Clementia Pharmaceuticals Inc.

Clinical Study Protocol

MO-Ped Trial

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Palovarotene in Subjects with Multiple Osteochondromas

Study Number: PVO-2A-201

Trial Registration
EudraCT: 2017-002751-28
NCT Identifier: NCT03442985

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Amendment 2: 23 April 2019

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Protocol Signature Page

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Palovarotene in Subjects with Multiple Osteochondromas

Signature of Approval for Protocol PVO-2A-201, Amendment 2 (23 April 2019)

CLEMENTIA PHARMACEUTICALS INC.
PPD

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Protocol Amendment Summary

This second amendment to the protocol for Study PVO-2A-201 was finalized on 23 April 2019. The following table summarizes major and minor changes.

Section	Change	Rationale
Major changes that affect the clinical conduct of the study:		
Synopsis (Table 1) Section 5.4 Section 8.4.6	Stipulated that only clinically significant abnormal clinical laboratory results at the EOT, which includes hematology parameters, will require retesting at the safety follow-up visit, rather than all abnormal clinical laboratory findings.	To limit unnecessary procedures to only those that are clinically significant, thereby decreasing subject burden.
Section 5.1 Section 6.4	Changed the definition of FOCBP from Tanner 2+ to age >13 years or post-menarchal, whichever is earlier.	To align with published guidelines on pregnancy testing of adolescents participating in clinical research.
Synopsis (Table 1) Section 8.4.6 (Table 7)	Added 25-hydroxyl vitamin D assessments at the discretion of the Investigator to evaluate changes in BMD.	To provide additional relevant laboratory measures for changes in bone density.
Section 8.5.3	Amended the requirement for a confirmatory DXA scan to only those that would result in a dose modification (ie, >5% loss in spine aBMD and -1 change from baseline in height-adjusted z-score in lumbar spine BMD).	The emerging BMD data showed significant variability and multiple false positives due to technical issues related to DXA assessments in children. Limiting confirmatory scans to those that may result in a dose modification decreases subject burden and radiation exposure without affecting subject safety.
Other changes that affect the clinical conduct of the study:		
Synopsis Section 4.1	Removed some of the age restrictions on subject enrollment for sites in the EU.	To indicate that enrollment is now open to subjects from 2 to <7 years of age at all clinical sites. The change was made following the favorable DMC assessment of the 6-month bone safety data from at least 20 skeletally immature subjects in the FOP program. This update, which is applicable to EU sites only, was implemented in accordance with previously established and approved plans.
Section 6.4	Defined effective and highly effective forms of birth control.	To align with the CTFG guidance for effective contraception. Note that this change has been in effect since 13 September 2018 per an addendum to the protocol and will now be formally incorporated into the protocol.
Section 8.4.6	Added that the Investigator should review the subject's condition to determine whether a missed clinical laboratory test or non-evaluable test should be repeated for that time point.	To provide guidance to the Investigator regarding missed clinical laboratory tests or non-evaluable laboratory tests.

Section	Change	Rationale
Synopsis and Table 1 Section 4.1 Overview of Study Design Section 8.1 Overview of Study Procedures	Stipulated that subjects enrolled in Japan will have on-site clinic visits every 3 months.	Requested by the Japanese regulatory authority.
Minor changes that do not affect the clinical conduct of the study:		
General	Corrected minor errors, clarifications, and formatting inconsistencies; updated persons responsible for study conduct.	To provide a current and clear presentation.
Title page Groups Responsible for the Conduct of the Study	Changed to sponsor address.	The sponsor's headquarters relocated sine the last protocol amendment
Groups Responsible for the Conduct of the Study	Revised the vendor contract information.	To ensure that contact information is up-to-date.
Section 1.3.3	Provided the FOP clinical study numbers and updated safety data from these studies.	To present the most recent safety data from the FOP program.
Section 4.3.3.4 (Table 5)	Updated observed palovarotene pharmacokinetic values in the pediatric population.	To present the most recent pharmacokinetic data from the FOP program.

CTFG, Clinical Trial Facilitation Group; DMC, Data Monitoring Committee; DXA, dual x-ray absorptiometry; EOT, end of treatment; EU, European Union; FOCBP, females of childbearing potential; FOP, fibrodysplasia ossificans progressiva.

Persons Responsible For Study Conduct

Task	Vendor or Responsible Person(s)
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Protocol Synopsis

Title	**MO-Ped Trial:** A Phase 2, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Palovarotene in Subjects with Multiple Osteochondromas.
Sponsor	Clementia Pharmaceuticals Inc.
Objectives	Primary Objective • To evaluate the efficacy of two dosage regimens of palovarotene compared with placebo in preventing new osteochondromas (OCs) in subjects with multiple osteochondromas (MO) due to exostosin 1 (Ext1) or exostosin 2 (Ext2) mutations. Secondary Objectives Secondary objectives will be to compare the following effects of palovarotene with placebo: • The volume of OCs as assessed by magnetic resonance imaging (MRI). • The proportion of subjects with no new OCs. • The rate of new or worsening skeletal deformities. • The rate of MO-related surgeries. Additional secondary objectives: • Overall palovarotene safety. • The pharmacokinetics of palovarotene at steady-state. • The palatability of drug product when sprinkled onto specific foods. Exploratory Objectives Exploratory objectives will be to compare the following effects of palovarotene with placebo: • The changes in volume of OC cartilage caps as assessed by MRI. • The rate of new or worsening functional limitations. • Pain and pain interference due to OCs. • Quality of life.
Study Design	Study PVO-2A-201 will be a multicenter, randomized, double-blind, placebo-controlled study assessing various aspects of disease progression in pediatric subjects with MO. The primary efficacy analysis will compare the effect of two palovarotene dosage regimens with placebo on the rate of new OCs over 2 years. The study will also compare the changes from baseline in the total volume of OCs as assessed by MRI, the rate of new or worsening skeletal deformities, the rate of new or worsening functional limitations, the rate of MO-related surgeries, pain due to OCs, and quality of life. To ensure consistency in assessments of OCs and deformities, imaging by whole body MRI and radiographs of the upper and lower extremities will be interpreted by a treatment-blinded central imaging laboratory using standardized procedures. For sites in the European Union, subjects from 7 to less than 15 years of age were to be enrolled first. Younger subjects (2 to <7 years of age) were to be enrolled after the 6-month bone safety data from at least 20 skeletally immature subjects in the palovarotene fibrodysplasia ossificans progressiva (FOP) program were deemed favorable by the independent Data Monitoring Committee (DMC). On 28 January 2019, a favorable decision by the DMC permitted enrollment of subjects from 2 to 14 years of age in the European Union.

Protocol Synopsis

Study Design (cont.)	Prior to enrollment, tolerance for the MRI procedure will be assessed in subjects ≤7 years of age and in subjects who are deemed by the Investigator to require procedural sedation. A pediatric sedation team will perform assessments of the level of procedural sedation the subject may require to complete an MRI session. At baseline, eligible subjects will be examined with whole body MRI and radiographs of the upper and lower limbs to determine the number, size, and location of OCs, joint deformities, and other skeletal abnormalities. On Study Day 1, eligible subjects will be randomized 1:1:1 to one of two active treatments (weight-adjusted daily dose equivalent to 2.5- or 5.0-mg palovarotene, administered orally) or placebo, stratifying by age, sex, and Ext1/2 mutation. Alternating on-site and remote visits (eg, at home or at a local medical facility) will occur every 3 months unless the Investigator deems that a site visit is necessary or the subject is in enrolled in Japan. Urine pregnancy tests will be performed each month for females of childbearing potential. At the site visits every 6 months, most procedures performed at baseline (including knee and hand/wrist radiographs for the assessment of growth plates and dual x-ray absorptiometry [DXA]) will be repeated. Whole body MRIs and upper/lower limb radiographs will be performed every 12 months. Subjects will undergo all assessments and procedures specified in the Schedule of Assessments provided in Table 1. At the end of the study, subjects will have the option of participating in an open-label extension study (PVO-2A-202).
Number of Subjects	Approximately 240 subjects will be enrolled; 80 per treatment group.
Number of Sites	Approximately 30 investigational sites.
Study Population	Inclusion Criteria Subjects must meet all the following criteria to be eligible for enrollment: 1. Written, signed, and dated informed subject/parent consent and age-appropriate assent (performed according to local regulations). 2. A clinical diagnosis of MO with a disease-causing Ext1 or Ext2 mutation confirmed by a central laboratory. 3. Male and female subjects with a chronological age of 2-14 years, inclusive. 4. Female subjects must be premenarchal at screening. 5. Bone age at screening of ≤14 years, 0 months per the Greulich-Pyle method as assessed by a central reader. 6. Symptomatic MO, defined as the occurrence of any one of the following at screening: • Five or more clinically-evident OCs and the presence of a new or enlarging OC in the preceding 12 months. • Five or more clinically-evidence OCs and the presence of a painful OC. • A skeletal deformity. • A joint limitation. • Prior surgery for a MO-related complication. 7. If a subject had a prior surgery for MO, the subject should not be screened until at least 8 weeks post-surgery to allow for at least 12 weeks of stabilization of symptoms prior to first dose. Surgical orthopedic implants are allowed if they were in situ for ≥12 weeks prior to the baseline MRI. 8. If a subject is currently receiving pain medications, the dose must be stable (ie, <20% variance) for 2 weeks prior to screening.

Protocol Synopsis

Study Population (cont.)

9. The ability to undergo whole body MRI with or without sedation/general anesthesia.
10. Male and female subjects of child bearing potential who are heterosexually active must agree to use two effective methods of birth control, one of which must be highly effective during treatment and for 1 month after treatment discontinuation, unless they commit to true abstinence from heterosexual sex. Heterosexually active females of child bearing potential (FOCBP), must also agree to start effective methods of birth control at screening. An FOCBP is defined as a female who is ≥13 years of age or is post-menarchal, whichever is earlier.
11. Subjects must be accessible for treatment with study drug and follow-up.

Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for enrollment:

1. A weight <10 kg.
2. Other known syndromic conditions such as Langer-Giedion or Potocki-Shaffer syndromes.
3. Any subject with neurologic signs suggestive of spinal cord impingement.
4. If subject is 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. For eligibility, no washout is required prior to the first dose of study drug.
5. Exposure to synthetic oral retinoids within 4 weeks prior to enrollment.
6. Concurrent treatment with tetracycline or any tetracycline derivatives, due to the potential increased risk of pseudotumor cerebri.
7. History of allergy or hypersensitivity to retinoids, gelatin, or lactose (other than lactose intolerance).
8. Concomitant medications that are strong inhibitors or inducers of cytochrome P450 (CYP450) 3A4 activity.
9. Amylase or lipase >2 times the above the upper limit of normal (>2×ULN) or with a history of chronic pancreatitis.
10. Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5x ULN.
11. Fasting triglycerides >400 mg/dL with or without therapy.
12. Subjects with uncontrolled cardiovascular, renal, hepatic, pulmonary, gastrointestinal, endocrine, metabolic, ophthalmologic, immunologic, psychiatric, or other significant disease. These include subjects requiring glucocorticoid at doses >0.2mg/kg or up to 10 mg prednisone equivalent daily.
13. Subjects experiencing suicidal ideation (type 4 or 5) or any suicidal behavior within the past month or any suicidal behavior within the past year as defined by the Columbia-Suicide Severity Rating Scale (C-SSRS).
14. Subjects unable or unwilling to complete the study or all study-related procedures, including imaging.
15. Any surgical implant that is contraindicated for MRI. Dental braces are permitted.
16. Participation in any clinical research study within 4 weeks prior to enrollment or simultaneous participation in any clinical research study.
17. 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.

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Investigational Product Dose/Route/Regimen

Palovarotene is 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.

Palovarotene 2.5 mg (adjusted for weight as shown in the table) / taken orally with food / at approximately the same time once daily, preferably immediately following the first meal of the day, for 24 months.

Palovarotene 5.0 mg (adjusted for weight as shown in the table) / taken orally with food / at approximately the same time once daily, preferably immediately following the first meal of the day, for 24 months.

Weight range category	5.0-mg Equivalent	2.5-mg Equivalent
10 to <20 kg	2.5 mg	1.0 mg
20 to <40 kg	3.0 mg	1.5 mg
40 to <60 kg	4.0 mg	2.0 mg
≥60 kg	5.0 mg	2.5 mg

Comparator Product Dose/Route/Regimen

Placebo is supplied as powder-filled hard gelatin capsules / taken orally with food / at approximately the same time once daily, preferably immediately following the first meal of the day, for 24 months.

Efficacy Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint will compare palovarotene with placebo on the annualized rate of new OCs as assessed by whole body MRI.

Secondary Efficacy Endpoints

Secondary efficacy endpoints will compare palovarotene with placebo on the following:

- The change from baseline in the total volume of OCs as assessed by whole body MRI at Months 12 and 24.
- The proportion of subjects with no new OCs as assessed by whole body MRI at Months 12 and 24.
- The annualized rate of new or worsening deformities as assessed by radiographic imaging of both upper and lower limbs.
- The annualized rate of MO-related surgeries. Surgeries include any procedure indicated for the treatment of MO, such as an excision of a symptomatic OC or correction of a limb deformity.

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Efficacy Endpoints (cont.)	Exploratory Efficacy Endpoints Exploratory endpoints will compare palovarotene with placebo on the following: • The change from baseline in the total volume of cartilage caps of OCs as assessed by whole body MRI at Months 12 and 24. • The annualized rate of new or worsening functional limitations. Functional limitations are defined as restrictions in joint range of motion. • The effect of pain on daily activities, as assessed with the Patient Reported Outcomes Measurement Information System (PROMIS) pain interference pediatric item bank at Months 6, 12, 18, and 24. • Pain intensity, as assessed with the Faces Pain Scale – Revised (FPS-R) at Months 6, 12, 18, and 24. • Quality of life, as assessed with the Pediatric Quality of Life Inventory (PedsQL, version 4.0) at Months 6, 12, 18, and 24.
Other Endpoints	Pharmacokinetic Endpoint • To evaluate the pharmacokinetics of palovarotene at steady-state. Palatability Endpoint • To evaluate the palatability of drug product versus placebo when sprinkled onto specific foods following the first dose and at Month 1.
Safety Assessments	• Adverse events and serious adverse events: 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. • Electrocardiograms, vital signs (temperature, respiratory rate, blood pressure, and heart rate), physical examination, body weight and height, and laboratory parameters (hematology, biochemistry, and urinalysis). • Pregnancy tests (blood or urine) performed each month for female subjects of childbearing potential. • Growth will be assessed by o Measures of linear height (by stadiometer) and bilateral knee height (by knee caliper) in triplicate every 6 months. o Growth plate assessment by radiographs of the knee and hand/wrist every 6 months. o Bilateral bone (ulna, radius, tibia, fibula, and femur) lengths by radiograph every 12 months. • Bone mineral density at the lumbar spine, hip, and mid-third radius will be assessed with DXA every 6 months. • Presence of potential osteonecrosis of the hip, shoulders, and knees assessed by MRI every 12 months. • Sexual development: Tanner staging will be performed at baseline and every 12 months. • Columbia-Suicide Severity Rating Scale (C-SSRS): subjects 8 years of age and older will be assessed for suicidal ideation and behavior every 3 months using the age appropriate form of the C-SSRS.

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Genotyping	Central laboratory genotyping will confirm the presence of a disease-causing Ext1 or Ext2 mutation prior to randomization. Any subject found not to have a relevant mutation will not be randomized.
Monitoring	A Data Monitoring Committee (DMC) will oversee the safety of subjects during the study. The DMC can recommend changes to the conduct of the study or temporarily stop the study at any time for significant safety concerns. The DMC Charter includes safety stopping and dose modification rules. One interim efficacy analysis is planned when subjects complete 12 months of treatment (see Statistical Analysis). Based on the interim results, the DMC may recommend stopping the study early for efficacy or futility, or moving subjects from one palovarotene treatment group to the other.
Statistical Analysis	The primary efficacy endpoint is the annualized rate of new OCs as assessed by whole body MRI. The primary efficacy analysis comparing the rate of OCs between palovarotene-treated subjects and placebo-treated subjects will be conducted using a negative binomial regression model. Covariates in the model will include treatment group indicators, baseline age, sex, and Ext1/2 mutation status. An offset variable equal to the log of the number of years of follow-up will also be included. The estimated rate ratio comparing the rate of OCs between palovarotene-treated subjects and placebo-treated subjects and the associated Wald statistics will be used for hypothesis testing. The primary efficacy hypothesis testing will compare 5.0-mg palovarotene with placebo and 2.5-mg palovarotene with placebo; the multiple comparisons will be accounted for with a Bonferroni adjustment. There will be one interim efficacy analysis (planned for when all subjects complete 1 year of treatment) and a final analysis. The O'Brien-Fleming alpha-spending function will be used to specify the alpha-level threshold for determining treatment effect significance at the interim and final analyses. Assuming 50% statistical information at the interim analysis, the one-sided p-value significance threshold used in the interim analysis comparing the 5.0-mg palovarotene and placebo groups and the 2.5-mg palovarotene and placebo groups is 0.0007. Likewise, the one-sided p-value significance threshold in the final analysis will be 0.0122. Study success is defined as having one or both palovarotene groups demonstrate a statistically significant treatment effect. The sample size was determined via simulation using information from an MO patient registry. Assuming 80 subjects will be randomized to each treatment group, and a 50% palovarotene treatment effect in one treatment group and no effect in the other, the probability of declaring study success at the interim analysis is 0.34, whereas the overall probability of study success is 0.87. If there is a 50% palovarotene treatment effect for both dosage regimens, the probability of declaring study success at the interim analysis is 0.49 and the overall probability of study success is 0.95.

Table 1. Schedule of Assessments

	Screening	Baseline[1]/ Treatment	Treatment				End of Treatment	Safety Follow-up[3]	
	-35 Days	Study Day 1	Month 1 ±7 Days	Months 3, 9, 15, 21 ±7 Days[2]	Months 6, 18 ±7 Days	Month 12 ±7 Days	Month 24 ±7 Days	4 Weeks After EOT	6 Months After EOT
Assessment/Procedure	**Site**	**Site**	**Remote[4]**	**Remote[4]**	**Site**	**Site**	**Site**	**Remote[3,4]**	**Site**
Informed consent/assent	X								
Assessment of inclusion/exclusion criteria	X	X							
MRI sedation screening[5]	X								
Knee and hand/wrist radiograph for assessment of growth plate[6]	X				X	X	X		X
Genotyping[7]	X								
Linear growth assessment (via stadiometry) and bilateral knee height (via caliper)[8]		X			X	X	X		X
Medical history	X[9]								
Physical examination	X	X			X	X	X		X
Hearing and visual acuity tests[10]		X				X	X		
Tanner staging[11]		X				X	X		
Columbia-Suicide Severity Rating Scale[12]	X			X	X	X	X		
PedsQL, PROMIS, FPS-R[13]		X			X	X	X		
Joint range of motion[14]		X			X	X	X		
Body weight	X	X		X	X	X	X		
Vital signs	X	X		X	X	X	X	X	X
Electrocardiogram	X	X				X	X		
Hematology	X	X		X[15]	X	X	X	X[3]	X[3]
Biochemistry (includes lipids)	X	X		X[15]	X	X	X	X[3]	X[3]
Parathyroid hormone[16]		X		X[16]					
Pharmacokinetics[17]			X						
Urinalysis	X	X		X[15]	X	X	X	X[3]	X[3]
Blood pregnancy test[18]	X			X	X	X	X		
Urine pregnancy test[19]		X	Every month except at visits where blood samples are obtained[20]					X	X

Table 1. Schedule of Assessments

	Screening	Baseline[1]/ Treatment	Treatment				End of Treatment	Safety Follow-up[3]	
	-35 Days	Study Day 1	Month 1 ±7 Days	Months 3, 9, 15, 21 ±7 Days[2]	Months 6, 18 ±7 Days	Month 12 ±7 Days	Month 24 ±7 Days	4 Weeks After EOT	6 Months After EOT
Assessment/Procedure	**Site**	**Site**	**Remote[4]**	**Remote[4]**	**Site**	**Site**	**Site**	**Remote[3,4]**	**Site**
Whole body MRI[10]		X				X	X		
Radiographs of upper/lower limbs (weight bearing)[10]		X				X	X		
DXA[10]		X			X	X	X		X
Randomization via IWRS		X							
Study drug dispensing[21]		X			X	X			
Study drug accounting					X	X	X		
Study drug treatment[22]		Study drug treatment (QD)							
Palatability of sprinkled drug product[23]		X	X						
Prior/concomitant medications	At every subject contact								
Inquiry of MO-related surgeries	At every subject contact								
Adverse events	At every subject contact								

1 Baseline procedures are to be performed prior to any study drug administration.

2 Visit times should follow the original scheduled visit whenever possible.

3 Two safety follow-up visits are required for subjects who do not participate in the open-label extension study. Only clinically significant abnormal safety laboratory result(s) observed at the end-of-treatment visit are to be repeated at the safety follow-up visit. If the safety laboratory results are normal or if abnormalities are not clinically significant at the 4-week safety follow-up visit, they do not need to be repeated at the 6-month safety follow-up visit. The 4-week safety follow-up visit will be performed remotely at the subject's home by qualified study personnel, or at a local medical facility, unless the Investigator deems that a clinic visit is necessary.

4 Remote visits will take place at Months 1, 3, 9, 15, 21, and 4 weeks after EOT. If deemed necessary by the Investigator or the subject is enrolled in Japan, remote visits will be substituted with site visits. In months where there is no scheduled clinic visit, remote visits for urine pregnancy testing will be performed at the subject's home by qualified study personnel, or at a local medical facility, unless the Investigator deems that a clinical visit is necessary.

[5] Any subject deemed by the Investigator to require procedural sedation will be assessed by a pediatric sedation team to determine the subject's tolerance for MRI and the level of sedation required for completion of the MRI procedures. Screening will be performed by a pediatric sedation team based on (but not limited to) age, gender, the ASA-PS class, and comorbidities.

[6] Hand/wrist and knee radiographs will be obtained at screening and every 6 months. Whenever possible, the left hand and left knee should be used. However, if a surgical procedure has been performed in the past year then the other limb should be used. The same hand/wrist and knee should be used in the subsequent assessments. The screening hand and knee radiographs will be used to determine bone age at screening and serve as baseline for safety assessments. Once a subject has achieved 100% skeletal maturity (ie, complete fusion of growth plates) as determined by the knee and hand/wrist radiographs, further radiographs will not be necessary. If 100% skeletal maturity is not achieved at both anatomical regions, then only the region that is still maturing needs to be monitored.

[7] Genotyping will be conducted on each subject, regardless of whether prior genotyping was performed.

[8] Measurements of linear growth (via stadiometer) and bilateral knee height (via caliper) will be performed in triplicate. If a subject does not exhibit any growth from the preceding 6-month height measure, the subject will have his/her height reassessed after 3 months at the site to confirm growth retardation.

[9] Medical history at screening will include prior MO-related surgeries and all history related and not related to MO.

[10] Assessments/procedures may be performed within a ±4-week visit window.

[11] Tanner staging will continue on an annual basis until Tanner Stage V is reached.

[12] C-SSRS for subjects 8 years of age and older. The screening C-SSRS will be used as baseline.

[13] For the PedsQL, the teen report form will be used for ages 13-18; the child report form for ages 8-12; the parent report form for young children ages 5-7 and the parent report for toddlers ages 2-4; the PROMIS assessment will use the pain interference pediatric short form for subjects ages 8-14 years and parent proxy short form for ages 2-7 years; the FPS-R is appropriate for the assessment of pain intensity for subjects from ≥4 years of age.

[14] Range of motion will be measured using a goniometer by a treatment-blinded, trained assessor.

[15] Hematology, biochemistry, and urinalysis at Months 15 and 21 are waived if no clinically significant laboratory abnormalities are observed during the first 12 months of study treatment.

[16] Parathyroid hormone levels will be obtained at baseline and assessed with 25-hydroxy vitamin D, as-needed by the Investigator, for evaluation of changes in BMD.

[17] Pharmacokinetic sampling should be performed at Month 1. A qualified site personnel may obtain pharmacokinetic samples during a remote visit. Samples will be obtained pre-dose, and at 3, 6, 10, and 24 hours post-dose. If samples cannot be obtained at Month 1, then one additional attempt will be made at a subsequent visit.

[18] In FOCBP, serum pregnancy tests will be performed at visits where blood sampling was obtained.

[19] On Study Day 1, a urine pregnancy test will be performed instead of a serum pregnancy test to confirm eligibility for FOCBP. Urine pregnancy tests will be performed at the EOT safety follow-up visits for FOCBP.

[20] Remote visits for urine pregnancy testing will be conducted in FOCBP only. Urine pregnancy tests will not be performed at visits where blood samples are obtained (except for Study Day 1; see Note 15). Urine pregnancy remote visits will occur on Months 2, 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, and Months 15 and 21 if no blood samples were obtained.

[21] Study drug may be dispensed at 3-month intervals if necessary.

[22] Palovarotene or placebo will be administered as 2.5- or 5.0-mg weight-adjusted equivalent doses as in Table 6.

[23] Palatability will we assessed with a 5-point hedonic face scale in subjects ≥4 years of age who sprinkle the drug product or placebo onto a spoonful of specific foods.

ASA-PS, American Society of Anesthesiologists – Physical Status; BMC, bone mineral content; BMD, bone mineral density; C-SSRS, Columbia–Suicide Severity Rating Scale; DXA, dual x-ray absorptiometry; EOT, end of treatment; FOCBP, females of child-bearing potential; FPS-R; Faces Pain Scale – Revised; IWRS, Interactive Web Response System; MRI, magnetic resonance imaging; OLE, open-label extension; PedsQL, Pediatric Quality of Life Inventory; PROMIS, Patient-Reported Outcomes Measurement Information System; QD, once daily.

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List of Abbreviations

Abbreviation	Expanded Form
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASA-PS	American Society of Anesthesiologists Physical Status
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	area under the plasma concentration-time curve over 24 hours
BEIR	biologic effects of ionizing radiation
BMD	bone mineral density
BMP	bone morphogenetic protein
CFR	Code of Federal Regulations
C_{max}	maximum or peak measured plasma concentration
COPD	chronic obstructive pulmonary disease
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	CYP450 isoform
DMC	Data Monitoring Committee
DXA	dual x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form
ED_{50}	dose at half-maximum response
EOT	end-of-treatment
EU	European Union
Ext	exostosin gene
FAS	Full Analysis Set
FDA	United Sates Food and Drug Administration
FGF	fibroblast growth factor
FOCBP	female of child-bearing potential
FOP	fibrodysplasia ossificans progressiva
FPS-R	Faces Pain Scale – Revised
$Fsp1\text{-}Ext1^{CKO}$	fibroblast-specific protein 1 conditional Ext1 knockout
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practice
HDL	high-density lipoprotein
HO	heterotopic ossification
HS	heparan sulphate
HNSTD	highest non-severely toxic dose

List of Abbreviations

Abbreviation	Expanded Form
HSPG	heparan sulphate proteoglycans
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IOR	Instituto Orthopedico Rizzoli
IRB	Institutional Review Board
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MO	multiple osteochondromas
MRI	magnetic resonance imaging
OC	osteochondroma
OMIM	Online Mendelian Inheritance in Man
PCS	potentially clinically significant
PedsQL	Pediatric Quality of Life Inventory
PG	proteoglycans
PP	Per Protocol Set
PS	Pharmacokinetic Set
PROMIS	Patient Reported Outcomes Measurement Information System
QD	once daily
RAR	retinoic acid receptor
RARγ	retinoic acid receptor gamma
REM	Registry for Multiple Exostoses
ROM	range of motion
SS	Safety Set
SD	standard deviation
SOP	standard operating procedure
ULN	upper limit of normal
US	United States
VLDL	very low-density lipoprotein

1 Introduction

1.1 Multiple Osteochondromas

Multiple osteochondromas (MO), or multiple hereditary exostoses (MHE), is an autosomal-dominant skeletal disorder primarily caused by loss-of-function mutations in exostosin 1 (Ext1) or exostosin 2 (Ext2) genes, with almost complete penetrance (>95%). About 10% of individuals with MO have de novo mutations. Although rare, with prevalence estimated at 1 per 50,000 population in the United States (US) and Europe, MO is among the most common inherited skeletal disorders.[1–3]

The key clinical features of MO are benign cartilage-capped bone tumors emerging from the growth plates of long bones, ribs, vertebrae, and pelvis, known as osteochondromas (OCs).[3–5] Osteochondromas are caused by dysplasia in the periphery of the growth plate due to a disruption in chondrocyte maturation and perichondral bone formation.[6] Osteochondromas begin to develop and continue to grow during the first and second decades of life, and cease development and growth when growth plates close at puberty.[4] Thus, MO is a disease that manifests exclusively in children, with a mean age at diagnosis/onset of about 4 years.[1,7]

Patients with MO have considerable variability in the number of anatomical sites with OCs. An analyses of registry data from 529 European-based pediatric and adult patients with MO showed 62% had from 5-20 OCs and 19% had more than 20 OCs.[8] In most patients, OCs involve the hands, proximal humerus, distal radius and ulna, distal femur, and the proximal and distal tibia and fibula. Less common sites include the proximal femur the vertebrae, talus, clavicle, navicular bone, proximal radius, and pubis.[1,9] The development and growth of OCs often result in a broad range of skeletal sequelae. About two-thirds of patients with MO experience orthopedic complications such as limb-length discrepancies, restricted range of motion, varus and valgus deformities, short stature, spinal stenosis, and scoliosis.[4,5,9] The severity of the sequelae varies considerably, from patients with few OCs experiencing minimal restrictions in joint range of motion, minimal deformities, and no pain; to those with severe physical disabilities and pain.[1,2,8]

With the high incidence of OCs near joints, impaired articular function is a common reason for restricted movement and physical dysfunction affecting patients' quality of life and social well-being. Positive correlations are observed between the number of OCs, disease severity, and number of surgeries, with the latter negatively correlated with quality of life.[8,10] Yet excisions are common—a US-based analysis of medical records reported 66% of patients with MO having at least one operation to remove OCs.[9]

Pain is another prominent clinical feature of MO that has a pervasive effect on quality of life. In a national cohort study of 283 patients with MO in the Netherlands (including 99 children with a mean age of 9 years), pain was present in 76% of cases.[2] In children, pain affected sleep, and was exacerbated by walking, cycling, sports, playing, and lifting objects. Additionally, MO resulted in functional limitations in school, such as difficulty with (or withdrawal from) sports, and problems with writing and the use of computers. Difficulties associated with MO persisted into adulthood and continued after the growth of OCs had ceased. Adults reported cessation of sporting activities, and some either needed to change their occupation or were medically unfit to

work. A similar study of Italian subjects found that 46% of adults and 27% of children were unable to participate in sports activity due to MO.[10]

Currently there is no medicinal treatment to prevent the development of OCs and the clinical sequelae of skeletal deformities, functional limitations, and pain. Surgical excisions are performed when OCs cause pain, restrict function, or lead to cosmetic complaints, but carry a risk of irreversible damage to growth plates.[4,11] Thus, there is a significant unmet medical need for a medicinal therapy to prevent the formation and growth of OCs.

1.2 The Exostosin Gene Mutation

Exostosin 1 and 2 genes encode for glycosyltransferases that catalyze the biosynthesis of linear heparan sulphate (HS) chains on specific proteoglycans (PGs). Both Ext1 and Ext2 genes are needed for HS synthesis, as the proteins form multimeric complexes in the Golgi. Loss-of-function mutations in either Ext1 (on chromosome 8q23-24) or Ext2 (on chromosome 11p11-p12) cause premature termination of Ext proteins, which leads to disrupted interactions and lower enzymatic activity resulting in the production of short HS chains and reduced production of HSPGs.[6,12]

The HS chains of HSPGs affect several signaling proteins critical to skeletal development, such as Indian Hedgehog, fibroblast growth factor (FGF), Wnt, and bone morphogenetic protein (BMP). The HSPGs function as co-receptors for some of these proteins, but can also influence their distribution, stability, and action on target cells.[13] The pathogenesis of MO is thought to result from a deficiency of HS and HSPG production resulting from Ext mutations, causing dysregulation of factors such as Indian Hedgehog and FGF, and increased BMP bioactivity with increased pSmad1/5/8 signaling. Increased local BMP expression leads to the differentiation of perichondrial chondrocytes to hypertrophic chondrocytes, which ultimately results in the growth of OCs oriented 90 degrees from the growth plate.[6,11]

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, an orally bioavailable retinoic acid receptor gamma (RARγ) selective agonist. Palovarotene was in-licensed from Roche Pharmaceuticals (Roche) following the completion of Phase 2 studies in subjects with chronic obstructive pulmonary disease (COPD); this program was discontinued due to lack of efficacy and is being developed by Clementia Pharmaceuticals Inc. for the treatment of fibrodysplasia ossificans progressiva (FOP) and MO. In a MO mouse model, palovarotene potently inhibits OC formation by decreasing BMP signaling through the overall reduction in the abundance of phosphorylated Smads (pSmad1/5/8) (data on file).

1.3.1 Nonclinical Data

The toxicology of palovarotene was 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 juvenile toxicology program included a

3-week dose range-finding study and a 6-week Good Laboratory Practice (GLP) toxicology study in juvenile rats.

The GLP juvenile rat toxicology results mirror the toxicity profile of palovarotene observed in older rats, where effects occur primarily in the skeleton and skin. The skeletal effects of palovarotene in 3-week postpartum juvenile rats (corresponding to a human age of >2 years) included decreased bone growth with effects on bone size, shape, and density; and on growth in general, with some evidence of reversibility at 0.5 mg/kg/day. Changes in bone mass and geometry were considered related to the effect on skeletal growth and development and not directly related to an effect on bone tissue mineral density, as only bone mineral density (BMD) evaluated by dual x-ray absorptiometry (DXA) was affected, not BMD evaluated by peripheral quantitative computed tomography. As an areal BMD assessment, BMD per DXA was influenced by the size of the bone.

The effects observed in the high-dose group (1.2 mg/kg/day) were more severe and more widespread, including growth plate abnormalities, small bone size and abnormal shape, and avascular necrosis (AVN) of the hip. Notably, there were no clinical observations observed in this dose group except that the animals were small for their age. Skeletal effects were limited in that they were mild and showed evidence of reversibility when dosing was stopped. The predicted exposures of the highest weight-based equivalent daily doses of 5.0 mg to be used in Study PVO-2A-201 are expected to be below the systemic exposure in juvenile rats at 0.5 mg/kg/day ($AUC_{0\text{-}24h}$, 855 h•ng/mL after first dose, 365 h•ng/mL after last dose).

A detailed summary of these studies and the observed effects is provided in the Investigator's Brochure.

1.3.2 Primary Pharmacology

A study using a fibroblast-specific protein 1 (Fsp1) conditional Ext1 knockout (Fsp1-Ext1^{CKO}) mouse model of MO evaluated the efficacy of orally administered palovarotene for preventing OCs.[14] This novel model, based on Ext1 ablation targeted to the perichondrium, develops bony protrusions by 4 weeks of age in bones of the limbs, ribs, and vertebrae consistent with the histological features of OCs in humans, and displays rib cage deformity and swelling of the chondro-osseous junction consistent with the clinical features of MO.

Fsp1-Ext1^{CKO} mice received three doses of palovarotene (low dose, 0.269 mg/kg; mid dose, 0.882 mg/kg; high dose, 1.764 mg/kg) for 28 consecutive days starting at Day 14 postpartum (P14 cohort), or for 21 consecutive days starting at Day 21 postpartum (P21 cohort). At the end of treatment (Day 42 postpartum), whole-mount skeletal preparations were prepared from each animal, in which OCs were identified and counted on the ribs and long bones under a dissection microscope. The data demonstrated that palovarotene treatment had a statistically significant ($p<0.0001$) effect on the inhibition of OC formation in a dose dependent manner compared with vehicle controls at all doses and at all starting ages. Greater efficacy was observed with earlier and longer dosing in the P14 cohort compared with the P21 cohort (see Section 4.3.2.1). Examination of the whole-mount skeletal preparations also revealed that swelling of the chondro-osseous junction at the rib bones and the deformity of the rib cage were considerably reduced with palovarotene daily treatment.

1.3.3 Palovarotene Safety

The initial human experience with palovarotene was based on ten completed clinical pharmacology studies in healthy subjects, three multiple dose-ranging studies in subjects with COPD/emphysema, and two Phase 2 studies in subjects with COPD. Across these studies, over 800 subjects received at least one dose of palovarotene, with 91 healthy volunteers receiving one or two doses between 0.02 and 50 mg; 124 healthy volunteers receiving multiple doses between 0.02 and 10 mg for up to 4 weeks; and 611 subjects with COPD receiving multiple doses between 0.2 and 5 mg daily for up to 24 months. Additional human experience is from the clinical development program in FOP, including one pharmacokinetic (ethnobridging) study in Japanese and non-Asian healthy volunteers and two Phase 2 studies that evaluated four palovarotene dosage regimens:

- Episodic flare-up based treatment
    - 5 mg once daily for 14 days followed by 2.5 mg once daily for 28 days (5/2.5-mg regimen in Study PVO-1A-201)
    - 10 mg once daily for 14 days followed by 5 mg once daily for 28 days (10/5-mg regimen in Studies PVO-1A-201 and PVO-1A-202/Part A)
    - 20 mg once daily for 28 days followed by 10 mg once daily for 56 days (20/10-mg regimen in Study PVO-1A-202/Part B)
- Chronic/flare-up based treatment with 5 mg daily doses and the 20/10-mg regimen at the time of a flare-up (chronic/episodic 20/10-mg regimen in Study PVO-1A-202/Parts B and C).

Note that Study PVO-1A-202 includes data from Study PVO-1A-204 in France.

The adverse effects of systemic retinoids are well described in the literature.[15] The most common are mucocutaneous toxicities (cheilitis, dry skin, pruritus, and conjunctivitis), ophthalmologic effects (dry eyes and blepharoconjunctivitis), myalgias and arthralgias, neurologic effects (headache, fatigue, and lethargy), elevated triglycerides, and abnormal liver function tests and amylase levels. Palovarotene is a gamma receptor selective agonist, contrasting with other non-selective retinoids such as all-trans retinoic acid and isotretinoin that target equally the alpha, beta, and gamma retinoid receptors.

In subjects with COPD receiving 5-mg palovarotene daily for up to 24 months, the most frequently reported adverse events were associated with subjects' underlying disease: COPD, bronchitis, upper and lower respiratory tract infection, dyspnea, cough, influenza, pneumonia, and infective exacerbations of COPD. The incidence of these events was similar in the placebo and palovarotene groups.

Consistent with other retinoids, palovarotene-treated subjects with COPD had a higher incidence of mucocutaneous and dermatologic adverse events than placebo-treated subjects. The most frequently reported mucocutaneous and dermatologic events included dry skin, dry lips, pruritus, rash, erythema, and cheilitis. In general, the incidence, total number, intensity, and duration of

mucocutaneous and dermatologic events increased with increasing palovarotene dose. Most of these events were mild or moderate in severity and generally resolved without sequelae after completion of palovarotene treatment. These events were primarily treated with symptomatic therapy including analgesics, emollients, lip moisturizers, artificial tears, and topical steroids.

Laboratory abnormalities occurring in subjects treated with palovarotene included elevations of serum amylase, lipase, triglycerides, and liver enzymes. These laboratory abnormalities were transient and not accompanied by clinical symptoms, except for the one healthy volunteer in the palovarotene/ketoconazole drug-drug interaction study who had acute pancreatitis.

The most commonly reported adverse events across all palovarotene dosage regimens in the FOP interventional studies were mucocutaneous and dermatologic events such as dry skin and lips, erythema, and pruritus. In general, the incidence and intensity of mucocutaneous and dermatologic events increased with increasing palovarotene dose. Most of these events were mild or moderate in severity; the most severe were serious adverse events (SAEs). Musculoskeletal events such as arthralgia, pain in extremity, and condition aggravated were also commonly reported. Condition aggravated is the Medical Dictionary for Regulatory Activities (MedDRA) preferred term used to capture reports of FOP flare-ups that are unique to the FOP population.

No subjects discontinued treatment or required a dose reduction during episodic flare-up treatment with the 10/5-mg regimen in Studies PVO-1A-201 and PVO-1A-202/Part A. Four subjects discontinued from Study PVO-1A-202/Parts B and C and two subjects discontinued from Study PVO-1A-301 due to adverse events.

No emerging safety signal has been identified for clinical safety laboratory assessments or electrocardiograms (ECGs) in the FOP or MO studies.

The potential effects of retinoids on bone and long bone growth are most relevant to children. Premature epiphyseal closure has been reported in three children receiving high-dose isotretinoin (between 0.5 and 3.5 mg/kg/day) long term (>4.5 years) for severe dermatologic conditions.[16] Irreversible changes have not been observed in other conditions. For example, in a key study of the use of isotretinoin in children with FOP,[17] patients with a median age of 14 years (range, 3 to 21 years) received isotretinoin daily (median dose of 1.7 mg/kg; range, 0.5 to 8 mg/kg) for a median treatment duration of 3 years (range, 4 months to 10 years). Seven of the patients (33%) developed dense metaphyseal bands (growth arrest lines) after 1 year of therapy; all bands disappeared after a dose reduction to 2 mg/kg/day.[18]

Subjects with open epiphyses enrolled in Study PVO-2A-201 and in the Phase 2 and 3 studies in FOP undergo knee and hand/wrist radiographs (anterior/posterior view) for assessment of epiphyseal growth plate; and linear and knee height measurements for assessment of growth. Overall, at baseline across the FOP studies, the most common epiphyseal growth plate abnormality were growth recovery lines (dense metaphysical lines) and sclerosis of adjacent growing bone. Subjects rarely had new or worsening post-baseline growth recovery lines and new sclerosis on follow-up radiographs. Potential premature partial closure of the epiphysis is closely monitored, and data are reviewed quarterly by an independent Data Monitoring Committee (DMC).

There were no apparent delays in linear height or knee height.

Further information on palovarotene is available in the Investigator's Brochure.

1.4 Evaluation of Study Benefits and Risks

1.4.1 Risk/Benefit Justification for Age Range

Nonclinical data from the MO mouse model (Section 1.3.2) and preliminary clinical data in FOP provide evidence supporting the potential therapeutic benefit of palovarotene for treating MO. The risks of palovarotene in pediatric subjects with MO are based on the safety profile derived from juvenile rat toxicology and clinical studies (Section 1.3.3). Based on the sponsor's comprehensive benefit/risk evaluation from these data, subjects to be enrolled in PVO-2A-201 will include those from the ages of 2 to 14 years, with a genetic diagnosis of MO and evidence of disease progression.

1.4.2 Potential to Ameliorate the Condition Under Investigation

Synthesizing the following nonclinical data in MO and nonclinical and clinical data from a related condition (FOP) supports the potential for palovarotene to inhibit OC growth and development:

- Retinoid signaling is a strong inhibitor of chondrogenesis.[19]
- Unliganded RAR transcriptional repressor activity is needed for chondrogenic differentiation.[20,21] RARγ agonists exert their action on bone formation by suppressing the downstream effectors of BMP signaling, namely the phosphorylated Smads through the ubiquitin-proteosomal degradation pathway.
- In vivo animal pharmacology consistently demonstrated the ability of palovarotene to reduce OC numbers in a dose dependent manner. These results suggest that weight-adjusted daily doses equivalents to 2.5 and 5.0 mg should be effective with minimal skeletal adverse effects.
- The clinical efficacy data in the FOP clinical program support the hypothesis that palovarotene has a beneficial effect of reducing chondrogenesis and subsequent endochondral ossification in FOP.

Therefore, the benefits of palovarotene to subjects will be the potential inhibition of OC growth and the ensuing reduction of clinical sequelae of pain, limb deformities, and functional limitations. Moreover, if palovarotene is effective in diminishing the development and growth of OCs, the need for surgical excision should be reduced.

1.4.3 Potential Risks Associated With Palovarotene

Potential risks of palovarotene in subjects with MO were compiled from four sources: literature on the treatment of children with systemic nonspecific retinoids, the palovarotene juvenile toxicology program, palovarotene clinical safety data from over 800 adult subjects including 200 healthy volunteers and 611 subjects with COPD, and the preliminary safety data from the Phase 2 studies in subjects with FOP (PVO-1A-201 and PVO-1A-202).

The palovarotene dosage regimen of 2.5 or 5.0 mg once daily (weight adjusted) for 24 months is based on animal pharmacology and nonclinical and clinical safety data. These doses were chosen to evaluate palovarotene's potential for inhibiting OC growth while minimizing risk (described further in Section 4.3). Weight-based dosing will further minimize the risk of palovarotene by minimizing the excursions above the anticipated C_{max} and AUC values in subjects with a lower weight. These dosages have been well tolerated in previous and ongoing clinical trials in adults and children, with mucocutaneous adverse events that are manageable. These events were primarily treated with symptomatic therapy including analgesics, emollients, lip moisturizers, artificial tears, and topical steroids or, if necessary, dose de-escalation or discontinuation. Current clinical safety data in pediatric subjects with FOP receiving episodic treatment with palovarotene, up to weight-adjusted daily dosages of 20 mg for 4 weeks and 10 mg for 8 weeks, revealed no treatment-related effects on growth plate or linear height.

Study PVO-2A-201 will include safety monitoring for any potential skeletal effects associated with growth plates, linear growth, bone mineral density (BMD), and osteonecrosis. Monitoring for potential growth plate and linear growth abnormalities will be performed with hand/wrist and knee plain radiographs and linear and knee height measurements every 6 months; and with bilateral radiographic evaluations of long bone lengths (ulna, radius, tibia, fibula, and femur) every 12 months. To monitor for potential effects of palovarotene on bone mineral deposition and BMD, DXA of the lumbar spine, hip (one side), and mid-third radius (one side) will occur every 6 months. Based on skeletal abnormalities in juvenile rats, including avascular necrosis of the femoral head, MRI scans obtained every 12 months for the assessments of OCs will also be evaluated for potential osteonecrosis of the hip, shoulders, and knees.

Based on these safety measures, the risks of palovarotene represent minor increases over minimal risks, can be monitored in the clinic, and are manageable. In addition, the potential for a direct benefit associated with palovarotene as described is sufficient to support the inclusion of pediatric subjects into the clinical program despite the potential risks.

1.4.4 Potential Risks Associated With Study Procedures

Risks associated with procedures in Study PVO-2A-201 include blood draws, sedation for magnetic resonance imaging (MRI), and radiation exposure from radiographs and DXA.

The per-protocol clinical laboratory assessments obtained from blood sampling and blood pressure measurements are necessary for the safety monitoring of palovarotene. Risks are being minimized by employing experienced personnel to minimize the loss of blood volume.

Study PVO-2A-201 includes procedures such as whole body MRI and yearly radiographs to obtain a standardized assessment of the MO disease state. These imaging procedures exceed the standard of care, which focuses only on the anatomical regions with OC symptoms. Magnetic resonance imaging is the best imaging modality to evaluate the morphology and size of OCs and to visualize the effect of OCs on surrounding anatomical structures.[22] Also, MRI can better image and accurately evaluate the OC cartilage cap compared with imaging with radiographs or computerized tomography. This is particularly relevant to young children in whom cartilage comprises a greater proportion of the OC relative to the osseous component. The use of whole body MRI also permits the assessment of disease processes across all anatomical regions in one

session without exposing pediatric subjects to radiation.[22,23] Limiting radiation exposure in pediatric subjects is of particular importance given that the potential risk for cancer induction in this population is about 10 times higher than in adults.[24] Consequently, MRI will be the primary imaging modality to assess the number and size of OCs.

While the risks associated with MRI are minimal, obtaining evaluable images requires that subjects remain motionless for approximately 1 to 2 hours depending on the MRI facility. This procedural risk was evaluated and mitigated in accordance with recommendations by the Pediatric Ethics Subcommittee on sedation for non-therapeutic procedures.[25] The MRI acquisition parameters in Study PVO-2A-201 were developed in consultation with pediatric MRI radiologists with expertise in MO and have been previously tested in children. Clinical sites have well-established pediatric medical facilities with a dedicated pediatric MRI imaging service and procedural sedation teams.

The ability of young children under 7 years of age to undergo non-sedated MRI is highly variable. To determine the depth of sedation necessary for MRI acquisition and the ability of these subjects to undergo sedation, a pediatric sedation team will perform screening based on, but not limited to, age, gender, the American Society of Anesthesiologists (ASA) Physical Status (PS) class (Table 2), and comorbidities.

Table 2. American Society of Anesthesiologists Physical Status Classification

Class I	A normally healthy patient
Class II	A patient with mild systemic disease (eg, controlled reactive airway disease)
Class III	A patient with severe systemic disease (eg, a child who is actively wheezing)
Class IV	A patient with severe systemic disease that is a constant threat to life (eg, a child with status asthmaticus)
Class V	A moribund patient who is not expected to survive without the operation (eg, a patient with severe cardiomyopathy requiring heart transplantation)

Table from reference.[26]

When procedural sedation is required, sedation should not exceed the level that is absolutely required to successfully perform the MRI acquisition. Procedural sedation for MRI will adhere to the standard practice of the clinical site, which may include general anesthesia as this provides a well-controlled environment for successful image acquisition and subject safety.[27] During MRI acquisition, the pediatric sedation team must have close monitoring and rescue equipment in place to respond to any complication. Subjects and their parents will be appraised of the benefits and risks of sedation for MRI as part of informed consent and child assent. Under these circumstances and risk mitigation, the procedural sedation for MRI can be considered a minor increase over a minimal risk per criteria described by the Pediatrics Ethics Subcommittee of the FDA Pediatric Advisory Committee.[28,29]

To ensure consistent assessment of joint deformities, radiographs of both forearms and lower extremities will be obtained at baseline and every 12 months. Because joint deformities are common clinical sequelae of OCs, yearly radiographic assessment of deformed/affected limbs

are considered standard of care, and necessary for evaluation and treatment decisions. The evaluation of a wide range of MO-related deformities, from potentially unaffected joints to major deformities, is necessary to standardized assessments across the broad spectrum of deformities that occur with MO.

The radiation exposure in Study PVO-2A-201 is dependent on age-related radiosensitivity. Considering the scaling factors for the relative sensitivity,[30] the estimated yearly total exposures for subjects are as in Table 3.

Table 3. Estimated Yearly Radiation Exposure

Age Range (Years)	Cumulative for Study (mSv)	Annual Exposure (mSv)
2-7	3.78	1.89
8-12	3.30	1.65
13-17	2.65	1.33

One additional set of DXA and growth plate assessments will be performed in subjects who do not participate in the open-label extension study. These assessments will be performed 6 months after the end-of-treatment and will increase the cumulative radiation exposure slightly from 0.04 to 0.07 mSv, depending on the age of the subject.

These exposures are below the annual background radiation of 3 mSv and below the 5-mSv per year value recommended by the US Food and Drug Administration (FDA) (dated 02 February 2015), based on US 21 CFR 361.1.[31] The sponsor recognizes that subjects will undergo several radiographic examinations throughout their lifetime and have elevated cumulative radiation exposure compared with unaffected children. However, should palovarotene be effective the risk of deformities would be reduced, and consequently the need for future radiographs.

Exposure above the average annual background radiation levels of 3 mSv has the potential to increase the risk of malignancy in later life. The Biologic Effects of Ionizing Radiation (BEIR) VII report defines low doses of radiation ranging from 0 to 100 mSv;[32] and that a linear, no-threshold, dose-response relationship between exposure and subsequent cancer represents the best model to estimate risk. On average, assuming a sex and age distribution similar to that of the entire US population, the BEIR VII lifetime risk model predicts that approximately one in 100 individuals would develop cancer (solid cancer or leukemia) from a dose of 100 mSv, while approximately 42 of 100 individuals would develop solid cancer or leukemia from other causes. Lower radiation doses would produce proportionally lower risks. For example, it is predicted that approximately one in 1000 individuals would develop cancer from exposure to 10 mSv, although statistical limitations make it difficult to evaluate cancer risk in humans at doses less than 100 mSv.

Study PVO-2A-201 is designed to minimize radiation exposure in subjects, while maintaining the ability to assess palovarotene's potential treatment benefit (preventing OC growth and subsequent deformities) and its potential adverse effects on growth plates. By incorporating MRI and limiting radiographs for deformity assessments to 12-month intervals, it is proposed

that the potential radiation exposure resulting from participation in this study is acceptable and represents a minimal risk.

2 Study Objectives

2.1 Primary Objective

The primary objective of Study PVO-2A-201 is to compare the efficacy of two dosage regimens of palovarotene with placebo in preventing the formation of new OCs in subjects with MO due to Ext1 or Ext2 mutations.

2.2 Secondary Objectives

Secondary study objectives are to compare the effect palovarotene treatment with placebo on the volume of OCs and on the proportion of subjects with no new OCs as assessed by whole body MRI; and on the annualized rates of new or worsening skeletal deformities and MO-related surgeries. The overall safety of palovarotene and treatment effects on linear growth and the growth plate will also be evaluated. The pharmacokinetics of palovarotene at steady-state will also be evaluated as a secondary objective.

2.3 Exploratory Objectives

The effect of palovarotene versus placebo on the change in volume of OC cartilage caps as assessed by MRI, the annualized rates of new functional limitations, pain due to OCs, pain interference on daily activities, and quality of life are exploratory objectives.

3 Study Endpoints

3.1 Primary Efficacy Endpoint

The primary efficacy endpoint will compare palovarotene with placebo on the annualized rate of new OCs as assessed by whole body MRI.

3.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints will compare palovarotene with placebo on the following:

- The change from baseline in the total volume of OCs as assessed by whole body MRI at Months 12 and 24.
- The proportion of subjects with no new OCs as assessed by whole body MRI at Months 12 and 24.
- The annualized rate of new or worsening deformities as assessed by radiographic imaging of both upper and lower limbs.
- The annualized rate of MO-related surgeries. Surgeries include any procedure indicated for the treatment of MO, such as an excision of a symptomatic OC or correction of a limb deformity.

3.3 Pharmacokinetic Endpoint

This study will evaluate the pharmacokinetics of palovarotene at steady-state.

3.4 Palatability Endpoint

This study will evaluate the palatability of drug product versus placebo when sprinkled onto specific foods following the administration of the first dose (Day 1) and at Month 1 (to coincide with pharmacokinetic assessments).

3.5 Exploratory Efficacy Endpoints

Exploratory endpoints will compare measures of joint function, pain, and quality of life across palovarotene and placebo treatment groups as follows:

- The change from baseline in the total volume of cartilage cap of OCs as assessed by whole body MRI at Months 12 and 24.
- The annualized rate of new or worsening functional limitations. Functional limitations are defined as restrictions in joint range of motion.
- The effect of pain on daily activities, as assessed with the Patient-Reported Outcomes Measurement Information System (PROMIS) pain interference pediatric item bank at Months 6, 12, 18, and 24.
- Pain intensity, as assessed with the Faces Pain Scale – Revised (FPS-R) at Months 6, 12, 18, and 24.
- Quality of life, as assessed with the Pediatric Quality of Life Inventory (PedsQL, version 4.0) at Months 6, 12, 18, and 24.

Further details on secondary and exploratory endpoints are provided in Section 8.3.

3.6 Safety Endpoints

The following safety endpoints will be evaluated over 24 months of treatment:

- The incidence and severity of adverse events at all time points.
- The incidence and severity of adverse events known to be associated with retinoids (eg, mucocutaneous events) at all time points.
- Electrocardiograms, vital sign measurements (temperature, respiratory rate, blood pressure, and heart rate), physical examination, body weight, and laboratory parameters (hematology, biochemistry, and urinalysis).
- Growth will be assessed by
    - Height and knee height measures.
    - Growth plate assessments.
- Ulnar, radial, tibial, fibular, and femoral lengths by radiograph.
- Bone mineral density at lumbar spine, hip, and mid radius as assessed by DXA.

- Assessment for potential osteonecrosis at hips, shoulders, and knees by MRI.
- Sexual development through Tanner staging.
- Suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS).

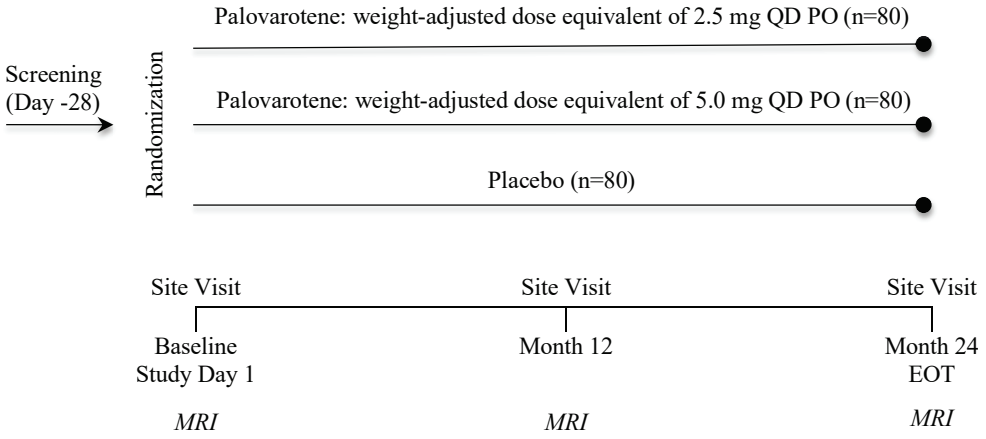
4 Study Design

4.1 Overview of Study Design

Study PVO-2A-201 is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of two dosage regimens of palovarotene administered for up to 2 years in pediatric subjects with MO. Approximately 240 subjects will be randomized in a 1:1:1 ratio to one of two treatments of weight-adjusted dose equivalents of 2.5 or 5.0 mg palovarotene (detailed in Section 7.3) or a placebo, administered orally, once daily. Randomization will be stratified by age, sex, and by Ext1 and Ext 2 mutations.

After randomization, site visits are planned every 6 months, with remote visits planned at Months 1, 3, 9, 15, and 21. If deemed necessary by investigator, or a subject is enrolled in Japan, a clinic visit will replace remote visits. The primary efficacy endpoint of new OC and secondary endpoints of OC volume and rate of skeletal deformities require whole body MRI and radiograph assessments at baseline and at Months 12 and 24, or at study discontinuation. One interim efficacy analysis will be performed when all subjects complete 12 months of treatment to potentially stop the study for efficacy or futility. Discontinuation of one of the palovarotene treatment groups for safety or futility may also be considered. Figure 1 provides a schematic of the study design and key milestones.

Figure 1. Study Design Schematic Highlighting Key Milestones



EOT, end of treatment; MRI, magnetic resonance imaging; PO, orally; QD, once daily.

For sites in the European Union, enrollment of subjects from 7 to less than 15 years of age were to be enrolled first. Younger subjects (2 to <7 years of age) were to be enrolled after the 6-month bone safety data from at least 20 skeletally immature subjects in the palovarotene FOP

program were deemed favorable by the independent DMC. On 28 January 2019, a favorable decision by the DMC permitted enrollment of subjects from 2 to 14 years of age in the EU.

Subjects will follow all procedures and undergo all assessments as specified in the Schedule of Assessments in Table 1. Details on the primary and secondary assessments of efficacy and the assessment of safety are provided in Section 8. At the end of the study, subjects may be eligible for participation in an open-label extension study (PVO-2A-202).

4.2 Study Rationale

In MO, the ability of palovarotene to prevent OC formation is supported by a novel Fsp1-Ext1^{CKO} mouse model of MO (Section 1.3.2), which demonstrated a dose-dependent inhibition of OC development. If results in Fsp1-Ext1^{CKO} mice translate to humans, it is reasonable to expect that palovarotene will provide a significant therapeutic benefit in pediatric patients by preventing OCs and their debilitating sequelae. Based on the dose-exposure response, daily doses of 2.5 and 5.0 mg are anticipated to provide maximal efficacy with a safe and tolerable profile.

In addition to MO, Clementia is developing palovarotene for the proposed indication of the treatment of FOP. Fibrodysplasia ossificans progressiva (OMIM #135100) is an ultra-rare and serious life-threatening disease characterized by painful, recurrent episodes of soft tissue swelling (flare-ups) and extraskeletal bone formation, known as heterotopic ossification (HO), in muscles, tendons, and ligaments. Multiple osteochondromas and FOP share the pathogenic process of excess BMP signaling resulting in chondrogenesis and ensuing endochondral ossification. Thus, the efficacy of palovarotene in treating FOP provides further insight as to the clinical utility of palovarotene in inhibiting OC formation in subjects with MO.

Preliminary data from the Phase 2 FOP program from 103 prospectively assessed flare-ups demonstrate that palovarotene prevents HO formation. Compared with placebo/untreated flare-ups, the palovarotene 10/5-mg episodic regimen (described in Section 1.3.3) reduced the proportion of flare-ups with new HO by 45%; and decreased the volume of new HO at the flare-up location by 75%. There was a 65% reduction in the proportion of flare-ups with new HO and a 98% reduction in new HO volume in flare-ups treated with the palovarotene chronic/flare-up 20/10-mg regimen compared with placebo/untreated flare-ups. Additional details of efficacy in the FOP program are provided in the Investigator's Brochure.

Study PVO-2A-201 is intended to support the indication of palovarotene for the treatment of MO.

4.3 Dosage Rationale

The dosage rationale for Study PVO-2A-201 is based on a synthesis of nonclinical efficacy and safety data, predicted exposure from weight-adjusted doses of palovarotene, preliminary pharmacokinetic data from subjects with FOP, and clinical safety data from subjects with COPD and FOP. The following sections summarize the relevance of each component underlying the rationale for using weight-adjusted doses of 2.5 or 5.0 mg palovarotene once daily during the 24-month treatment period.

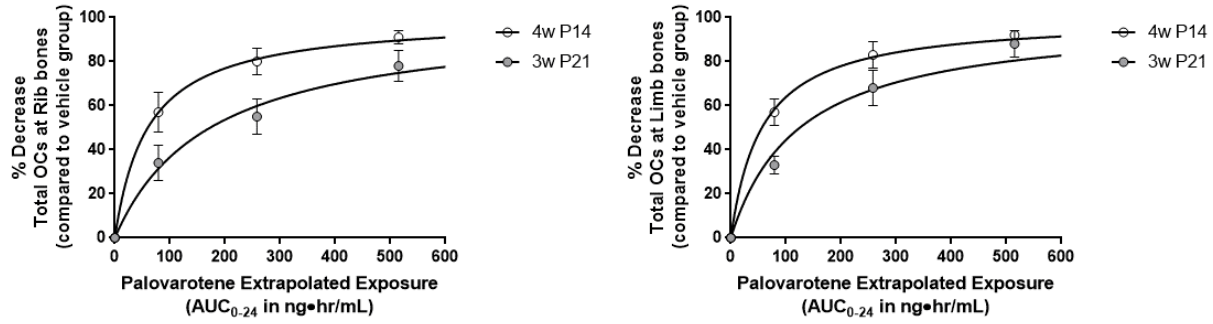
4.3.1 Nonclinical Efficacy Data

Efficacious exposures of palovarotene for the treatment of MO are based on data from Fsp1-Ext1^{CKO} mice, in which a P14 cohort received 4 weeks of dosing starting at 14 days postpartum and a P21 cohort received 3 weeks of dosing starting at 21 days postpartum (see Section 1.3.2).

As no pharmacokinetic data were available from Fsp1-Ext1^{CKO} mice, drug exposure (area under the concentration-time curve from 0 to 24 hours, $AUC_{0\text{-}24h}$) was extrapolated from pharmacokinetic data in adult wild-type mice, with the assumption that the pharmacokinetics of palovarotene in these mice were similar to juvenile Fsp1-Ext1^{CKO} mice.

A single palovarotene dose at 1 mg/kg in adult mice resulted in an average $AUC_{0\text{-}24h}$ of 292 ng•h/mL. The extrapolated $AUC_{0\text{-}24h}$ for the palovarotene doses were 79 ng•h/mL for the low dose, 258 ng•h/mL for the mid dose, and 515 ng•h/mL for the high dose. The percentage decrease in total OC numbers at rib and limb bones are presented as a function of the extrapolated exposure in Figure 2; the $AUC_{0\text{-}24h}$ at the dose at half-maximum response (ED_{50}) is 57-60 ng•h/mL for the P14 cohort and 125-173 ng•h/mL for the P21 cohort.

Figure 2. Dose Response of Palovarotene to Inhibit OC Formation in Fsp1-Ext1^{CKO} Mice



Cohort	ED_{50} (ng•h/mL)
4w P14	60
3w P21	173

Cohort	ED_{50} (ng•h/mL)
4w P14	57
3w P21	125

4w P14, 4 weeks of dosing starting at 14 days postpartum; 3w P21, 3 weeks of dosing starting at 21 days postpartum; ED_{50}, dose at half-maximum response; OCs, osteochondromas.

4.3.2 Nonclinical Safety Data

4.3.2.1 The Fsp1-Ext1^{CKO} Mouse Model of Multiple Osteochondromas (Non-GLP Study)

In the previously described Fsp1-Ext1^{CKO} mouse model of MO (Sections 1.3.2 and 4.3.1) bone lengths were assessed at the end of treatment to determine the effect of palovarotene on bone growth. In the P14 cohort, limb lengths were reduced at mid and high doses of palovarotene from 3% to 22%, with most reductions from 12% to 18%. No reductions were observed with the

palovarotene low-dose group. Moreover, no reduction was noted at any dose in the P21 cohort, suggesting that potential skeletal effects are dose and age dependent.

4.3.2.2 Nonclinical Juvenile Toxicity Study

In juvenile rats, the threshold for dose-limiting skeletal toxicity increased with age, and the skeletal effects of palovarotene showed evidence of reversing after dosing was stopped at 0.5 mg/kg/day, which was designated as the highest non-severely toxic dose (HNSTD). The systemic exposure (ie, $AUC_{0\text{-}24h}$) in juvenile rats at 0.5 mg/kg/day was 855 ng•h/mL after the first dose and 365 ng•h/mL after the last dose.

4.3.3 Clinical Data

4.3.3.1 Clinical Safety Data in COPD

Palovarotene has been administered to over 800 adult subjects, including over 200 healthy volunteers and 611 subjects with COPD, with 450 subjects with COPD receiving daily dosing of 5.0 mg palovarotene for up to 24 months. Adverse events associated with the use of palovarotene were dose-related, similar to those reported for other retinoids, and primarily related to mucocutaneous events (eg, rash, dry skin, cheilitis). At daily dosing of 5.0 mg, 16.8% of palovarotene recipients discontinued due to adverse events versus 9.5% of placebo recipients.

4.3.3.2 Clinical Safety Data in FOP

Per safety data available at the time of study design, most adverse events in subjects with FOP treated with palovarotene were associated with systemic retinoids, were mild or moderate in severity, and similar to adverse events observed in subjects with COPD. Updated safety data from FOP studies are provided in Investigator's Brochure (Section 6.4.2).

4.3.3.3 Predicted Exposure to Palovarotene

A pharmacokinetic analysis was performed to determine the appropriate weight-adjusted doses for pediatric subjects to provide similar exposure as adults (ie, ≥60 to 80 kg) receiving either 2.5 or 5.0 mg palovarotene daily. The analysis was based on the pharmacokinetic data from two single-dose studies and five multiple-dose studies, which collectively included 137 healthy volunteers who received at least one dose of palovarotene. The AUC and maximum plasma concentration (C_{max}) predictions for body weight are summarized in Table 4. Weight-based regimens provided exposures across the different weight categories ranging from 85 to 147 ng•h/mL for the 2.5-mg equivalent doses and 211 to 294 ng•h/mL for the 5.0-mg equivalent doses.

Table 4. Predicted Pharmacokinetic Parameters in the Pediatric Population Using a Weight-Based Dosage Regimen

Weight Category	2.5-mg Equivalent				5.0-mg Equivalent			
	10 to <20 kg	>20 to 40 kg	>40 to 60 kg	≥60 to 80 kg	10 to <20 kg	>20 to 40 kg	>40 to 60 kg	≥60 to 80 kg
Actual dose, mg	1.0	1.5	2.0	2.5	2.5	3.0	4.0	5.0
$AUC_{0\text{-}24h}$, h•ng/mL	85-91	107-126	118-143	115-147	211-227	214-252	235-285	231-294
C_{max}, ng/mL	14-15	18-21	20-24	20-25	34-37	36-41	40-48	40-50

$AUC_{0\text{-}24h}$, area under the plasma concentration-time curve from 0 to 24 hours; C_{max}, maximum plasma concentration.

4.3.3.4 Observed Exposure for Weight-Based Dosing of Palovarotene

Table 5 summarizes the mean and median $AUC_{0\text{-}24h}$ values for skeletally immature subjects with FOP receiving 2.5- and 5.0-mg equivalent daily doses of palovarotene compared with fixed doses in adults. Skeletally mature subjects received fixed-dose regimens, while the skeletally immature subjects <18 years of age received weight-adjusted equivalent doses. The observed exposures using weight-based dosing tended to be lower than fixed dosing but should be interpreted with caution as the number of subjects providing samples in the 2.5-mg group is low. These results will be updated as data become available.

Table 5. Observed Pharmacokinetic Values in the Pediatric Population With a Weight-based Dosing Regimen

	Palovarotene 2.5 mg QD		Palovarotene 5.0 mg QD	
	Fixed Dose (N=4)	Weight-Adjusted Equivalent (N=3)	Fixed Dose (N=27)	Weight-Adjusted Equivalent (N=14[1,2])
$AUC_{0\text{-}24h}$, ng•h/mL				
Mean (SD)	177 (86)	98 (73)	305 (131)	249 (105)
Median	149	78	296	207
Min, max	107, 302	37, 179	92, 667	134, 448
AUC Ratio (A/P)				
Mean (SD)	1.2 (0.7)	0.8 (0.6)	1.3 (1.1)	1.1 (0.4)
Median	0.9	0.6	1.0	0.9
Min, max	0.6, 2.2	0.3, 1.4	0.3, 5.8	0.5, 1.9

[1] One 18-year-old subject (54.4 kg) was dosed using weight-based equivalent for 5 and 10 mg.

[2] One 13-year-old subject (27.9 kg) was dosed using weight-based equivalent for 5 mg.

$AUC_{0\text{-}24h}$, area under the plasma concentration-time curve from 0 to 24 hours; A/P, actual versus predicted; QD, once daily.

One other parameter that is known to impact systemic exposure of palovarotene is food. For the FOP clinical studies, all subjects are instructed to administer study medication at approximately the same time each day and following a full meal.

4.3.4 Summary and Conclusions

The dosage selection for Study PVO-2A-201 was based on the efficacy and safety data from Fsp1-Ext1^{CKO} mice and juvenile toxicity. While high-dose palovarotene resulted in a greater reduction of OCs in Fsp1-Ext1^{CKO} mice, the extrapolated exposure exceeds the HNSTD identified in juvenile toxicology studies. Based on the adverse skeletal effects observed in nonclinical models, chronic dosing targeting systemic exposures at or below 365 ng•h/mL are planned to minimize potential skeletal toxicity. This exposure would provide near maximal effects on OC development (Figure 2; based on the flat part of the dose-response curve in the MO mouse model) and corresponds to a 5.0-mg dose in humans (Table 4; ≥60 to 80 kg). The minimum exposure to achieve 50% efficacy based on the P21 cohort is 125-173 ng•h/mL (Figure 2), which corresponds approximately to the 2.5-mg dose in humans.

Accordingly, the weight-adjusted palovarotene doses of 2.5 and 5.0 mg once daily were chosen to evaluate palovarotene's potential for inhibiting OC growth while minimizing risk. These doses have been well tolerated in previous and ongoing clinical studies in adults and children, with mucocutaneous adverse events that are manageable. Study PVO-2A-201 will include safety monitoring to identify any potential skeletal effects associated with the growth plates, bone mineral density, and linear growth. Modalities will include hand/wrist and knee plain radiographs; DXA of the lumbar spine, hip, and mid-third radius; linear and knee height measurements (Section 8.5); and treatment-emergent adverse event monitoring (Section 11.2).

4.4 Justification for Placebo Control

The design of Study PVO-2A-201 incorporates a placebo control to provide rigorous hypothesis testing and unequivocal scientific data to evaluate the efficacy and safety profile of palovarotene in the MO patient population. The use of placebo will, by necessity, expose some subjects to a treatment with no potential for direct benefit. There is currently no biomarker or efficacy endpoint that is sensitive to changes in MO severity or progression over a reasonably brief period. Because the development and growth of OCs are slow, concurrent with the growth of the subject, treatment durations from 1 to 2 years may be required to discern effects of active treatment on changes in the number and volume of OCs.

To assess safety and efficacy and to potentially stop the study based on pre-specified rules, an interim analysis is planned when all subjects complete 12 months of treatment. If the study was stopped early for success, subjects may be offered enrollment into an open-label extension study. The use of placebo over the 2-year treatment duration is ethically justified in this study for the following reasons:

- As there is no current medical therapy for the inhibition of OC growth, subjects randomized to placebo are not being denied alternative or effective treatment.
- The risk of placebo treatment is minimal. The risk of not receiving a potential effective treatment is that the subject may develop pain, a joint deformity, or a functional limitation as part of the natural progression of MO. As Study PVO-2A-201 is the first clinical study in subjects with MO, there are no clinical data demonstrating that palovarotene can reduce OC development and growth. Therefore, at present, there is a clinical equipoise between palovarotene and placebo.

- All subjects will benefit from the knowledge gained about their health status through study assessments and frequent physician evaluation of their disease. There may be greater opportunity for intervention if medically indicated.
- The randomization ratio of 1:1:1 to 2.5- or 5.0-mg palovarotene or placebo gives subjects a 67% probability of being assigned active treatment.
- All subjects who enroll in the study will remain on their current concomitant pain medications. Subjects may increase pain medication if symptoms increase during the study or undergo surgical excision for progressive pain, a deformity, or a functional limitation as per the standard of care. If subjects experience increased or persistent clinical disease progression, they have the option to withdraw from the study at any time.
- Subjects participating in this study may be eligible to participate in the proposed open-label extension study (PVO-2A-202) in which all subjects will receive palovarotene.

4.5 Clinical Meaningfulness of the Efficacy Endpoints

The multiplicity of symptoms associated with MO is reflected in the diversity of clinical measures used to determine disease severity and/or progression. Clinical features of MO such as deformity, presence of dislocations, functional limitations, the number and/or location of OCs, the age of MO onset, reduced stature, and number of surgical procedures have been used to define disease severity and progression.[7,12,33,34] Moreover, as no medical treatment currently exists for MO, there are no registrational endpoints defined for MO clinical studies.

To derive clinically meaningful efficacy endpoints to support the marketing authorization of palovarotene, data from the Instituto Orthopedico Rizzoli (IOR) Registry for Multiple Exostoses (REM) were analyzed. The REM is a standardized registry that includes patients from two different European MO referral centers coordinated by the Medical Genetics and Rare Orthopaedic Diseases Department and Clinical Bioinformatics Laboratory of the IOR in Bologna, Italy. The rates of new OCs, functional limitations, deformities, and surgical procedures over time were assessed in 190 pediatric patients included in the REM. The results provided guidance for the design of Study PVO-2A-201 with respect to subject eligibility, endpoint selection, sample size estimation, and study duration.

Complementing the REM analysis, a review of published literature provided support for the clinical meaningfulness of the chosen efficacy endpoints. The primary efficacy endpoint will assess the efficacy of palovarotene in terms of inhibition of new OC growth, analogous to the efficacy demonstrated in Fsp1-Ext1^{CKO} mice (Section 1.3.2). Osteochondromas are a pathognomonic feature of MO associated with disease severity. A greater OC burden is associated with more skeletal deformities and functional limitations, and associated with increased pain.[8,35] The secondary endpoint assessing the annual change from baseline in total OC volume by whole body MRI will also assess the efficacy of palovarotene in terms of reducing OC burden. Additional secondary endpoints will assess the efficacy of palovarotene in terms of rates of new or worsening skeletal deformities and MO-related surgeries, whereas exploratory endpoints will assess the rate of new or worsening functional limitations and patient reported outcomes on pain and quality of life. By inhibiting the development and growth of

OCs, it is anticipated that there will be a reduction in limb deformities, functional limitations, and pain, reducing the need for MO-related surgeries. Reducing the number of surgeries is itself clinically meaningful; a retrospective review of medical records indicated that more surgeries reduce quality of life in patients with MO.[10] So by reducing OC burden, reducing skeletal sequelae, and the need for MO-related surgeries, an improved quality of life is also anticipated with palovarotene treatment. Together, the efficacy endpoints provide a comprehensive and clinically meaningful assessment of MO that is suitable for the age range of subjects that will be enrolled in the study.

4.6 End of Study Definition

A subject is at the end of the study if he or she has completed all phases of the study, including the safety follow-up visit 6 months after the end of treatment at Month 24 (for subjects who terminate early or those who elect not to participate in the open-label extension study), or the last scheduled follow-up procedure as in the Schedule of Assessments (Table 1).

4.7 Study Termination

This study may be prematurely terminated if, in the opinion of the Investigator or the sponsor, there is 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 the following:

- 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.

Study termination may also occur under the auspices of a DMC. Based on the interim analysis, the DMC may recommend stopping the study early for efficacy or futility. Additional details are provided in Section 11.3.

5 Selection of the Study Population

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a subject. Subjects may be rescreened once for disqualifying laboratory abnormalities.

5.1 Inclusion Criteria

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

1. Written, signed, and dated informed subject/parent consent and age-appropriate assent (performed according to local regulations).

2. A clinical diagnosis of MO with a disease-causing Ext1 or Ext2 mutation confirmed by a central laboratory.
3. A chronological age from 2 to 14 years (inclusive) for male and female subjects.
4. Female subjects must be premenarchal at screening.
5. A bone age at screening of ≤14 years, 0 months per the Greulich-Pyle method, as ascertained by a central reader.
6. Symptomatic MO, defined as the occurrence of any one of the following at screening:
    - Five or more clinically-evident OCs and the presence of a new or enlarging OC in the preceding 12 months.
    - Five or more clinically-evident OCs and the presence of a painful OC.
    - A skeletal deformity.
    - A joint limitation.
    - Prior surgery for an MO-related complication.
7. If a subject had a prior surgery for MO, the subject should not be screened until 8 weeks post-surgery to allow for 12 weeks of stabilization of symptoms prior to first dose. Surgical orthopedic implants are allowed if they were in situ ≥12 weeks prior to the baseline MRI.
8. If a subject is currently receiving pain medications, they may participate in the study provided that the dose is stable (ie, <20% variance) for 2 weeks prior to screening.
9. The ability to undergo whole body MRI with or without sedation/general anesthesia.
10. Male and female subjects of child bearing potential who are heterosexually active must agree to use two effective methods of birth control, one of which must be highly effective during treatment and for 1 month after treatment discontinuation, unless they commit to true abstinence from heterosexual sex. Heterosexually active females of child-bearing potential (FOCBP) must also agree to start effective methods of birth control at screening. An FOCBP is defined as a female who is ≥13 years of age or is post-menarchal, whichever is earlier.
11. Subjects must be accessible for treatment with study drug and follow-up.

5.2 Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for enrollment:

1. A weight under 10 kg.
2. Other syndromic conditions such as Langer-Giedion or Potocki-Shaffer syndromes.
3. Any subject with neurologic signs suggestive of spinal cord impingement.
4. 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. No washout is required prior to the first dose of study drug.

5. Exposure to synthetic oral retinoids within 4 weeks prior to enrollment.
6. Concurrent treatment with tetracycline or any tetracycline derivatives, due to the potential increased risk of pseudotumor cerebri.
7. History of allergy or hypersensitivity to retinoids, gelatin, or lactose (other than lactose intolerance).
8. Concomitant medications that are strong inhibitors or inducers of cytochrome P450 (CYP450) 3A4 activity.
9. Amylase or lipase >2 times the above the upper limit of normal (>2×ULN) or with a history of chronic pancreatitis.
10. Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) above 2.5×ULN.
11. Fasting triglycerides above 400 mg/dL with or without therapy.
12. Uncontrolled cardiovascular, renal, hepatic, pulmonary, gastrointestinal, endocrine, metabolic, ophthalmologic, immunologic, psychiatric, or other significant disease including diseases requiring glucocorticoid treatment with ≥0.2 mg/kg or up to 10 mg prednisone or prednisone equivalent per day.
13. Subjects experiencing suicidal ideation (type 4 or 5) in the past month or any suicidal behavior within the past year as defined by the C-SSRS.
14. Unable or unwilling to complete the study or all study-related procedures, including imaging.
15. Any surgical implant that is contraindicated for MRI.
16. Participation in any clinical research study within 4 weeks prior to enrollment or simultaneous participation in any clinical research study.
17. 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.

5.3 Subject Withdrawal or Early Termination from Study

Subjects can voluntarily withdraw from the study at any time for any reason. The study personnel should make all reasonable efforts to determine the reason for withdrawal. Subjects will be considered lost to follow-up if no response is received despite 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 7.4.

In the event of an early discontinuation of the study drug, subjects should be encouraged to complete all study assessments and continue in the study until the end of study. In the event of an early termination from the study, the study personnel should make all reasonable efforts to have the subject complete all study assessments for Month 24 per the Schedule of Assessments (Table 1).

5.4 Safety Follow-up

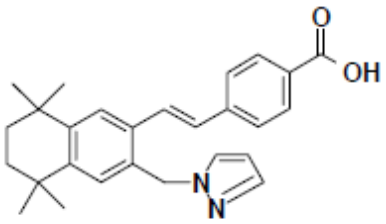
Subjects who do not continue to the open-label extension study or who end treatment early will require two safety follow-up visits: 4 weeks and 6 months after the last dose at the end-of-treatment visit. The end-of-treatment visit will document adverse events related to skin and bone parameters. The safety follow-up will include clinical laboratory assessments of ongoing clinically significant abnormal findings to determine whether any are resolved or stabilized; the pregnancy status for a female of childbearing potential (FOCBP) will also be determined. Additional safety follow-up may be required past the 6-month follow-up to ensure that ongoing adverse events have resolved or stabilized.

6 Study Treatments

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, an orally bioavailable RARγ selective agonist. The structure of palovarotene is shown in Figure 3.

Figure 3. Chemical Structure of Palovarotene



6.2 Placebo

Placebo will be supplied as powder filled hard gelatin capsules that are indistinguishable from palovarotene capsules and contain the same ingredients except for palovarotene. The capsules may be swallowed whole or opened and the contents added onto specific foods.

6.3 Concomitant Medications

It is important to be aware of and document all concomitant medications including prescription, non-prescription, and herbal medications.

Medications that are taken in the screening period will be documented as prior medications. Medications taken after the first dose of study drug has been administered will be documented as concomitant medications. All concomitant medications taken during the study must be recorded in the CRF with indication (as appropriate), daily dose and start and stop dates of administration. Subjects will be queried about concomitant medication at each study visit.

6.3.1 Pain Medications

Pain medications, including but not limited to acetaminophen, nonsteroidal anti-inflammatory drugs, or opioids taken to treat pain associated with OCs will be documented in the electronic

case report form (eCRF). Adjustments in pain medications should be undertaken after evaluation of the subject's pain symptoms; the increase in pain should be captured as an adverse event. Changes in dosing or pain medication must be documented in the eCRF with indications for use.

6.3.2 Restrictions on Prior and Concomitant Medications

Several human CYP450 (CYP) isoforms (3A4, 2C8, and 2Cl9) oxidize palovarotene to its metabolites. However, CYP3A4 is the major isoform responsible for the in vitro transformation. In healthy humans, 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), and did not change consistently with midazolam (a CYP3A4 substrate). Palovarotene did not impact the pharmacokinetics of midazolam, a standard CYP3A4 substrate, or the pharmacokinetics of prednisone. Based on this information, concomitant medication guidelines during study treatment (ie, from the time of signature of the Informed Consent Form [ICF] to the end of study) are as follows:

- Strong CYP3A4 inhibitors should not be taken concomitantly with palovarotene (Appendix 1). If the subject requires such a medication, then contact the medical monitor.
- Strong CYP3A4 inducers should not be taken concomitantly with palovarotene (Appendix 1). If the subject requires such a medication, then contact the medical monitor.
- It is acceptable to use CYP3A4 substrate drugs (those metabolized by CYP3A4) concomitantly with palovarotene.

The following medications are also not allowed during the study:

- Vitamin A or beta carotene, multivitamins containing vitamin A or beta carotene, herbal preparations, or fish oil. No washout is required prior to starting study drug.
- Synthetic oral retinoids are not permitted 4 weeks prior to enrollment or during the study.
- 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. Should the subject experience 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. If the duration of study drug interruption in context of treatment with tetracyclines exceeds 7 days, the subject should be withdrawn from the study.

6.4 Other Restrictions

Males of reproductive potential and females of childbearing potential that have reached puberty must agree to undergo physician-approved reproductive education. The Investigator must discuss the adverse effects of the study therapy on reproduction with these subjects and their caregiver(s). In alignment with the guidance on pregnancy testing of adolescents participating in

research,[36] an FOCBP is defined as a female subject who is ≥13 years of age or is post-menarchal, whichever is earlier.

Medically supervised serum pregnancy tests with a sensitivity of at least 50 mIU/mL must be conducted in FOCBP, including those who commit to abstinence. Both male subjects of reproductive potential and FOCBP subjects must, as appropriate to age and at the discretion of the Investigator, either commit to true abstinence from heterosexual contact or agree to use two effective methods of birth control during and for 1 month after treatment. Abstinence is only acceptable as "true abstinence." True abstinence occurs when it is in line with the preferred and usual lifestyle of the subject.

Additionally, heterosexually active FOCBP subjects must already be using two effective methods of contraception 1 month before treatment begins. Two effective forms of birth control consist of the concurrent use of AT LEAST one **highly** effective method of birth control comprising the following:

- 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.

It is well recognized that retinoids are teratogens associated with a high risk for fetal abnormalities in women who become pregnant during treatment with such agents. The agreement to remain abstinent from heterosexual sex or to use two effective methods of birth control will be clearly defined in the ICF. Subjects or legally authorized representatives (eg, parents, caregivers, or legal guardians) must sign this specific section per institutional practice.

In addition, pregnancy testing (via blood or urine) will be performed before and during study drug administration and at the end of treatment.

In the 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 and the pregnancies of female partners of male subjects within 24 hours of notice 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; the health status of the baby will be verified.

7 Study Drug Administration and Management

7.1 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 0EL oblong hard gelatin capsules using standard USP/EP/JP grade excipients in the following dosage strengths: 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, and 5.0 mg.

Placebo will be supplied as powder-filled hard gelatin capsules indistinguishable from palovarotene capsules containing the same ingredients except for palovarotene.

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.

7.2 Randomization and Blinding

Treatment will be assigned through randomization performed using a centralized Interactive Web Response System (IWRS). Approximately 240 subjects will be randomized to one of three treatment groups (2.5-mg palovarotene, 5.0-mg palovarotene, placebo) with a 1:1:1 ratio. Randomization will be stratified by age (≤7 years, >7 years), sex, and gene mutation (Ext1/Ext2). Blocks of fixed size will be used within each of the eight strata determined by the unique combinations of the stratification variables.

The Investigators, site staff, sponsor, subjects, contract research organization (CRO), and central imaging laboratory will remain blinded to treatment. The Investigator may unblind a subject's treatment only in an emergency for which it is medically imperative that the identity of the treatment administered be revealed. To unblind the subject's treatment, the Investigator will follow the study's unblinding procedure. Whenever possible, the Investigator should contact the medical monitor or designee prior to unblinding.

7.3 Administration

Subjects will receive orally administered palovarotene 2.5 or 5.0 mg (weight-adjusted as in Table 6) or placebo once daily for up to 24 months.

Table 6. Weight-Adjusted Palovarotene Doses for Skeletally Immature Subjects

Weight Range Category	5.0-mg Equivalent	2.5-mg Equivalent
10 to <20 kg	2.5 mg	1.0 mg
20 to <40 kg	3.0 mg	1.5 mg
40 to <60 kg	4.0 mg	2.0 mg
≥60 kg	5.0 mg	2.5 mg

The first day that study drug is administered for treatment will be defined as Study Day 1. Details for handling, preparing, storing, and discarding study drug will be provided to subjects and caregivers. Medications will be taken with food, at approximately the same time once daily, preferably immediately following the first meal of the day. The initial amount of study drug provided will be sufficient for once daily dosing for 3 or 6 months.

Because younger pediatric subjects may have difficulty swallowing intact capsules, subjects or caregivers may sprinkle the contents of the capsule onto a spoonful of specific foods (as specified in the dosing instructions) to facilitate study drug administration. The study drug should be ingested immediately following the first meal of the day. The capsule should be swallowed whole, or if sprinkled onto a spoonful of food, the entire serving must be eaten. Subjects should be told 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 palovarotene, subjects and caregivers will be instructed to wear protective gloves when handling study drug capsules. Pregnant persons should not handle study drug capsules.

7.4 Dose Modification

Skin and mucous membrane reactions are the most common adverse effects associated with treatment with retinoids. Therefore, to mitigate possible adherence issues due to expected adverse events, a guidance describing recommended treatment for the most common mucocutaneous adverse events will be distributed to each subject at the initiation of study treatment.

Should a subject experience an adverse event 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 adverse event and determine an appropriate treatment or mitigation strategy. The Investigator will assess the adverse event and if appropriate, will instruct the subject to decrease the frequency of study drug dosing to every other day for 1 month or until the adverse event is resolved, whichever is longer. The subject

will be followed until resolution or improvement of the adverse event. Once the adverse event has resolved or sufficiently improved, the subject should resume once daily dosing. If the adverse event recurs and is again intolerable upon resuming once daily dosing, the subject should return to every other day dosing for the remainder of the study. Should the adverse event remain intolerable after the dose modification to every other day dosing then the study drug will be discontinued, and the subject will continue to be followed with all study procedures performed per protocol. Should a subject experience an adverse event that requires immediate discontinuation of the study drug (eg, acute pancreatitis) then the study drug will be discontinued, and the subject will be followed until resolution or stabilization. Details on adverse event reporting are provided in Section 11.2.

Dose modification may also be required due to potential bone safety findings as described in the Bone Safety Management Plan (see Section 8.5.1). To address potential adverse effects of the study drug on bone density and growth, the study treatment may be modified or discontinued should subjects fulfill the criteria described in Section 8.5.3 for changes in BMD and Section 8.5.4 for changes in linear growth.

7.5 Study Drug Accountability

The Investigator has the ultimate responsibility for study drug accountability at the study site. The Investigator or a designated individual (eg, pharmacist or other appropriate personnel) will maintain records of the study drug's delivery to the study site, inventory at the site (used and unused product containers), use by each subject, and return of unused medication to the sponsor or alternative disposition.

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 end 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 subjects in this study.

7.6 Assessment of Subject Compliance

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

Any issues related to adherence will be discussed with the subjects and their caregivers. Subjects and/or caregivers should be encouraged to call the site between visits should any issues related to the study drug or adherence arise.

8 Study Procedures and Assessments

8.1 Overview of Study Procedures

Study procedures are summarized in the Schedule of Assessments (Table 1). The anticipated length of study participation in Study PVO-2A-201 is 26 months, which may be extended if additional safety follow-up is needed. At the end of the study, subjects will have the option to

participate in an open-label extension study. Details of the extension study will be provided in a separate study protocol.

Site visits will occur at screening, baseline, and at Months 6, 12, 18, and 24. Remote visits will occur at subjects' homes or at local medical facilities between site visits at Months 1, 3, 9, 15, and 21. Remote visits will be switched to site visits if preferred by the subject and site personnel, or the subject is enrolled in Japan.

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside the control of the Investigator, that may make it unfeasible to perform the test. In these cases, the Investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the Investigator and/or delegate will document the reason and any applicable corrective and preventive actions in the source document.

8.2 MRI Sedation Screening

At the screening visit, tolerance for the MRI procedure will be assessed in all subjects ≤7 years of age and in subjects who are deemed by the Investigator to require procedural sedation. A pediatric sedation team will perform assessments of procedural tolerance and include the level of sedation a subject will require to complete the MRI scanning session. The assessment will be based on, but not limited to, age, gender, ASA-PS class (Table 2), and comorbidities. The screening will determine a priori the appropriate depth of sedation required to perform whole body MRI and the ability of subjects to tolerate MRI with the selected sedative.

8.3 Efficacy Assessments

8.3.1 Assessment of Osteochondroma Number and Volume by Whole Body MRI

Whole body MRI will be performed at baseline and at Months 12 and 24, and at early termination for subjects who terminate participation prior to study completion. The MRI may be performed within ±4 weeks of a study visit to allow flexibility of scheduling. Full details of MRI procedures will be provided in a separate imaging acquisition guideline document.

To obtain evaluable images, the subject must be still for 1 to 2 hours. Distraction may be employed to allow MRI without sedation. When procedural sedation is required, the depth of sedation should not exceed the level that is absolutely required to successfully perform the MRI acquisition. The choice of sedative agent and method will be based on the subject status and clinical experience of the pediatric sedation team. Procedural sedation for whole body MRI will adhere to the standard practice of the clinical site, which may include general anesthesia as this provides a well-controlled environment allowing for airway management to ensure subject safety.[27] During the sedated MRI acquisition, the pediatric sedation team must have close monitoring and rescue equipment in place to respond to any complication. Imaging acquisition will be terminated if a complication of sedation arises.

Interpretation of the MRIs will document the number and anatomic distribution of OCs, the volume of total body OCs, and the volume of the total cartilage cap at baseline and at Months 12

and 24. All images will be interpreted by a treatment-blinded, central imaging laboratory using standardized procedures detailed in an imaging read charter.

8.3.2 Assessment of Joint Deformity by Radiograph

Radiographs to assess limb deformity will be performed at baseline and at Months 12 and 24. Radiographs may be performed within ±4 weeks of a study visit to allow flexibility of scheduling. Assessments will comprise weight-balanced, full-length anterior/posterior radiographs of the lower extremities and lateral and anterior/posterior radiographs in supination and pronation of the forearms. Full details for radiographic procedures will be provided to the site for consistency of image acquisition. A central imaging laboratory with trained readers who are blinded to treatment will read radiographs to ensure consistent assessments.

MO-related deformities will not be recorded as adverse events. Major MO-related deformities will include, but may not be limited to the following measurements:

Upper Extremities

- Ulnar length and ulnar length/linear height ratio
- Radial articular angle
- Status of radiocapitellar articulation (normal, displaced, subluxation, dislocated)

Lower Extremities

- Lateral distal tibial angle to assess ankle valgus or varus deformity
- Medial proximal tibial angle to assess knee valgus or varus deformity
- Femoral neck shaft angle
- Lateral distal femoral angle
- Leg length discrepancy

Lengths of paired bones (radius, ulna, tibia, and fibula) will also be assessed.

Descriptions of these and other additional measurements to assess MO-related deformities and criteria for a new or worsening deformity will be defined in the imaging read charter provided to the central image reader.

8.3.3 Surgeries Related to Multiple Osteochondromas

MO-related surgeries performed after subject enrollment will be documented in the eCRF. The documentation will include the indications for each procedure. Planned or unplanned MO-related surgery will not be recorded as adverse events unless it results in complications, prolongation of hospitalization, or meets any other criteria for a serious adverse event.

An MO-related surgery is a secondary efficacy endpoint, which may include excisions to remove symptomatic OCs (pain, neurovascular, or tendon impingement) or procedures to correct deformities and/or functional limitations. However, surgical practices for the correction of

deformities differ across study sites and geographic regions. To provide standards for assessing these surgical events for efficacy endpoints, corrections for deformities of a ≥10° angle deviation, 2.5-cm leg length discrepancy, or restricted joint movement will be counted as an endpoint event. Planned surgeries within 6 months of enrollment to remove symptomatic OCs present at baseline, or to correct deformities present at baseline, will be recorded but not contribute to the endpoint. Similarly, surgical procedures that are a continuation of a previous procedure, such as removal of a surgical plate for guided growth, will not be counted as a separate MO-related surgery endpoint event.

8.3.4 Functional Limitations

A functional limitation will be defined as a restriction in joint range of motion. Range of motion will be assessed using a goniometer, by a treatment-blinded, trained assessor at baseline and at Months 6, 12, 18, and 24. Whenever possible, the same assessor should be used to standardize the performance of procedures and to minimize variability. The following joint ranges of motion will be assessed:

- Hip extension/flexion
- Knee flexion and extension
- Shoulder flexion
- Elbow flexion, extension, supination, and pronation
- Ankle dorsiflexion and plantarflexion

Details on how to perform measures for joint range of motion will be provided in a manual. A functional limitation is defined as a deviation >2 standard deviations from the mean range of motion per age category and gender versus normal individuals. Normative values are from the normal ranges of motion in individuals from 2 to 19 years of age as published in the Normal Joint Range of Motion Study conducted by the Center of Disease Control and Prevention (CDC).[37] A worsening restriction is defined as a further decrease of >5º or >20% of the CDC age category-by-gender mean range of motion, whichever is greater.

8.3.5 The Pediatric Quality of Life Inventory

The Pediatric Quality of Life Inventory (PedsQL) version 4.0 is a reliable and validated pediatric quality-of-life survey for children from the ages of 2 to 18 years, designed to measure core health dimensions outlined by the World Health Organization. It comprises 23 items, with eight items assessing physical health and 15 items assessing psychosocial health.[38] The Parent Proxy Report form for toddlers will be used for subjects 2 to 4 years of age, the Parent Proxy Report will be used for subjects 5 to 7 years of age, the Child Self Report will be used for subjects from 8 to 12 years of age, and the Teen Self Report will be used for subjects 13 years of age and older (Appendix 2).

8.3.6 Pain Interference

To assess the effect of pain on subject well-being, this study will use the Patient-Reported Outcomes Measurement Information System (PROMIS) pain interference pediatric item bank

(Appendix 3). The PROMIS pain interference items assesses the extent to which pain hinders social, psychological, physical, recreational activities and sleep over the preceding 7 days.[39] The pain interference short forms are universal rather than disease-specific. For this study, self-report forms will be used for subjects 8 to 17 years of age and parent proxy forms will be used for subjects from 2 to 7 years of age.

8.3.7 Pain Intensity

Pain will be further evaluated using the six-face Faces Pain Scale – Revised (FPS-R), which is a pediatric subject self-report measure of acute pain intensity (Appendix 4). The FPS-R was adapted from the original FPS to make it possible to score pain on a numeric rating scale from 0 (no pain) to 10 (very much pain). The validity of the FPS-R is supported by strong correlations with visual analogue scales in pediatric patients from 4 to 12 years of age.[40,41] The FPS-R is appropriate for the assessment of pain intensity for pediatric subjects ≥4 years of age.

8.4 Safety Assessments

8.4.1 Medical History

A complete medical history is to be documented at screening. All MO-related surgeries performed prior to enrollment should be documented in the MO specific history eCRF.

8.4.2 Physical Examination

A comprehensive physical examination will be performed by a physician at screening, baseline, every 6-months (Months 6, 12, 18, and 24), and at the 6-month safety follow-up and will monitor whether objective changes occur. Any post-baseline abnormal findings assessed as clinically significant will be recorded as an adverse event.

8.4.3 Body Weight

Body weight will be recorded at screening, baseline, and every 3 months.

8.4.4 Vital Signs

Vital signs (temperature, respiratory rate, blood pressure, and heart rate) will be assessed at screening, baseline, every 3 months during site and remote visits during treatment and safety follow-up, if appropriate. Blood pressure and heart rate will be obtained following a resting period of at least 5 minutes. Blood pressure should be measured on the same arm and in the same position unless physical changes such as onset of deformities preclude repeat measures on the original arm. The instruments (the one at the site and the one for the remote visit) should also remaining consistent at each visit.

8.4.5 Electrocardiograms

A 12-lead electrocardiogram (ECG) will be performed at screening, baseline, and at Months 12 and 24. Measures should be obtained with subjects in the supine position following a resting period of 5 minutes. Any post-baseline abnormal ECG assessed as clinically significant will be recorded as an adverse event.

8.4.6 Clinical Laboratory Tests

Blood and urine samples for each subject will be collected for hematology, biochemistry (includes lipids and serum pregnancy test, when applicable), and urinalysis assessments at screening, baseline, and every 3 months. Parathyroid hormone is obtained at baseline. Samples may be collected at other times if medically necessary. If no clinically significant abnormalities in hematology, biochemistry, or urinalysis are observed after 12 months of dosing, the frequency of clinical laboratory testing may be decreased to every 6 months to decrease subject burden.

Blood/urine pregnancy testing is discussed in Section 8.4.7. The blood volume drawn at each visit will be approximately 6 mL, representing less than 2.5% of total blood volume. An extra 3 mL will be collected at screening for the genotyping sample and 10 mL will be required at Month 1 for pharmacokinetic samples (Section 8.6). Thus, the total blood volume drawn from a subject over the course of the entire study (screening to 24 months, totaling 11 visits) will be approximately 75 mL. Should a subject have clinically significant abnormal laboratory results at the end-of-treatment visit and not participate in the open-label extension study, an additional 2 to 12 mL may be collected at the safety follow-up visits, and 4 weeks and 6 months after the end-of treatment. If the safety laboratory results are normal or if abnormalities are not clinically significant at the 4-week safety follow-up visit, they do not need to be repeated at the 6-month safety follow-up visit. When multiple blood samplings are performed at one visit, as with pharmacokinetic blood samples, an intravenous blood drawing catheter may be used to minimize needle punctures. If 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. This will ensure that the total blood volume drawn is within the established limits.

Sample collection and preparation will be performed by qualified and trained study personnel at the study site and/or the subject's home per protocol, according to the clinical laboratory manual and applicable regulations. To ensure consistent generation and interpretation of results, a central testing laboratory will perform analyses of clinical laboratory samples. Samples will be packaged and shipped to the designated laboratory for testing.

The Investigator will be copied on all laboratory reports and will review and assess the clinical significance of all results that are outside of normal limits. Any post-baseline abnormal laboratory value assessed as clinically significant will be recorded as an adverse event.

The Investigator will be notified of any protocol-specified laboratory test that could not be obtained. The Investigator will assess whether test attempts should be repeated for the current time point or whether to reassess the subject at the next scheduled visit according to the subject's current clinical status (eg, adverse events, vital signs) and previous laboratory results.

Table 7 presents the clinical laboratory parameters that will be assessed in this study.

Table 7. Clinical Laboratory Parameters

Biochemistry	
Sodium	Globulin
Potassium	Alkaline phosphatase (ALP)
Chloride	Aspartate transaminase (AST)
Bicarbonate	Alanine transaminase (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	Parathyroid hormone (at baseline)[3]
Lipid Profile[1]	
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[2]	
pH	Blood (free hemoglobin)
Protein	Nitrite
Glucose	Urobilinogen
Ketones	Specific gravity
Bilirubin	Color and appearance

[1] Non-fasting lipid profile will be obtained. If the triglyceride is abnormal, a fasting triglyceride should be repeated.

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

[3] Tests for parathyroid hormone and 25-hydroxy vitamin D may be performed as-needed to evaluate clinically significant changes in bone mineral density.

8.4.7 Pregnancy Testing

Pregnancy testing will be conducted on subjects of child-bearing potential at screening, baseline, and every month thereafter until completion of the 4-week safety follow-up (if applicable). If the screening sample is positive, the subject will not be enrolled. Urine pregnancy testing will be performed on the months that do not coincide with site or remote visits that have blood sampling. For site and remote visits requiring blood sampling for safety (ie, every 3 months), a serum pregnancy test will be performed (with sensitivity of at least 50 mIU/mL). Any positive pregnancy test during study participation will result in immediate discontinuation of the study drug.

8.4.8 Adverse Events

Adverse event monitoring will be conducted throughout the study. The adverse event and serious adverse event reporting period begins at the time of informed consent and continues through study completion. The Investigator will follow-up on all adverse events to the end of the reporting period or until the symptoms stabilize and follow-up is no longer necessary.

Definitions, documentation, and reporting of adverse events are described in Section 11.2. Serious adverse events must be reported within 24 hours of awareness as described in Section 11.2.8. If a subject or female partner of a male subject becomes pregnant during the study, they will be followed throughout their pregnancy and the health status of the baby will be verified (Section 11.2.9).

Attention should be paid to mucocutaneous effects, serum lipids, liver enzymes, and other potential retinoid side effects (see details listed in Section 8.5). In addition, limb/joint adverse events in subjects with open epiphyses will be evaluated by clinical or radiographic assessments deemed appropriate by the Investigator.

8.5 Special Safety Assessments

Considering the established safety profile of the currently marketed oral systemic retinoids and hypothesized potential concerns, clinical and laboratory monitoring of select adverse events and laboratory abnormalities in subjects in this study is indicated. Specific safety concerns that will be monitored in the study are described in the subsections that follow.

8.5.1 Bone Safety Management Plan

To enhance subject safety monitoring, a Bone Safety Management Plan has been developed to supplement per-protocol safety monitoring. The plan provides further details for monitoring of growth plates (Section 8.5.2), bone density (Section 8.5.3), growth (Sections 8.5.4 and 8.5.5), and osteonecrosis (Section 8.5.6). 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.

8.5.2 Knee and Hand/Wrist Radiographs for Bone Age

All subjects will undergo left hand/wrist and left knee radiographs at screening unless surgery was performed on that limb within the preceding 12 months. If such surgery did occur, the contralateral limb should be imaged. Subsequent radiographs should be performed on the same limbs imaged at screening. The screening hand and knee radiographs will be used to determine bone age and serve as baseline for safety assessments. To be eligible for the study, the screening bone age must be ≤14 years, 0 months as assessed by a central reader using the Greulich-Pyle method.

Due to the theoretical potential for palovarotene to cause adverse effects on long bone growth, all subjects will undergo knee and hand/wrist radiographs (anterior/posterior view) at screening and every 6 months (Months 6, 12, 18, and 24), and at the 6-month safety follow-up visit, if appropriate.

Once a subject has achieved 100% skeletal maturity (ie, complete fusion of 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 anatomical locations, then only the location that is still maturing needs to be monitored.

A central imaging laboratory will read all radiographs to ensure consistent assessment of the radiographs for growth plates abnormalities. The Investigator will be provided with 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 adverse event.

8.5.3 Bone Densitometry

Due to the potential effects of palovarotene on bone mineral deposition, bone mineral content (BMC), areal bone mineral density (aBMD), and bone area at the lumbar spine, hip, and the mid-third radius will be assessed with DXA at baseline, every 6 months (Months 6, 12, 18, and 24), and at the 6-month safety follow-up, if appropriate. Scans may be performed within ±4 weeks of a study visit to allow flexibility of scheduling. To optimize subject positioning for DXA, the unaffected or the least affected hip or radius should be scanned, with subsequent scans performed on the same region. Analyses will be conducted to evaluate BMC, aBMD, and bone area (percentage changes from baseline) in the lumbar spine, hip, and mid-third radius. Spine BMC and aBMD z-scores (changes from baseline) will be calculated (per availability of reference data) and adjusted for height.

The following summarizes the stepwise process for evaluating decreases in aBMD and aBMD-loss-triggered stopping criteria:

1. An aBMD loss of 5% in the lumbar spine, hip, and/or the one-third radius from baseline will be set as an alert threshold for further evaluation.

2. An aBMD decrease of 5% or more from baseline in the spine and a change from baseline in the height-adjusted spine aBMD z-score of ≤-1 will require a repeat DXA scan to confirm that differences are not artefactual (eg, due to subject positioning). Relevant laboratory assessments, such as those for parathyroid hormone and 25-hydroxy vitamin D, may be obtained as needed to determine the underlying causes of bone mass loss. If aBMD loss in the spine (aBMD loss ≥5% and height-adjusted spine aBMD z-score of ≤-1) is confirmed, and no other factors account for the changes (eg, due to prolonged immobility), the subject should discontinue the study drug.

3. Any aBMD loss in a subject found in other anatomical regions meeting the 5% alert threshold will be provided to the Investigator. These subjects will continue the study and be re-evaluated at the next regularly scheduled 6-month assessment. Equivocal cases will be discussed with the medical monitor.

8.5.4 Growth Assessment

Growth will be assessed in all subjects by a stadiometer for linear growth and by measuring the knee-height in both knees at baseline, every 6 months (Months 6, 12, 18, and 24), and at the 6-month safety follow-up visit, if appropriate. Measurements will be performed in triplicate at the

study site by trained and qualified study personnel. The stadiometric measurement instructions will include practices that reduce measurement error including calibration of equipment, proper subject positioning, and measurement capture. To standardize the performance of procedures and minimize measurement variability, the same examiner should be used whenever possible.

If a subject does not exhibit any linear growth (measured by stadiometer) from the preceding 6-month height measure, the subject will visit the site to have his/her linear height reassessed after 3 months to confirm growth retardation. Negative height gains will not be acted on until confirmation, as this most likely represents measurement error. Questionable observations will be discussed with the medical monitor and may warrant an additional 3-month evaluation period prior to dose modification. If a lack of linear growth is confirmed, and no other reason for a normally expected lack of growth is evident (such as achievement of post-pubertal growth), the study drug regimen will be modified to every other day dosing. As the potential effects of retinoids on long bone development is dose dependent, this dosage modification is expected to ameliorate retinoid-associated growth retardation. If growth arrest continues despite dosage modification, the study drug will be permanently discontinued. If the growth improves, subjects will continue with the modified regimen.

8.5.5 Bone Lengths

Linear lengths of the ulna, radius, tibia, fibula, and femur will be assessed with bilateral upper and lower extremity anterior/posterior radiographs at baseline and at Months 12 and 24.

8.5.6 Osteonecrosis

Due to the presence of AVN of the femoral head in wild-type rats receiving high-dose palovarotene (Section 1.3.1), whole body MRI scans obtained for the primary efficacy analysis will undergo safety reads by two blinded independent radiologists for signs of osteonecrosis at the hips, shoulders, and knees. If the assessment indicates possible or probable osteonecrosis, then palovarotene will be discontinued while further assessment is performed to determine whether osteonecrosis is definite. If osteonecrosis is definite, then palovarotene will be permanently discontinued. In the event of an early discontinuation of the study drug, subjects should be encouraged to complete all study assessments and continue in the study until the end of study.

8.5.7 Tanner Staging

To assess growth and development, Tanner staging will be performed at baseline and at Months 12 and 24. Tanner staging will no longer be necessary once Stage V is reached.

8.5.8 Mucocutaneous Effects

At every visit during the treatment period, subjects will be monitored for adverse events, which includes mucocutaneous events (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 11.2.3), all mucocutaneous adverse events will be rated according to the most recent version of the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03, 14 June 2010 (Appendix 5).

To minimize the occurrence of mucocutaneous effects, preventive therapy (skin emollients, lip moisturizers, artificial tears, or other helpful treatments) should be used. Additional symptomatic therapy may be given if deemed necessary by the Investigator.

Although palovarotene has not been proven to be phototoxic, precautionary measures for phototoxicity are recommended. 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).

Dose modification is recommended for intolerable mucocutaneous effects that would otherwise result in discontinuation from the study. Dose modification procedures are described in Section 7.4.

8.5.9 Columbia-Suicide Severity Rating Scale

In accordance with the Guidance for Industry Suicidal Ideation and Behavior – Prospective Assessment of Occurrence in Clinical Trials (2012),[42] all subjects 8 years of age and older will be assessed for suicidal ideation and behavior using the C-SSRS (Appendix 6). The pediatric form will be used for subjects 8 to 11 years of age and the adult form will be used for subjects 12 years of age and older. Study personnel administering the questionnaire will receive formal training to ensure accuracy and consistency in application of the instrument.

Subjects will be assessed at screening, baseline, and every 3 months during each site and remote visit during the treatment period. Study personnel administering the questionnaire will receive formal training to ensure accuracy and consistency in application of the instrument.

Any subject experiencing suicidal ideation (type 4 or 5) in the past month or any suicidal behavior within the past year as defined by the C-SSRS will not be eligible to receive study drug. Any subject experiencing type 4 or type 5 suicidal ideation or any suicidal behavior during treatment will have the study drug immediately withheld. The Investigator will refer all such subjects to a mental health professional for evaluation and counseling as appropriate.

8.5.10 Serum Lipids

With oral retinoid therapy, elevations in triglycerides may occur after 2 to 4 weeks of treatment. To minimize discomfort of pediatric subjects, a complete non-fasting lipid profile will be obtained from all subjects as part of the biochemistry testing at screening and every 3 months. If no abnormalities are observed after 12 months of dosing, serum lipid monitoring may be decreased to every 6 months.

If a non-fasting serum triglyceride test result is abnormal, a fasting lipid panel should be repeated. If fasting serum triglyceride levels are ≥800 mg/dL, the study drug should be immediately discontinued, with follow-up assessments performed per protocol.

8.5.11 Liver Enzymes

Monitoring liver enzymes is required to establish the clinical safety profile of palovarotene. Alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP),

total bilirubin, and gamma glutamyl transferase (GGT) determinations will be made per the Schedule of Assessments (Table 1).

Treatment 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, abdominal pain, malaise, nausea, and /or vomiting

Liver toxicity evaluation will follow the FDA Guidance for Industry *Drug-Induced Liver Injury: Premarketing Clinical Evaluation* (July 2009).[43] If no abnormalities are observed after 12 months of dosing, liver enzyme monitoring may be decreased to every 6 months.

8.5.12 Lipase/Amylase

Amylase and lipase will be monitored in all subjects as part of the biochemistry testing at screening and every 3 months. If no abnormalities are observed after 12 months of dosing, amylase and lipase monitoring may be decreased to every 6 months.

Lipase and/or amylase increases during 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 per the Investigator's judgment, with follow-up assessments performed per protocol.

8.5.13 Central Nervous System

Retinoid use has been associated with several cases of benign intracranial hypertension (also known as pseudotumor cerebri), with some involving concomitant use of tetracyclines.

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

However, subjects with a headache of unusual characteristics (eg, severity, location, pattern) should have contact with the Investigator. In case of such a headache, it is at the Investigator's discretion whether to refer subjects for neurological and/or ophthalmological examination to rule out benign intracranial hypertension.

8.5.14 Hearing and Visual Disturbances

Hearing and visual acuity testing will occur at baseline and at Months 12 and 24 with a visit window of ±4 weeks to allow for flexibility in scheduling. Hearing will be assessed with age-appropriate audiometry testing (play behavior or conventional). The assessments will determine auditory thresholds in response to frequency-specific stimuli (ie, pure tone). Speech threshold audiometry may be performed for subjects unable to undergo pure tone audiometry. Subjects with a hearing impairment at baseline or an impairment identified during testing should

receive an appropriate hearing evaluation to determine the severity and type (conductive, sensorineural, or mixed) of hearing impairment.

Impaired hearing has been reported in subjects taking retinoids. Subjects who experience tinnitus or hearing impairment during the study should be referred to specialized care on an ad hoc basis for further evaluation. The subject with a confirmed diagnosis of clinically significant hearing impairment (assessed as related to the study drug by the Investigator) will be discontinued from treatment.

Corneal opacities have occurred in subjects receiving retinoids and were reversible upon drug discontinuation. Subjects with unexplained visual impairment and corneal opacity should be referred for further ophthalmologic evaluation.

Decreased night vision has been reported during retinoid therapy. Because the onset in some subjects can be sudden, subjects should be informed and warned to be cautious when driving or operating vehicles at night.

8.5.15 Teratogenicity

Palovarotene must not be used by female subjects who are or 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 brief periods. 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; premature births are also 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 palates. Documented internal abnormalities with other retinoids include central nervous system abnormalities (such as cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit), cardiovascular and thymus gland abnormalities, and parathyroid hormone deficiency. In some cases, certain abnormalities previously noted with other retinoids resulted in death.

8.6 Pharmacokinetics

The steady-state pharmacokinetics of palovarotene will be assessed at Month 1. Pharmacokinetic samples may be obtained at the site or obtained by a visiting nurse during the remote visit at the discretion of the subject and investigator. Sparse pharmacokinetic blood sampling will be collected before dosing and at 3, 6, 10, and 24 hours post-dose. Pharmacokinetic sampling may be repeated at a subsequent visit if the first attempt was unsuccessful.

Palovarotene plasma concentrations will be determined using a validated liquid chromatography-mass spectrometry method. Exploration of any relationships with palovarotene exposure will be performed.

The time of sample collection relative to the time of dosing on the sparse sampling days will be recorded. Detailed instructions for the collection, storage, labeling, and shipment of all samples will be provided in the clinical laboratory manual.

8.7 Palatability of Sprinkled Drug Product

The palatability of drug product versus placebo sprinkled onto a spoonful of specific foods will be assessed following administration of the first dose (Day 1) and at Month 1 (concurrent with PK assessment). Only subjects ≥4 years of age will be assessed. The subject will be asked to mark how much he/she liked the capsule contents on a 5-point hedonic face scale (Appendix 7).[44] As the concentration of palovarotene within the capsules is low, the predominant taste is that of the inactive component lactose, which is slightly sweet (ie, nearly tasteless).

9 Data Collection, Management, and Quality Assurance

9.1 Data Capture and Management

The sponsor will provide the clinic 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 data entered in each subject's eCRF. Source documentation supporting eCRF data should indicate subjects' participation in the study and document the dates and details of study procedures, adverse events, and subject status.

The Investigator or designated representative should complete the eCRF according to the completion guidelines.

9.2 Data Quality Assurance

As per Good Clinical Practice (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 study. In addition, inspections may be conducted by regulatory authorities at their discretion.

If sites receive a request for an inspection, or written or oral inquiries from a regulatory authority regarding any aspect of the institution's or investigator's activities related to this study, the Investigator must immediately notify the sponsor of the request. Following the inspection and/or audit, the Investigator must notify the sponsor of any violation or deficiency noted by the regulatory authority.

10 Statistical Considerations

10.1 Sample Size Determination

The sample size required for this Phase 2 study was determined by simulation. The annualized rate of new OCs is assumed to be 1.15 based on analyses of the IOR REM (Section 4.5). Osteochondroma counts are assumed to follow a negative binomial distribution parameterized with a variance inflation factor of 2.0.

Multiple comparisons between the 5.0-mg palovarotene and placebo groups and the 2.5-mg palovarotene and placebo groups will be adjusted using the Bonferroni method. Therefore, the sample size simulations were conducted with a one-sided, overall type I error rate of 1.25% for each active treatment group comparison with placebo.

There will be one interim analysis (when all subjects complete 12 months of treatment) and a final analysis. At the interim and final analyses, the O'Brien-Fleming alpha-spending function will be used to specify the alpha level threshold for determination of treatment effect significance. Assuming 50% statistical information at the interim analysis, the one-sided p-value significance threshold used in the interim analysis comparing the 5.0-mg palovarotene and placebo groups and the 2.5-mg palovarotene and placebo groups is0.0007. Likewise, the one-sided p-value significance threshold in the final analysis will be 0.0122. Study success is defined as having one or both palovarotene treatment arms demonstrate a statistically significant treatment effect.

Assuming 80 subjects will be randomized to each treatment group and a 50% palovarotene treatment effect in one treatment arm and no effect in the other, the probability of declaring study success at the interim analysis is 0.34, whereas the overall probability of study success is 0.87. If there is a 50% palovarotene treatment effect for both dosages, the probability of declaring study success at the interim analysis is 0.49 and the overall probability of study success is 0.95.

The number of subjects per group accounts for 15% who may discontinue the study. Success at each analysis is achieved if one or both of the palovarotene treatment groups is significantly superior versus placebo.

10.2 Disposition of Subjects

Screened subjects will be defined as any patient who has signed the informed consent form.

10.3 Analysis Populations

The Randomized Set will include any subject allocated to a randomized treatment group, regardless of whether or not the study drug was administered.

The Full Analysis Set (FAS) will include randomized subjects who receive at least one dose of study drug. Analyses using the FAS will be according to the treatment group allocated by randomization and not the actual treatment received.

The Per-Protocol Set (PP) will be a subset of the FAS and include subjects with no major protocol deviations that will interfere with the assessment of the primary efficacy endpoint and

subjects with at least 80% compliance to the dosage regimen. This subset will be described further in the Statistical Analysis Plan (SAP).

The Safety Set (SS) will be a subset of the Randomized Set and include randomized subjects who receive at least one dose of study drug. The SS will be analyzed according to the randomized treatment received, unless otherwise specified.

The Pharmacokinetic Set (PS) will be a subset of the SS and include subjects with evaluable pharmacokinetics data.

10.4 Statistical Methods

10.4.1 Extent of Exposure

The extent of study treatment exposure and compliance will be summarized for the SS. The duration of study drug exposure is defined as [last dose date – first dose date + 1 day] regardless of unplanned intermittent discontinuations.

Treatment compliance, the number of dose interruptions, and the percentage of subjects with compliance <80% will be summarized.

10.4.2 Analyses of Efficacy Endpoints

10.4.2.1 Primary Efficacy Analysis

The primary efficacy endpoint is the annualized rate of new OCs as assessed by whole body MRI. The primary efficacy analysis comparing the rate of OCs between palovarotene-treated subjects and placebo-treated subjects will be conducted using a negative binomial regression model using the FAS. Covariates in the model will include treatment group indicators, baseline age, sex, and Ext1/2 mutation status. Robust variance estimation will be used and an offset variable equal to the log of the number of years of follow-up will be included.

The estimated rate ratio comparing the rate of OCs between palovarotene-treated subjects and placebo-treated subjects and the associated Wald statistics will be used for hypothesis testing. The primary efficacy hypothesis testing will compare the 5.0-mg palovarotene and placebo groups and the 2.5-mg palovarotene and placebo groups; the multiple comparisons will be accounted for with a Bonferroni adjustment. There will be one interim efficacy analysis (planned for when all subjects complete 12 months of treatment) and a final analysis. The O'Brien-Fleming alpha-spending function will be used to specify the alpha level threshold for treatment effect significance at the interim and final analyses. Assuming 50% statistical information at the interim analysis, the one-sided p-value significance threshold used in the interim analysis in the 5.0-mg palovarotene versus placebo groups comparison and the 2.5-mg palovarotene versus placebo groups comparison is 0.007. Likewise, the one-sided p-value significance threshold in the final analysis will be 0.0122. Study success is defined as having one or both palovarotene treatment groups demonstrate a statistically significant treatment effect.

10.4.2.2 Secondary Efficacy Analyses

The change from baseline in the total volume of OCs as assessed by whole body MRI at Month 24 will be analyzed using a mixed model for repeated measures, with baseline total volume of OCs, baseline age, sex, and Ext1/2 mutation status as covariates and treatment group, visit, and treatment group by visit interaction as factor variables.

The proportion of subjects with no new OCs as assessed by whole body MRI will be analyzed with logistic regression using the same covariates included in the primary analysis described in Section 10.4.2.1.

The annualized rate of new and worsening deformities and MO-related surgeries will be analyzed as described from the primary endpoint analysis.

10.4.3 Analyses of Safety Data

All safety analyses will be performed on the SS. For the safety analyses, the baseline value is defined generally as the last available value before randomization. Safety analyses and the summary of results will be according to treatment group.

10.4.3.1 Adverse Events

Adverse event observation periods are as follows:

- Pre-treatment adverse events are adverse events that developed or worsened following informed consent but prior to the first dose of study drug.
- On-treatment adverse events are adverse events that developed or worsened from the first administration date of the study drug to the last administration date of the study drug.

The on-study period will include pre-treatment and on-treatment observation periods. Summaries of treatment-emergent adverse events will include all on-treatment adverse events.

All adverse events will be MedDRA coded. Mucocutaneous adverse events will be further graded according to CTCAE, Version 4.03, 14 June 2010 (Appendix 5).

Tables of the incidence of adverse event will be presented by system organ class and preferred term. Multiple occurrences of the same event in the same subject will be counted only once in the tables.

The incidence of treatment-emergent adverse events and adverse events associated with retinoids will be tabulated by severity (Section 11.2.3), and by relationship to treatment. In tabulating the severity of adverse events, the highest severity will be assigned to a subject with more than one occurrence of the same adverse event. Relationships of the adverse events to treatment will be categorized as not related, possibly related, probably related, or definitely related (defined in Section 11.2.4). The highest level of association will be reported in subjects with differing relationships for the same adverse event. Retinoid-associated adverse events will be tabulated by CTCAE grade.

Listings of adverse events and serious adverse events for all subjects will be provided. The listings will include the severity of the event, its relationship to treatment, the actions taken regarding treatment, and the outcome of the event.

The incidence of adverse events leading to study drug interruption and study drug discontinuations will also be summarized by treatment group, with details provided in the listings.

10.4.3.2 Special Safety Assessments

Linear growth as assessed by linear height, knee heights, and bone lengths of the tibia, femur, tibia, ulna, and radius will be summarized by time. In addition, z-scores of linear heights will be summarized by time.

Abnormalities in the hand/wrist and knee growth plates and changes from baseline will be summarized by time. Details of subjects with growth plate abnormalities will be provided in a listing.

The BMD and the percentage change from baseline of BMD at the lumbar spine, hip, and mid radius; and the height-adjusted z-score of areal BMD at the lumbar spine and hip will be summarized by time. Details of subjects developing osteonecrosis during the study will be provided in a listing.

Details of subjects with any type 4 or 5 suicide ideations in the C-SSRS or any suicide behavior during the study will be provided in a listing.

10.4.3.3 Clinical Laboratory and Other Safety Findings

Changes in ECGs, vital signs (temperature, respiratory rate, blood pressure, and heart rate), body weight, laboratory parameters (hematology, biochemistry, and urinalysis) will be assessed descriptively, with pre-treatment, on-treatment, and change from pre-treatment values calculated.

Any post-baseline findings assessed as clinically significant will be recorded as adverse events.

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

10.4.4 Pharmacokinetics Analysis

Serum concentrations of palovarotene will be summarized by visit using arithmetic and geometric means, standard deviations, standard errors of the means, coefficients of variation, minimums, medians, and maximums.

10.5 Interim Analysis

An interim efficacy and safety analysis will occur when all subjects have completed the 12 months of treatment. The analysis will be conducted by a treatment-blinded, external vendor under the auspices of a DMC (see Section 11.3) to assess whether efficacy is sufficiently demonstrated prior to study completion. The DMC may recommend stopping the study early for

efficacy based on the available interim efficacy and safety data. If the study is stopped early for efficacy, all subjects will be offered enrollment in the open-label extension study. The Month 24 primary efficacy analysis and the pre-specified significance thresholds are described in Section 10.4.2.1.

A futility analysis will be conducted concurrently with the interim efficacy analysis. Based on the results of this analysis, the DMC may recommend stopping the study early due to insufficient efficacy. The DMC may also recommend moving subjects from one palovarotene treatment group to another based on the futility analysis results and available safety data.

11 Monitoring and Reporting

11.1 Good Clinical Practice 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 study data are accurate, complete, and verifiable from source documents, and finally that the conduct of the study 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.

11.2 Safety Monitoring and Reporting

11.2.1 Adverse Event Definition

An adverse event is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product during a study and that does not necessarily have a causal relationship to treatment. Therefore, an adverse event can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, regardless of its assessment of relatedness.

Disease, signs, symptoms, and/or laboratory abnormalities already existing prior to informed consent are not considered adverse events 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, ECG, physical examination finding, or other objective finding should be reported as an adverse event, whether it represents an exacerbation or a new abnormality.

11.2.2 Serious Adverse Event or Adverse Drug Reaction Definition

A serious adverse event, experience, or reaction is an untoward medical occurrence at any dose that results in any of the following outcomes:

- Death.
- Life threatening situation (the subject was at risk of death at the time of the event), which does not refer to the hypothetical risk of death if the adverse event 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 a serious adverse event 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).

11.2.3 Severity of Adverse Events

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

- *Mild*: adverse events that are easily tolerated with no disruption of normal daily activity.
- *Moderate*: adverse events that cause sufficient discomfort to interfere with daily activity and/or require simple therapeutic treatments.
- *Severe*: adverse 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 (Appendix 5). Sites will be provided with specific criteria for the coding of adverse events.

11.2.4 Causality Assessment

For purposes of reporting adverse events, the assessment of causality will require that Investigators assess the relationship of any adverse event to the study drug. To promote consistency across assessments, investigators should take the following definitions into consideration, along with good clinical and scientific judgment when determining the relationship of the study drug to an adverse event:

- *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.

11.2.5 Action Taken with Study Drug

The action taken to remedy reported/observed adverse events will be defined as follows:

1. None
2. Study drug dosage modified
3. Study drug dosage interrupted
4. Study drug permanently discontinued

11.2.6 Outcome of Adverse Event

The outcome of adverse events will be recorded as follows:

1. Event resolved with no sequelae
2. Event resolved with sequelae
3. Event ongoing
4. Death

11.2.7 Adverse Event Documentation

An Adverse Event Report or Serious Adverse Event Report will be completed for all adverse events. Signs and symptoms of each adverse event should be described in detail: nature, date of onset, end date, duration, severity, relationship to study drug, action taken, and outcome.

11.2.8 Reporting of Serious Adverse Events

All serious adverse events must be reported within 24 hours to the appropriate Clinical Safety Group:

North America Serious Adverse Event Hotline

Tel: PPD
Fax: PPD

Latin America Serious Adverse Event Hotline

Tel: PPD
Fax: PPD

EMEA/APAC Serious Adverse Event Hotline

Tel: PPD
Fax: PPD

The Investigator will be requested to complete and transmit to the sponsor or designee the information of the serious adverse event using the electronic reporting form, or a paper form should the electronic system not be available. The paper serious adverse event form should only be used when the electronic reporting form via electronic data capture is unavailable.

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, serious adverse events, 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 serious adverse events 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 serious adverse events occurring during the study that are likely to affect subject safety or the conduct of the study.

11.2.9 Reporting of Pregnancy

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

11.2.10 Follow-up of Adverse Events and Serious Adverse Events

The adverse event and serious adverse event reporting period begins at the time of informed consent and continues through study completion. For subjects not enrolling into the open-label

extension, two follow-up safety visits 4 weeks and 6 months after completion of study drug treatment (the end-of-treatment visit) will be performed. Adverse events will be assessed at every site and remote visit. The Investigator will follow-up on all adverse events up to the end of the reporting period or until the symptoms stabilize and follow-up is no longer necessary.

11.2.11 Reporting Concomitant Medications

All concomitant medication taken by the subject during the study and the reason for use of the medication must be recorded in the source document. See Section 6.3 for restrictions on concomitant medications.

11.3 Data Monitoring Committee

A DMC will be established to review safety data periodically and on an ad hoc basis as outlined in the DMC Charter. The DMC Charter will be maintained separately from the study protocol. The DMC can recommend a temporary or permanent stop 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 analysis (see Section 10.5).

Safety information from both MO and FOP DMC safety reviews will be shared across the clinical programs. The FOP DMC will review the 6-month bone safety data from at least 20 skeletally immature FOP subjects. Assuming that the safety profile is deemed favorable by the FOP DMC, the MO DMC will be notified of the initiation of enrollment of 2- to <7-year-old subjects in the EU.

The DMC will include members with relevant clinical expertise. The methodology and the operating procedures for the safety reviews will be developed by DMC members in collaboration with the sponsor and will be documented in the DMC Charter.

12 Ethical, Regulatory, and Administrative Requirements

12.1 Ethical Conduct of the Study

This clinical study will be conducted in accordance with the protocol and with the ethical principles in the Declaration of Helsinki (Appendix 8), inclusive of any subsequent amendment(s); and principles consistent with the International Council for Harmonisation Good Clinical Practice (ICH GCP),[45] European Union Directive 2001/20/EC,[46] United States Food and Drug Administration (FDA) Code of Federal Regulations, and other applicable local regulatory requirements, whichever affords the greater subject protection.

12.2 Ethics Board Approval

The IRB/IEC will comply with ICH GCP and local regulatory requirements. The IRB/IEC 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 study site. The committee will review the science, medical aspects, and ethics of the clinical study.

The following documents will be submitted to the IRB/IEC for review:

- The final study protocol and amendment(s).
- The Investigator's Brochure.
- Written ICF and consent/assent form updates.
- Written information to be provided to subjects/caregivers.
- Subject recruitment procedures.
- Information about payments and compensation available to subjects and caregivers.
- Investigators' 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 documents to be used in Study PVO-2A-201 must be approved by the IRB/IEC prior to study initiation. 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 members, their qualifications, and their affiliations. The IRB/IEC will conduct a continuing review of the ongoing study at appropriate intervals.

The Investigator will be responsible for ensuring the initial approval of the study protocol, written ICF, consent form updates, subject recruitment materials, 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 serious adverse events likely to affect the subject safety 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.

12.3 Informed Consent Procedures

Of note, the word "caregiver(s)" is used throughout this protocol to denote legally authorized representatives of subjects who are under the age of majority according to local regulations.

Prior to a subject's enrollment, the Investigator and/or delegate must fully explain to the subjects and/or caregivers all aspects of the study that are relevant to the decision of participation in the study. The subject's and/or caregiver's informed consent is documented by means of a written, signed, and dated ICF (and age-appropriate assent form if the subject is a minor) per local requirements, prior to the start of the study. The ICF will be written in a language and in a manner understandable to the subjects/caregivers. The Investigator and/or delegate will also sign the ICF. Any modifications to the ICF required by the Investigator prior to submission to the IRB/IEC or requested by the IRB/IEC must be submitted to the sponsor or designee for approval prior to the implementation of the ICF.

One signed and dated copy of the ICF will be given to the subject/caregiver 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 study in his/her medical chart.

Institutions, investigators, CROs, and other persons/organizations 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 Directive on Data Protection, and any other similar regulations or legislation).

Additional considerations concerning informed consent of subjects is discussed in the overall evaluation of risks and benefits of this study in Section 1.4.

12.4 Subject Confidentiality

Any research information obtained about the subject in this study will be kept confidential. A subject will not be identified by name, only by subject number. The subject's name or any identifying information will not appear in any published reports related to this study.

Information obtained from a subject's participation in this study may be disclosed with his/her consent to healthcare providers for obtaining appropriate medical care. The subject's medical records/charts and tests that include his/her name may be made available to the appropriate CRO, the sponsor and its potential partners, and any regulatory authority. This is for verifying information obtained for this study. Confidentiality will be maintained throughout the study within 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 in a secure area under the supervision of the study investigator and will not be transferred outside of the study 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 remain in the study. No additional 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, to preserve the scientific integrity and quality of the study.

12.5 Publications 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 for the development of

palovarotene and may be disclosed to the 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 journals. A publications committee comprising investigators from the study and representatives from the sponsor, as appropriate, will be formed to oversee the publication of the study results, and will reflect the experience of all participating study sites. Subsequently, individual investigators may publish results from the study in compliance with their agreement with the sponsor.

12.6 Administrative Requirements

12.6.1 Amendments to the Protocol

Modifications to the protocol are only possible through approved protocol amendments authorized by the study sponsor. All protocol amendments will be approved by the appropriate regulatory authorities as well as each IRB/IEC 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 subject.

12.6.2 Protocol Deviations

The protocol must be read thoroughly, and the instructions followed exactly. A major deviation from the protocol must be reported as soon as possible to the sponsor. The governing reporting guidelines for protocol deviations must be adhered to by the Investigator.

12.6.3 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 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.

12.7 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.

13 Investigator Agreement

I have read Protocol PVO-2A-201, Amendment 2, dated 23 April 2019:

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Palovarotene in Subjects with Multiple Osteochondromas.

I agree to conduct the study as detailed herein and in compliance with ICH Guidelines for Good Clinical Practice 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

_____

_____

_____

Study site or name of institution and location (printed)

14 References

1. Schmale GA, Conrad EU 3rd, Raskind WH. The natural history of hereditary multiple exostoses. *J Bone Joint Surg Am*. 1994;76(7):986-992.

2. Goud AL, de Lange J, Scholtes VAB, Bulstra SK, Ham SJ. Pain, physical and social functioning, and quality of life in individuals with multiple hereditary exostoses in The Netherlands: a national cohort study. *J Bone Joint Surg Am*. 2012;94(11):1013-1020. doi:10.2106/JBJS.K.00406

3. Wuyts W, Schmale GA, Chansky HA, Raskind WH. Hereditary multiple osteochondromas. 2013. http://www.ncbi.nlm.nih.gov/books/NBK1235/. Accessed August 3, 2016.

4. Bovée JVMG. Multiple osteochondromas. *Orphanet J Rare Dis*. 2008;3:3. doi:10.1186/1750-1172-3-3

5. Pacifici M. Hereditary Multiple Exostoses: New Insights into Pathogenesis, Clinical Complications, and Potential Treatments. *Curr Osteoporos Rep*. May 2017. doi:10.1007/s11914-017-0355-2

6. Ryckx A, Somers JFA, Allaert L. Hereditary Multiple Exostosis. *Acta Orthop Belg*. 2013;79(6):597-607.

7. J ger M, Westhoff B, Portier S, et al. Clinical outcome and genotype in patients with hereditary multiple exostoses. *J Orthop Res Off Publ Orthop Res Soc*. 2007;25(12):1541-1551. doi:10.1002/jor.20479

8. Pedrini E, Jennes I, Tremosini M, et al. Genotype-phenotype correlation study in 529 patients with multiple hereditary exostoses: identification of "protective" and "risk" factors. *J Bone Joint Surg Am*. 2011;93(24):2294-2302. doi:10.2106/JBJS.J.00949

9. Wicklund CL, Pauli RM, Johnston D, Hecht JT. Natural history study of hereditary multiple exostoses. *Am J Med Genet*. 1995;55(1):43-46. doi:10.1002/ajmg.1320550113

10. D'Ambrosi R, Ragone V, Caldarini C, Serra N, Usuelli FG, Facchini RM. The impact of hereditary multiple exostoses on quality of life, satisfaction, global health status, and pain. *Arch Orthop Trauma Surg*. 2017;137(2):209-215. doi:10.1007/s00402-016-2608-4

11. Huegel J, Sgariglia F, Enomoto-Iwamoto M, Koyama E, Dormans JP, Pacifici M. Heparan sulfate in skeletal development, growth, and pathology: the case of hereditary multiple exostoses. *Dev Dyn Off Publ Am Assoc Anat*. 2013;242(9):1021-1032. doi:10.1002/dvdy.24010

12. Francannet C, Cohen-Tanugi A, Le Merrer M, Munnich A, Bonaventure J, Legeai-Mallet L. Genotype-phenotype correlation in hereditary multiple exostoses. *J Med Genet*. 2001;38(7):430-434.

13. Jones KB, Pacifici M, Hilton MJ. Multiple hereditary exostoses (MHE): elucidating the pathogenesis of a rare skeletal disorder through interdisciplinary research. *Connect Tissue Res*. 2014;55(2):80-88. doi:10.3109/03008207.2013.867957

14. Inubushi T, Lemire I, Irie F, Yamaguchi Y. Palovarotene inhibits osteochondroma formation in a mouse model of multiple hereditary exostoses. *J Bone Miner Res*. 2018;33(4):658-666. doi:10.1002/jbmr.3341

15. Mills CM, Marks R. Adverse reactions to oral retinoids. An update. *Drug Saf*. 1993;9(4):280-290.

16. DiGiovanna JJ. Isotretinoin effects on bone. *J Am Acad Dermatol*. 2001;45(5):S176-182. doi:10.1067/mjd.2001.113721

17. Glaser DL, Economides AN, Wang L, et al. In vivo somatic cell gene transfer of an engineered Noggin mutein prevents BMP4-induced heterotopic ossification. *J Bone Joint Surg Am*. 2003;85-A(12):2332-2342.

18. Zasloff MA, Rocke DM, Crofford LJ, Hahn GV, Kaplan FS. Treatment of patients who have fibrodysplasia ossificans progressiva with isotretinoin. *Clin Orthop*. 1998;(346):121-129.

19. Pacifici M, Cossu G, Molinaro M, Tato F. Vitamin A inhibits chondrogenesis but not myogenesis. *Exp Cell Res*. 1980;129(2):469-474.

20. Weston AD, Chandraratna RAS, Torchia J, Underhill TM. Requirement for RAR-mediated gene repression in skeletal progenitor differentiation. *J Cell Biol*. 2002;158(1):39-51. doi:10.1083/jcb.200112029

21. Weston AD, Blumberg B, Underhill TM. Active repression by unliganded retinoid receptors in development: less is sometimes more. *J Cell Biol*. 2003;161(2):223-228. doi:10.1083/jcb.200211117

22. Duque Orozco MDP, Abousamra O, Rogers KJ, Thacker MM. Magnetic Resonance Imaging in Symptomatic Children With Hereditary Multiple Exostoses of the Hip. *J Pediatr Orthop*. April 2016. doi:10.1097/BPO.0000000000000772

23. Chavhan GB, Babyn PS. Whole-body MR imaging in children: principles, technique, current applications, and future directions. *Radiogr Rev Publ Radiol Soc N Am Inc*. 2011;31(6):1757-1772. doi:10.1148/rg.316115523

24. Thukral BB. Problems and preferences in pediatric imaging. *Indian J Radiol Imaging*. 2015;25(4):359-364. doi:10.4103/0971-3026.169466

25. US Food and Drug Administration. *Background Document: Meeting of the Pediatric Ethics Subcommittee of the Pediatric Advisory Committee*. Silver Spring, MD: US Food and Drug Administration; 2015. https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/ucm433451.htm. Accessed August 26, 2017.

26. American Academy of Pediatrics, American Academy of Pediatric Dentistry, Cote CJ, Wilson S, the Work Group on Sedation. Guidelines for Monitoring and Management of Pediatric Patients During and After Sedation for Diagnostic and Therapeutic Procedures: An Update. *Pediatrics*. 2006;118(6):2587-2602. doi:10.1542/peds.2006-2780

27. Arlachov Y, Ganatra RH. Sedation/anaesthesia in paediatric radiology. *Br J Radiol*. 2012;85(1019):e1018-e1031. doi:10.1259/bjr/28871143

28. Pediatric Ethics Subcommittee. *Background Document. Meeting of the Pediatric Ethics Subcommittee of the Pediatric Advisory Committee*. FDA Pediatric Advisory Committee; 2015. https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/ucm416405.htm. Accessed May 18, 2018.

29. Pediatric Ethics Subcommittee. *Minutes of the Pediatric Ethics Subcommittee of the Pediatric Advisory Committee*. FDA Pediatric Advisory Committee; 2015. https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/ucm416405.htm. Accessed May 18, 2018.

30. Alessio AM, Kinahan PE, Manchanda V, Ghioni V, Aldape L, Parisi MT. Weight-based, low-dose pediatric whole-body PET/CT protocols. *J Nucl Med Off Publ Soc Nucl Med*. 2009;50(10):1570-1577. doi:10.2967/jnumed.109.065912

31. US Federal Government. Code of Federal Regulations Title 21. Section 361.1: Radioactive drugs for certain research uses. Electronic Code of Federal Regulations. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=361. Accessed November 21, 2017.

32. National Research Council (U.S.), ed. *Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2*. Washington, D.C: National Academies Press; 2006.

33. Porter DE, Lonie L, Fraser M, et al. Severity of disease and risk of malignant change in hereditary multiple exostoses. A genotype-phenotype study. *J Bone Joint Surg Br*. 2004;86(7):1041-1046.

34. Jo AR, Jung ST, Kim MS, Oh CS, Min BJ. An Evaluation of Forearm Deformities in Hereditary Multiple Exostoses: Factors Associated With Radial Head Dislocation and Comprehensive Classification. *J Hand Surg*. 2017;42(4):292.e1-292.e8. doi:10.1016/j.jhsa.2017.01.010

35. Mordenti M, Ferrari E, Pedrini E, et al. Validation of a new multiple osteochondromas classification through Switching Neural Networks. *Am J Med Genet A*. 2013;161A(3):556-560. doi:10.1002/ajmg.a.35819

36. Larcher V, Brierley J. Developing guidance for pregnancy testing of adolescents participating in research: ethical, legal and practical considerations. *Arch Dis Child*. 2016;101(10):980-983. doi:10.1136/archdischild-2016-310725

37. Centers for Disease Control and Prevention. Normal Joint Range of Motion Study. Centers for Disease Control and Prevention. https://www.cdc.gov/ncbddd/jointrom/index.html. Published November 29, 2010. Accessed August 26, 2017.

38. Hullmann SE, Ryan JL, Ramsey RR, Chaney JM, Mullins LL. Measures of general pediatric quality of life: Child Health Questionnaire (CHQ), DISABKIDS Chronic Generic Measure (DCGM), KINDL-R, Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales, and Quality of My Life Questionnaire (QoML). *Arthritis Care Res*. 2011;63(S11):S420-S430. doi:10.1002/acr.20637

39. Jacobson CJ, Kashikar-Zuck S, Farrell J, et al. Qualitative Evaluation of Pediatric Pain Behavior, Quality, and Intensity Item Candidates and the PROMIS Pain Domain Framework in Children With Chronic Pain. *J Pain Off J Am Pain Soc*. 2015;16(12):1243-1255. doi:10.1016/j.jpain.2015.08.007

40. Hicks CL, von Baeyer CL, Spafford PA, van Korlaar I, Goodenough B. The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement. *Pain*. 2001;93(2):173-183.

41. International Association for the Study of Pain. Faces Pain Scale - Revised Home. https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1519. Published 2017. Accessed June 12, 2017.

42. US Food and Drug Administration. Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials. https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm315156.htm. Accessed June 7, 2017.

43. US Food and Drug Administration. *Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation*. Silver Spring, MD: US Food and Drug Administration; 2009. https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072278.htm.

44. Cheung LC, Nguyen M, Tang E, et al. Taste evaluation of a novel midazolam tablet for pediatric patients: In vitro drug dissolution, in vivo animal taste aversion and clinical taste perception profiles. *Int J Pharm*. 2018;535(1-2):194-200. doi:10.1016/j.ijpharm.2017.10.060

45. International Conference on Harmonisation. Efficacy Guidelines : ICH Topic E6 - Good Clinical Practice (GCP) Guideline. http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html. Accessed August 28, 2017.

46. European Commission. Directive 2001/20/EC - Public Health - European Commission. Public Health. /health/human-use/clinical-trials/directive_en. Accessed August 28, 2017.

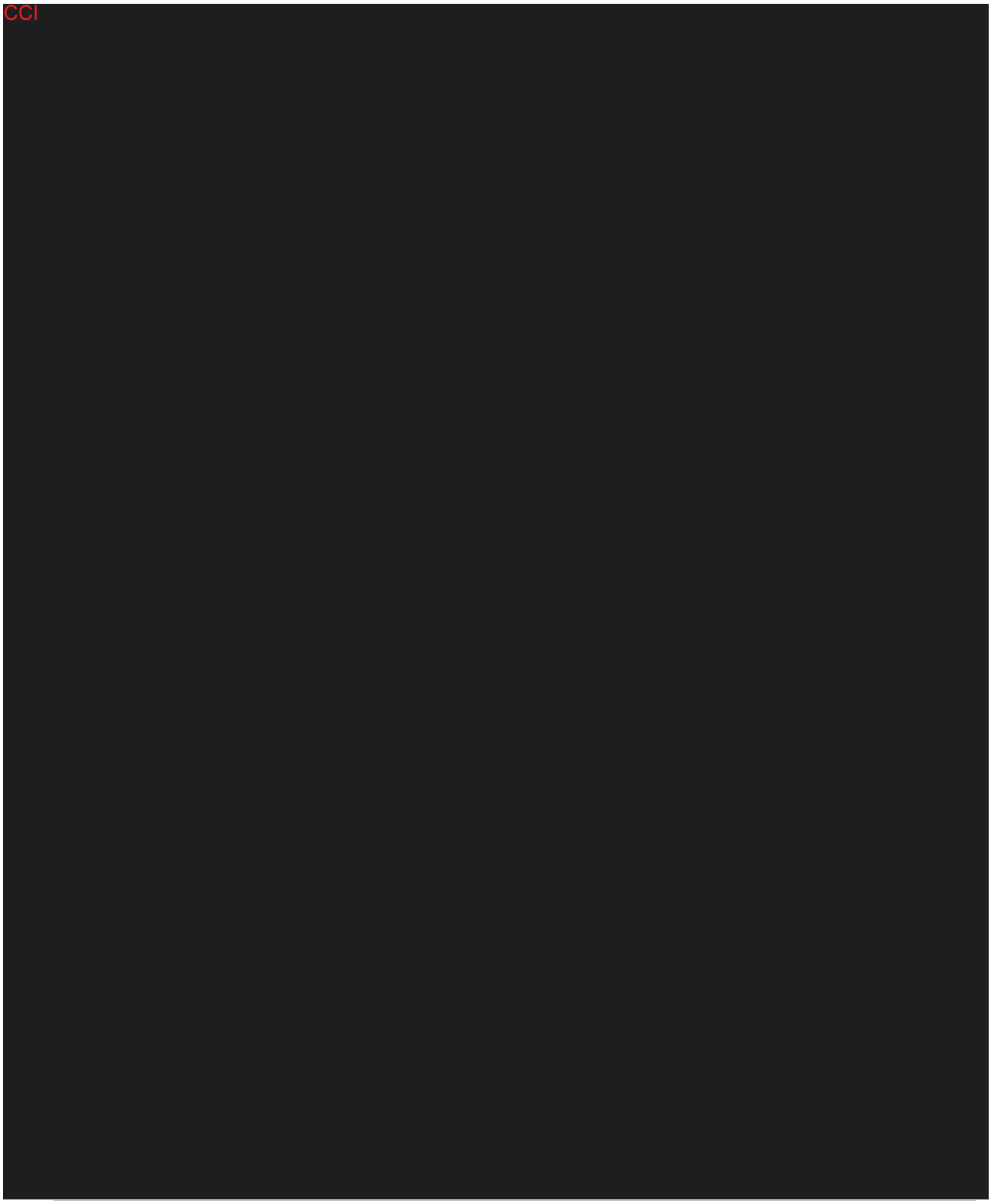
15 Appendices

Appendix 1 CYP450-3A4 Inducers or Inhibitors: Exclusionary Medications

Strong Inducers	Half-life (h)	Strong Inhibitors	Half-life (h)
Carbamazepine[a]	18-55, 12-17	Boceprevir	3.4
Phenobarbital	53-140	Clarithromycin	5-7
Phenytoin	24	Conivaptan	5-8
Rifabutin	16-69	Delavirdine	6
Rifampin	3-4	Fluvoxamine	8-28
St John's Wort[b]	43.1	Grapefruit juice	Not available
Troglitazone	16-34	Imatinib	18-20
Avasimibe	20	Indinavir	1.4-2.2
		Itraconazole[c]	15-27, 64
		Ketoconazole	8
		Lopinavir/ritonavir	5-6
		Mibefradil	17-25
		Nefazodone	2-4
		Nelfinavir	3.5-5
		Posaconazole	20-66
		Ritonavir	3-5
		Saquinavir	7-12
		Telaprevir	9-11 (at steady state)
		Telithromycin	10
		Troleandomycin	1.1
		Voriconazole	6-9 (dose-dependent)
		Suboxone	24-42

[a] Half-life 18-55 hours after a single dose and 12-17 hours after multiple doses.
[b] Major ingredient hyperium's half-life.
[c] Half-life 15-27 hours after a single dose and 64 hours at steady-state.

Appendix 2 Pediatric Quality of Life Inventory



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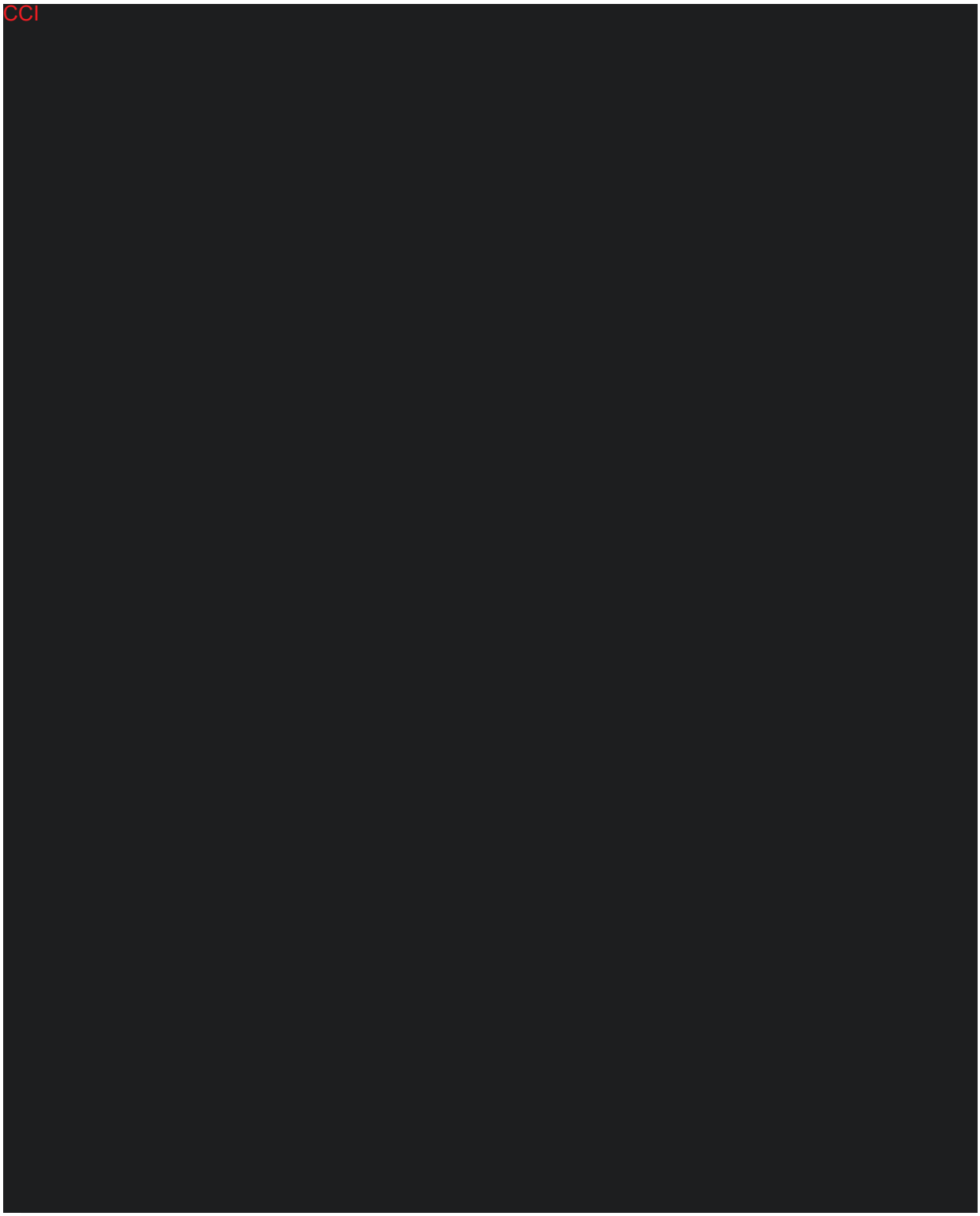

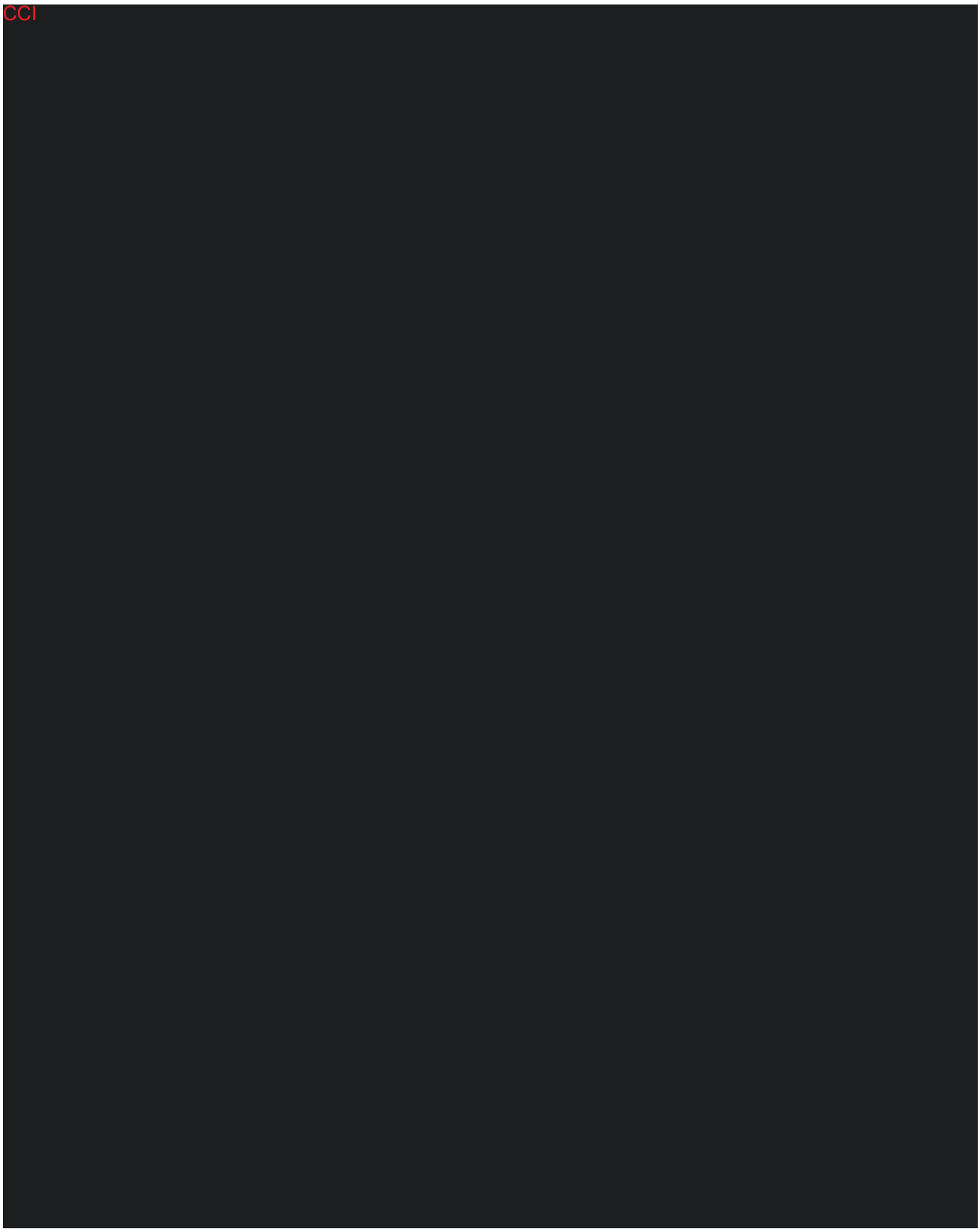
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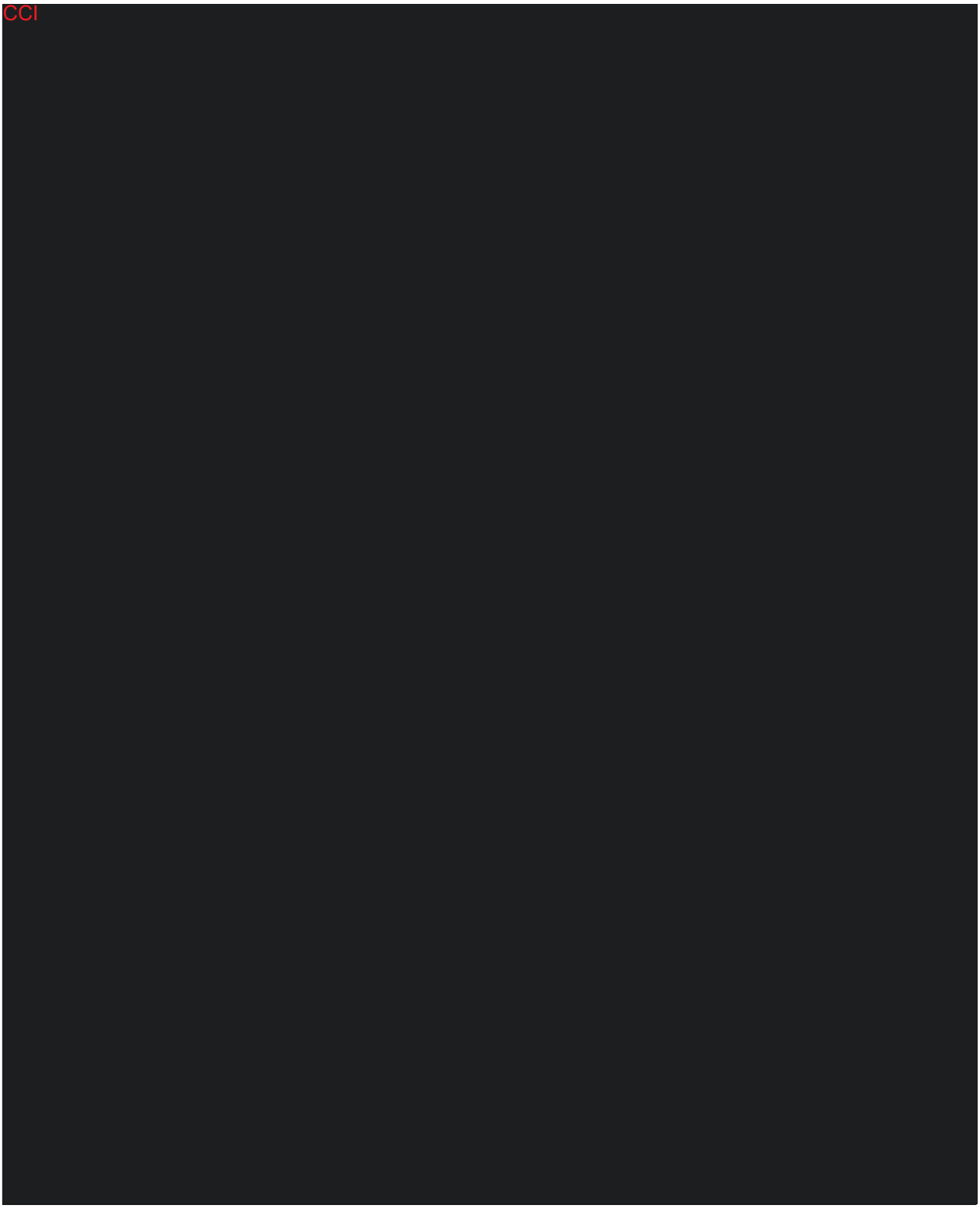

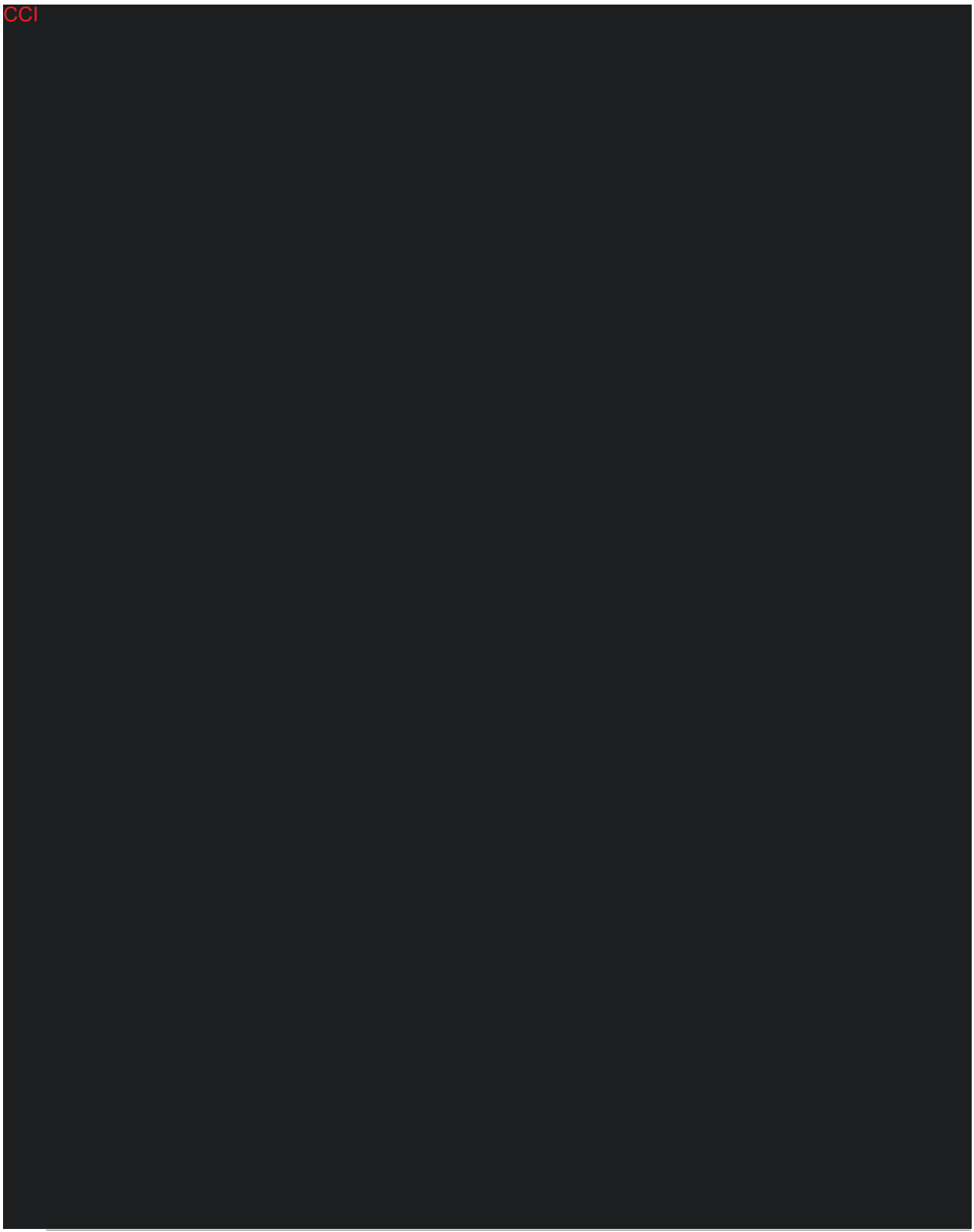
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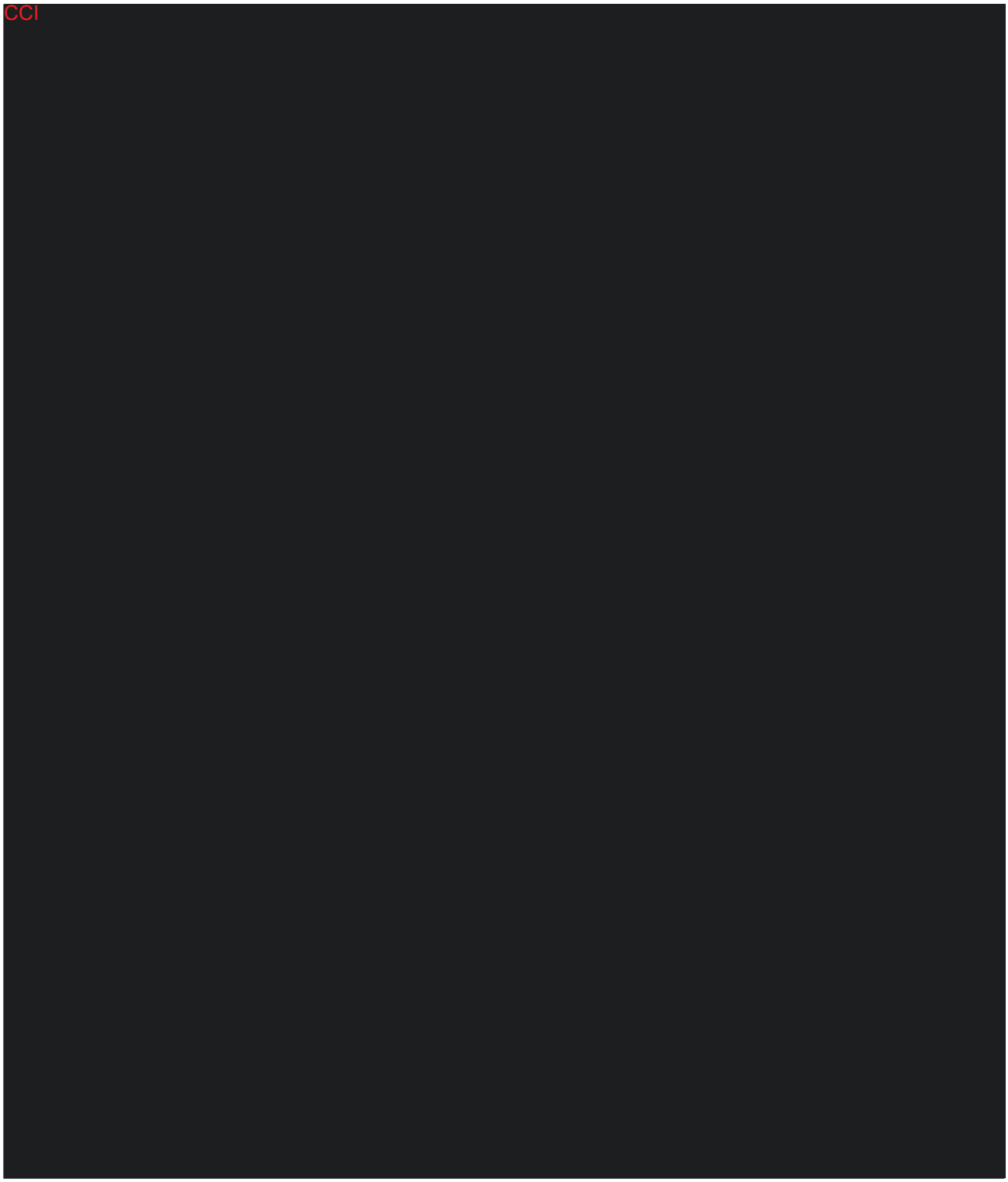
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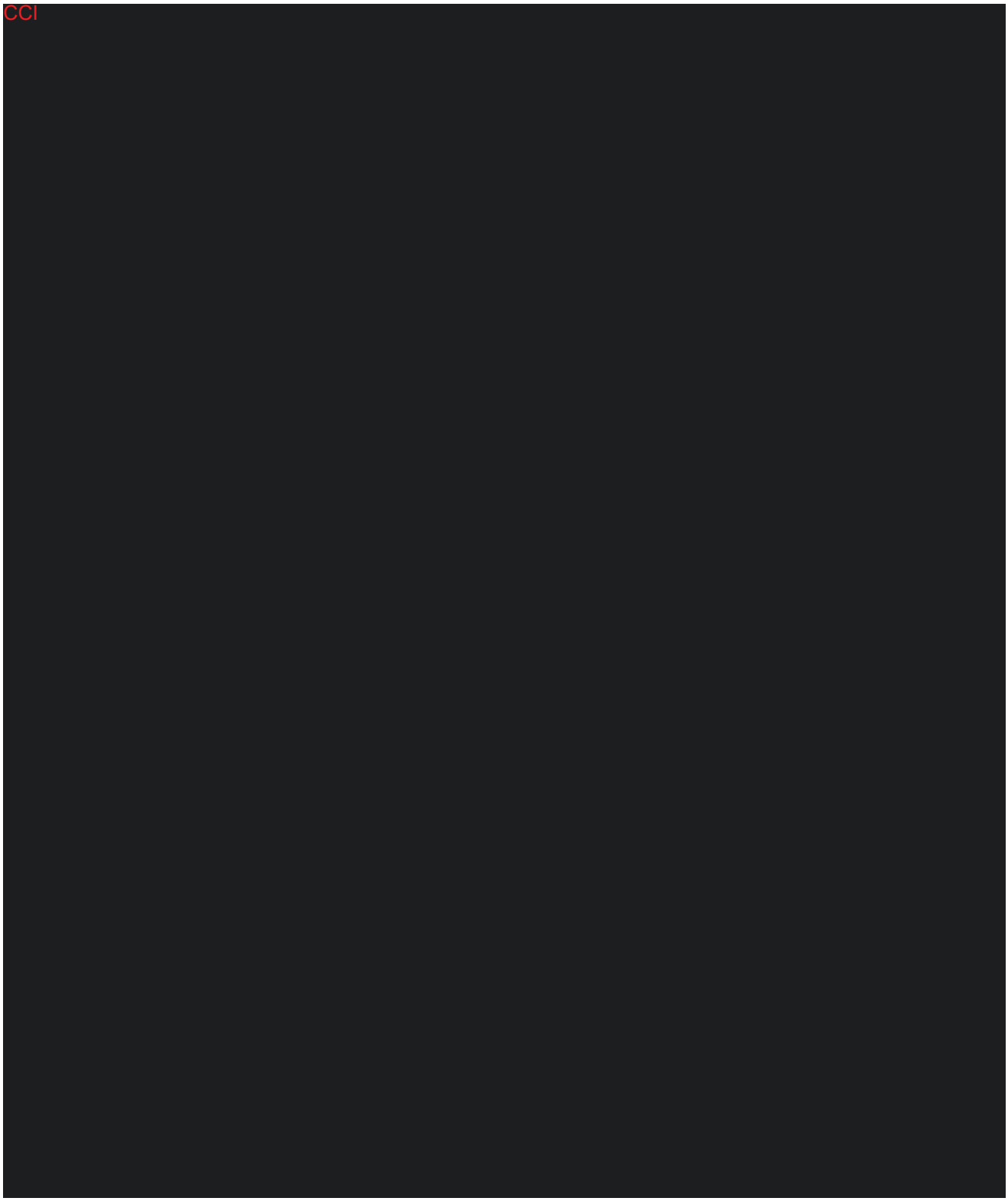
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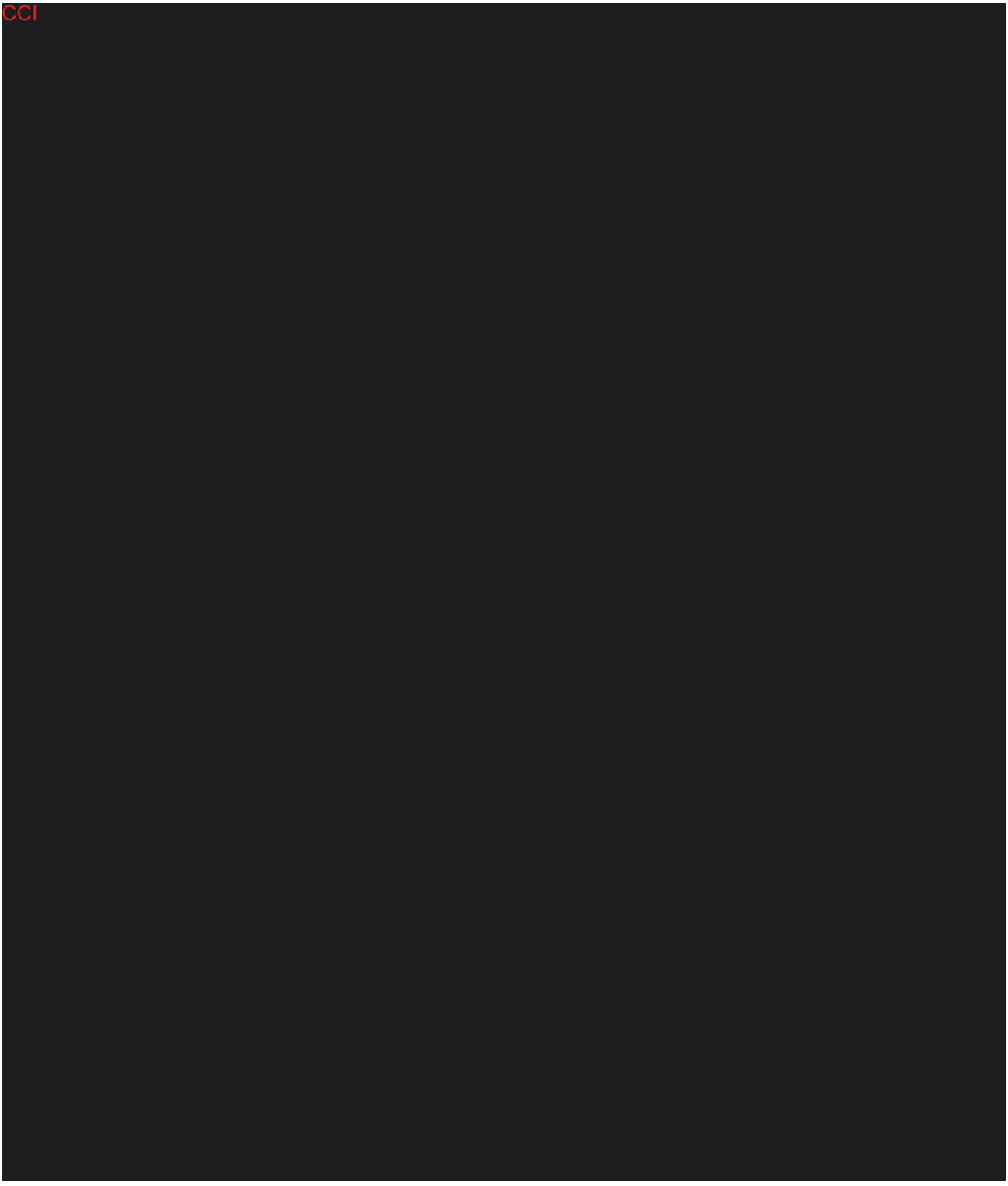
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Appendix 3 PROMIS Pain Interference Scales

Pediatric Self-Report Form (For Subjects Aged 8 to 17 Years)

PROMIS Pediatric Item Bank v2.0 – Pain Interference – Short Form 8a

Pediatric Pain Interference – Short Form 8a

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

	In the past 7 days…	Never	Almost Never	Sometimes	Often	Almost Always
1698bR1r	I felt angry when I had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2035R1r	I had trouble doing schoolwork when I had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3793R1r	I had trouble sleeping when I had pain.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
9004r	It was hard for me to pay attention when I had pain.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2045R1r	It was hard for me to run when I had pain .	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2049R1r	It was hard for me to walk one block when I had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
1703R1r	It was hard to have fun when I had pain.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2180R1r	It was hard to stay standing when I had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Last Updated: 28 July 2016

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Parent Proxy Form (Subjects Aged 2 to 7 Years)

PROMIS Parent Proxy Item Bank v2.0 – Pain Interference – Short Form 8a

Parent Proxy Pain Interference – Short Form 8a

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

	In the past 7 days…	Never	Almost Never	Sometimes	Often	Almost Always
Pf2pain5r	My child had trouble sleeping when he/she had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf3pain7r	My child felt angry when he/she had pain .	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf2pain2r	My child had trouble doing schoolwork when he/she had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf3pain2r	It was hard for my child to pay attention when he/she had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf2pain4r	It was hard for my child to run when he/she had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf1pain4r	It was hard for my child to walk one block when he/she had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf3pain4r	It was hard for my child to have fun when he/she had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pf4pain6r	It was hard for my child to stay standing when he/she had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Last Updated: 29 July 2016

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Appendix 4 The Faces Pain Scale – Revised

Scale for Subjects Aged ≥4 Years

Faces Pain Scale – Revised (FPS-R)

In the following instructions, say "hurt" or "pain", whichever seems right for a particular child.

"These faces show how much something can hurt. This face *[point to face on far left]* **shows no pain. The faces show more and more pain** *[point to each from left to right]* **up to this one** *[point to face on far right]* **- it shows very much pain. Point to the face that shows how much you hurt** [right now]."

*Score the chosen face **0, 2, 4, 6, 8,** or **10**, counting left to right, so "0" = "no pain" and "10" = "very much pain". Do not use words like "happy" or "sad". This scale is intended to measure how children feel inside, not how their face looks.*

Sources. Hicks CL, von Baeyer CL, Spafford P, van Korlaar I, Goodenough B. The Faces Pain Scale – Revised: Toward a common metric in pediatric pain measurement. Pain 2001;93:173-183. Bieri D, Reeve R, Champion GD, Addicoat L, Ziegler J. The Faces Pain Scale for the self-assessment of the severity of pain experienced by children: Development, initial validation and preliminary investigation for ratio scale properties. Pain 1990;41:139-150.

(fold along dotted line)

10 8 6 4 2 0

Appendix 5 Retinoid-Specific Adverse Events Assessed by CTCAE Severity Criteria

Adverse Event	CTCAE Page Number (Version 4.03, 14 June 2010)
Corneal ulcer	22
Conjunctivitis	22
Dry eye	23
Keratitis	24
Night blindness	24
Cheilitis	30
Dry mouth	33
Mucositis oral	45
Pancreatitis	48
Pharyngitis	81
Alanine aminotransferase increased	107
Aspartate aminotransferase increased	107
Blood bilirubin increased	107
Lipase increased	111
Serum amylase increased	112
Hypertriglyceridemia	116
Alopecia	179
Dry skin	179
Erythroderma	180
Photosensitivity	183
Pruritus	184
Rash maculo-papular	185
Skin and subcutaneous tissue disorders – other, specify	187

Appendix 6 Columbia-Suicide Severity Rating Scale

Pediatric C-SSRS for Screening (Subjects Aged 8 to 11 Years)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Screening

Version 6/23/10

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

Disclaimer:

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

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

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

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

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

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

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

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

Pediatric C-SSRS After Screening (Subjects Aged 8 to 11 Years)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Since Last Visit

Version 6/23/10

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

Disclaimer:

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

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

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

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

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

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

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

Adult C-SSRS for Screening (Subjects Aged ≥12 Years)

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.)*

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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 some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Past 1 Year**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**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 After Screening (Subjects Aged ≥12 Years)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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

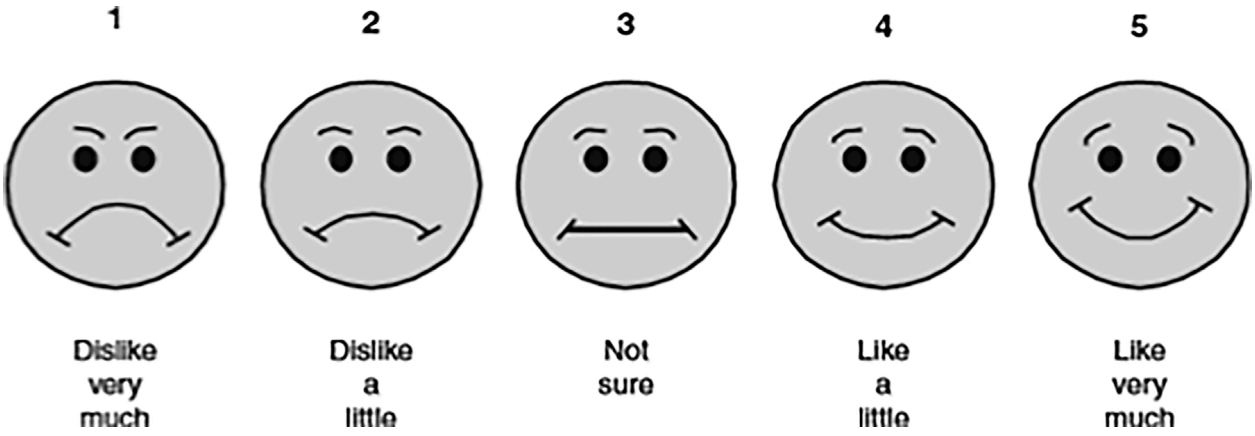
SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** 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 some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** **No** ☐ ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**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 7 Five-point Hedonic Face Scale

Hedonic Face Scale for Palatability of Sprinkled Drug Product (Subjects Aged ≥4 Years)



From Cheung et al (2012).[44]

Appendix 8 Declaration of Helsinki

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

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

Preamble

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

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

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

General Principles

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Risks, Burdens and Benefits

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

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

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

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

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

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

Vulnerable Groups and Individuals

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

All vulnerable groups and individuals should receive specifically considered protection.

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

Scientific Requirements and Research Protocols

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

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

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

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

Research Ethics Committees

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

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

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

Privacy and Confidentiality

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

Informed Consent

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

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

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

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

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

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

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

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

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

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

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

Use of Placebo

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

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

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

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

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

Post-Trial Provisions

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

Research Registration and Publication and Dissemination of Results

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

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

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

Unproven Interventions in Clinical Practice

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