (Moses and Schroeder et al. 1999; Hunter and Johnston et al. 1999; Rabkin and Smith et al. 1999; Fontana and McCashland et al. 1999). Given the availability of other effective NSAIDs, bromfenac was withdrawn from the market in June 1998. The two Hy's Law cases in the long-term-exposed population of about 1,000 subjects during drug development predicted an occurrence of severe hepatotoxicity during chronic use at a rate of about 1/5,000 to 10,000 people. Following approval, rates of acute liver failure for bromfenac were estimated to be in the range of 1/10,000 (Goldkind and Laine 2006).

Rezulin (troglitazone)

Troglitazone was approved by the FDA in January 1997 for the treatment of Type 2 diabetes mellitus. In reviews of the clinical trials of troglitazone conducted before approval there were no cases of liver failure among 2,510 subjects exposed to the drug in the NDA database, but 1.9 percent of troglitazone-treated subjects had ALT >3xULN compared to 0.3 percent of placebo-treated subjects, 1.7 percent had ALT >5xULN, and 0.2 percent (5 subjects) had ALT >30xULN (2 subjects in the last group also experienced jaundice). The median duration of troglitazone therapy before peak ALT elevation was 121 days. In the Diabetes Prevention Trial at the National Institutes of Health (NIH) performed after approval, 4.3 percent of 585 troglitazone-treated subjects had ALT ≥3xULN, 1.5 percent had ALT >8xULN, and 2 subjects had ALT >30xULN, compared to 3.6 percent of subjects with ALT ≥3xULN in the placebo group (Knowler and Hamman et al. 2005). One of the subjects in the Diabetes Prevention Trial with ALT >30xULN developed liver failure and died, despite receiving a liver transplant. The

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second subject recovered. These data suggest that the rate of severe liver injury would be about 1 in 3,000 to 10,000.

After marketing, there were numerous reports of acute liver failure associated with troglitazone use (Gitlin and Julie et al. 1998; Vella and deGroen et al. 1998; Herrine and Choudary 1999), and four letters were sent to practicing physicians between 1997 and 1999, urging monthly monitoring and careful use. These letters did not significantly affect the monitoring done by physicians, and AT monitoring recommended in the Dear Health Care Professional Letters and in the package insert was not regularly performed (Graham and Drinkard et al. 2001). Moreover, an analysis of 94 cases of liver failure reported spontaneously to the FDA showed that the progression from normal hepatic test results to irreversible liver injury occurred in less than a month (the recommended monitoring interval) in 19 patients. The onset of injury began after 3 days to more than 2 years of troglitazone use (Graham and Green et al. 2003; Graham and Drinkard et al. 2003). Time from jaundice to hepatic encephalopathy, liver transplantation, or death usually was rapid, averaging 24 days. Troglitazone was withdrawn from the U.S. market in March 2000, when other drugs in the same class with similar efficacy but little or no evidence of hepatotoxicity became available (i.e., rosiglitazone, pioglitazone).

Apart from constituting another example of the predictive value of evidence of hepatocellular injury accompanied by even two cases of elevated bilirubin, there were other lessons learned from the troglitazone experience: 1) monitoring recommendations may not be well followed by physicians, even after warning letters are sent to all practicing physicians; and 2) some cases of severe hepatotoxicity occur rapidly, within less than a reasonable and practical recommended interval for monitoring, indicating that monitoring would provide at best only partial protection, even if recommendations were followed.

Exanta (ximelagatran)

Exanta (ximelagatran), an oral anticoagulant (antithrombin), was not marketed in the United States because of hepatotoxicity and other concerns discovered during clinical trials. Issues related to potential liver toxicity of ximelagatran were presented and discussed at an FDA advisory committee meeting in September 2004 (He 2004). During short-term clinical trials of the drug for prevention of thromboembolic complications after joint replacement surgical procedures, there was no increased rate of transaminase elevations in the ximelagatran group compared to the enoxaparin-warfarin group, and no serious hepatotoxicity was seen. But in longer term trials (more than 35 days) in patients with chronic atrial fibrillation to prevent embolic or thrombotic strokes, an increase in ALT >3xULN occurred in 7.6 percent of 6,948 patients compared to 1.1 percent of patients receiving warfarin treatment; and 1.5 percent of ximelagatran-treated patients had ALT >10xULN.

Increases in AT typically occurred 1 to 6 months after the initiation of ximelagatran administration with peak levels within 2 to 3 months postrandomization. Among the 531 ximelagatran patients with ALT >3xULN, 39 percent completed the trial on treatment,

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while 61 percent discontinued the drug. Almost all patients with ALT >3xULN returned to <2xULN whether the drug was stopped or not, although the return to normal was faster if ximelagatran was stopped. Of 18 patients who resumed drug after ALT returned to normal, only 2 had elevations recur. Concomitant elevations of ALT >3xULN and bilirubin >2xULN were observed in 37 of about 7,000 patients with ximelagatran and 5 of 6,230 patients with comparator. At least 13 of 37 patients in the ximelagatran group had no alternative explanation for the concomitant ALT and bilirubin elevation. Nine of the 37 patients died, but in most cases the deaths were not clearly hepatotoxicity-related. Only one autopsy was done and it showed a small, friable and diffusely mottled liver suggestive of severe diffuse hepatic necrosis, but liver failure from ximelagatran might have contributed to some of the other deaths (He 2004; Lewis 2006; Kaplowitz 2006; Senior 2006; Temple 2006). Because severe hepatotoxicity was observed in an orthopedic surgery trial in an extended treatment of 35 days, Exanta was withdrawn in February 2006 from the 22 countries in which it had been approved, and further development in the United States was abandoned.

Again, short-term tolerance of ximelagatran, with resolution of even substantial elevations of ALT in most cases, did not predict long-term safety. The relatively high rate of Hy's Law cases, about 0.2 percent or 1/500 (13 cases among 7,000 exposed patients), predicted the occurrence of severe hepatotoxicity, at a rate of about 1/5,000 (10 percent of the rate of Hy's Law cases). In fact, at least one death occurred among the 7,000 exposed patients from subsequent liver toxicity, further supporting such an estimate.

Appendix 8A. 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

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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

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Appendix 8B. 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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Appendix 8C. 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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Appendix 9. 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,

"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

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

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

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.

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

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

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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