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Central Committee on research Involving Human Subjects (CCMO)
Attn: Competent Authority
Parnassusplein 5
2511 VX Den Haag

Bennekom, 07 April 2020

Re:	**Digital submission of Early Termination**
Protocol:	**PVO-2A-201**
EudraCT number:	**2017-002751-28**
NL number:	**NL67312.028.18**

Dear members of the Central Committee on Research Involving Human Subjects,

With this letter we would like to notify the Competent Authority (Central Committee on Research Involving Human Subjects) of the early termination of the research entitled: *"A Phase 2, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Palovarotene in Subjects with Multiple Osteochondromas"* registered under number NL67312.028.18.

Early Termination of Trial

Palovarotene is a retinoic acid receptor gamma (RARγ) selective agonist under clinical evaluation for two rare bone diseases, Fibrodysplasia Ossificans Progressiva (FOP; in Phase 2 and 3 trials) and Multiple Osteochondromas (MO; in the above-mentioned Phase 2 trial).

Following reports of adverse findings of premature epiphyseal closure in the FOP program and subsequent discussions with the U.S. FDA on 04 December 2019, a global partial clinical hold was placed on the ongoing palovarotene trials for subjects under 14 years of age. The MO-Ped study PVO-2A-201 was included under the partial clinical hold because premature closure was reported in subjects in FOP studies receiving weight-adjusted equivalent doses of 5 mg daily, the same as the highest dose evaluated in the MO-Ped study. Since the age limit for enrollment in the MO-Ped study PVO-2A-201 was 14 years, all subjects in the MO-Ped study had treatment halted.

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In the evaluation of the safety data from the Phase 3 FOP study, it was determined that premature epiphyseal closure is an identified and irreversible risk with high penetrance in FOP subjects treated with palovarotene. Analysis of the blinded safety data in PVO-2A-201 (02 Dec 2019 data cut-off) did not reveal clinically significant disruption in height attainment and bone age advancement. Postbaseline epiphyseal closure was noted in 5 subjects and was deemed not premature. A single serious adverse event (SAE) for a premature epiphyseal closure possibly related to blinded study treatment was reported on 18 March 2020 in a 13-year-old boy with closure already present at baseline.

We have taken the decision to terminate the MO-Ped trial to analyze the accumulated data to better inform on the efficacy, safety and future of palovarotene in MO. We chose this course of action for several reasons, including the time that the partial clinical hold has been in place leading to a significant gap in dosing which may compromise the integrity of the data, that the trial was not fully enrolled at the time the partial clinical hold was instituted (as such, very few patients had reached the trial midpoint), and there is no efficacy data available in this patient population currently to further inform a benefit/risk assessment.

In The Netherlands, 5 patients were enrolled in the study. No subjects in study PVO-2A-201 are currently on treatment as all were temporarily halted for the partial clinical hold and measures were previously taken to ensure that shipment of drug to all sites in the trial was stopped. Investigators have been contacted 24 March 2020 to inform all subjects and their legal guardians of the study termination and to return unused quantities of drug to their sites. Th communication with PIs and message for patients has been submitted to the responsible reviewing committee.
Planning of all activities related to the close-out of the study is underway. In accordance with the protocol and reduced feasibility due to COVID-19 local procedures, the last study visit (LPLV) will be scheduled 6 months after end of treatment. We anticipate this to be by the end of June/early July, there may be delays to due to the current COVID-19 crisis, however we will endeavour to complete these as soon as possible. An abbreviated clinical study report is planned to be generated within 6 months of LPLV. The report will be posted in the EudraCT database.

The study will be unblinded to conduct an analysis of the efficacy and safety of palovarotene for the treatment of MO to better inform the benefit and risk in the paediatric population. After evaluation of the accumulated data in study PVO-2A-201, Clementia may request the initiation of another study in MO if warranted by evidence of therapeutic response.

With this submission we declare that all relevant documents from the above-mentioned research dossier are signed by the authorised people. The signed documents are submitted for review to the responsible review committee specified in question I1 of the general assessment and registration form (ABR form).

Yours sincerely,

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Appendices:

- A1. Cover letter NL67312.028.18 dd 07Apr2020
- B7. EudraCT end of trial form