2 SYNOPSIS

Name of Sponsor/Company: Clementia Pharmaceuticals Inc.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Palovarotene	Volume:	
Name of Active Ingredient:	Page:	
Title of study:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Palovarotene in Subjects with Multiple Osteochondromas	
Investigator(s):	A list of Investigators is presented in Appendix 16.1.4.	
Study centers:	A total of 29 study sites located in Australia, Belgium, Canada, France, Japan, Netherlands, Portugal, Spain, Turkey, the United Kingdom, and the USA.	
Publication (reference):	Conrade EU, Jones KB, Shih FF. MO-Ped Trial: A Phase 2, randomized, double-blind, placebo-controlled efficacy and safety study of palovarotene therapy for pediatric multiple osteochondromas. Poster 187 at the Annual Meeting of Musculoskeletal Tumor Society, 10-12 October 2018, New York, NY. Shih FF, on behalf of the MO-Ped trial investigators and teams. MO-Ped Trial: A Phase 2, randomised, double-blind, placebo-controlled efficacy and safety study of palovarotene therapy for paediatric multiple osteochondromas. Poster 195 at the 14th Biannual International Skeletal Dysplasia Society Meeting, 11-14 September 2019, Oslo, Norway.	
Study period:	First subject enrolled: 22 March 2018 Last subject completed: 30 October 2020	
Phase of development:	Phase 2	
Objectives: <u>Primary Objective</u>	The primary objective was to compare the efficacy of two dosage regimens of palovarotene with placebo in preventing the formation of new osteochondromas (OCs) in subjects with multiple osteochondromas (MO) due to exostosin 1 (*EXT1*) or exostosin 2 (*EXT2*) mutations.	
<u>Secondary Objectives</u>	Secondary objectives were 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 as assessed by whole-body MRI. • The annualized rate of new or worsening skeletal deformities. • The annualized rate of MO-related surgeries.	

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Study design:	Study PVO-2A-201 was a Phase 2, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of two dosage regimens of palovarotene in pediatric subjects with MO for up to 2 years. Approximately 240 subjects were planned to be randomized in a 1:1:1 ratio to one of two treatments of weight-adjusted dose equivalents of palovarotene 2.5 or 5.0 mg or a placebo, administered orally, once daily (QD). Randomization was stratified by age, sex, and *EXT1* and *EXT2* mutations. The study was planned to have three periods: a screening period of up to 35 days; a double-blind treatment period of 24 months; and a safety follow-up period of 6 months. Effective 04 December 2019, all recruitment and dosing in Study PVO-2A-201 stopped, due to a partial clinical hold instituted by the Food and Drug Administration. Subjects were asked to remain in the study and complete their scheduled study visits. On 24 March 2020, the sponsor informed sites that Study PVO-2A-201 was terminating early. Subjects were encouraged to return to the sites for the safety follow-up visit 6 months after end of treatment (EOT).	
Number of subjects (planned and analyzed):	*Planned:* Approximately 240 subjects. *Analyzed:* 194 subjects were randomized; 193 subjects received study drug.	
Diagnosis and main criteria for inclusion:	Subjects were males and females aged 2 to 14 years at time of enrollment. Subjects had a clinical diagnosis of MO with a disease-causing *EXT1* or *EXT2* mutation confirmed by a central laboratory. At screening, subjects had symptomatic MO, defined as any of the following: • 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. Bone age at screening was required to be ≤14 years. Subjects were able to undergo MRI with or without sedation. Written, signed, dated informed subject/parent consent and age-appropriate assent were performed according to local regulations before the subject underwent any study procedures.	

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Test product, dose and mode of administration, batch number:	Palovarotene was provided in powder-filled opaque 0EL oblong hard gelatin capsules using standard US Pharmacopeia/European Pharmacopoeia/Japanese Pharmacopoeia grade excipients. Study drug capsules were taken orally QD with food, preferably immediately after the first meal of the day. Study drug capsules were to be swallowed whole; if the subject had difficulty swallowing intact capsules, the capsule could be opened and the contents sprinkled onto food. Batch number information is provided in Appendix 16.1.6.	
Reference therapy, dose and mode of administration, batch number:	Placebo was supplied as powder-filled hard gelatin capsules that were indistinguishable from palovarotene capsules and contained the same ingredients except for palovarotene. Mode of administration for placebo was the same as for palovarotene.	
Duration of treatment:	Planned duration of treatment was up to 2 years. Actual maximum duration of treatment was 595 days (approximately 1.6 years).	
Criteria for evaluation: Efficacy	The primary efficacy endpoint was the annualized rate of new OCs as assessed by whole-body MRI. Secondary efficacy endpoints included: • 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 included any procedure indicated for the treatment of MO, such as an excision of a symptomatic OC or correction of a limb deformity.	
Safety	5.1.1.c [redacted]	
Pharmacokinetics	5.1.1.c [redacted]	

Statistical methods:	In general, data were summarized across cohorts by randomized treatment groups (placebo, palovarotene 2.5 mg, and palovarotene 5.0 mg). Pooled palovarotene data (pooling all subjects treated with palovarotene) were provided for select outcomes. Continuous data were summarized using descriptive statistics (number, mean, standard deviation, standard error, median, minimum, and maximum). Categorical data were summarized using counts and percentages. When values for categorical data were missing, a "missing" category was included in summaries but was not included in percentages. "Missing" categories were not included in inferential analyses. For the primary efficacy analysis, the annualized rate for number of new osteochondromas was estimated using an unadjusted negative binomial regression model, offsetted by log-transformed follow-up time (years) to obtain annualized rate. The p-values were not adjusted for multiple testings due to small sample size. Similar models were used for analyses of other efficacy endpoints. [redacted] 5.1.1.c [redacted] 5.1.1.c [redacted]

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Efficacy results:	[redacted] 5.1.1.c [redacted] 5.1.1.c	
Pharmacokinetic results:	5.1.1.c	

Safety results:	• [redacted] 5.1.1.c [redacted] 5.1.1.c [redacted] 5.1.1.c [redacted] 5.1.1.c [redacted] 5.1.1.c [redacted] 5.1.1.c [redacted] 5.1.1.c

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Safety results, continued:	• [redacted] 5.1.1.c [redacted] 5.1.1.c [redacted] 5.1.1.c [redacted] 5.1.1.c	

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Conclusions:	• The sponsor terminated the study early. Recruitment was stopped before full enrollment was reached, and study drug administration was discontinued. The smaller-than-expected number of subjects and shorter-than-expected duration of treatment should be taken into consideration in interpretation of the results. • Analysis of OC counts and volumes by MRI did not reveal statistically significant differences between treatment groups in annualized rate of new OCs, volume of new OCs, or volume of OC cartilage. • The AE profile of palovarotene was consistent with systemic retinoids, consisting mainly of mucocutaneous AEs. Incidence of mucocutaneous AEs appeared to be dose dependent. • No cases of premature physeal closure were identified. Post-baseline closures were physiologic. There was no evidence of an effect of palovarotene on growth. • There was a trend toward lower BMC and aBMD accrual and aBMD loss in palovarotene-treated subjects that was dose dependent and time dependent, without an increase in fracture events. • Vital signs and ECG analysis did not identify clinically meaningful safety concerns. • The lack of a clear efficacy signal in the prevention and/or reduction in OC and the dose-dependent and time-dependent trend towards lower BMC accrual in subjects who received palovarotene did not result in a favorable benefit-risk profile for palovarotene in patients with MO.	
Date of the report:	19 July 2021	