Declaration of the End of Trial Form (cf. Section 4.2.1 of the *Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial*[1])

NOTIFICATION OF THE END OF A CLINICAL TRIAL OF A MEDICINE FOR HUMAN USE TO THE COMPETENT AUTHORITY AND THE ETHICS COMMITTEE

For official use

Date of receipt :	Competent authority registration number : Ethics committee registration number:

To be filled in by the applicant

A MEMBER STATE IN WHICH THE DECLARATION IS BEING MADE : The Netherlands

B TRIAL IDENTIFICATION

B.1 EudraCT number: 2017-002751-28
B.2 Sponsor's protocol code number: PVO-2A-201
B.3 Full title of the trial: MO-Ped Trial- A Phase 2, Randomised, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Palovarotene in Subjects with Multiple Osteochondromas

C APPLICANT IDENTIFICATION (please tick the appropriate box)

C.1	**DECLARATION FOR THE COMPETENT AUTHORITY**	☐
C.1.1	Sponsor	☐
C.1.2	Legal representative of the sponsor	☐
C.1.3	Person or organisation authorised by the sponsor to make the application.	☒
C.1.4	**Complete below**:	
C.1.4.1	Organisation : PPD Netherlands BV	
C.1.4.2	Name of person to contact : 5.1.2.e	
C.1.4.3	Address : Bornweg 12C, 6721 AH Bennekom, the Netherlands	
C.1.4.4	Telephone number : +31 (0)318 65 5.1.2.e	
C.1.4.5	Fax number : +31 (0)318 65 5.1.2.e	
C.1.4.6	E-mail: 5.1.2.e@ppdi.com	

C.2	**DECLARATION FOR THE ETHICS COMMITTEE**	☐
C.2.1	Sponsor	☐
C.2.2	Legal representative of the sponsor	☐
C.2.3	Person or organisation authorised by the sponsor to make the application.	☐
C.2.4	Investigator in charge of the application if applicable[2]:	
	• Co-ordinating investigator (for multicentre trial):	☐
	• Principal investigator (for single centre trial):	☐
C.2.5	**Complete below** :	
C.2.5.1	Organisation:	
C.2.5.2	Name :	
C.2.5.3	Address :	
C.2.5.4	Telephone number :	
C.2.5.5	Fax number :	
C.2.5.6	E-mail :	

1 OJ, C82, 30.3.2010, p. 1; hereinafter referred to as 'detailed guidance CT-1'.
2 According to national legislation.

D END OF TRIAL

D.1 Date of the end of the trial in this Member State ?[3]	yes ☐ no ☐
D.1.1. (YYYY/MM/DD):	

D.2 Date of the end of the complete trial in all countries concerned by the trial?[3]	yes ☐ no ☐
D.2.1 (YYYY/MM/DD):	

D.3 Is it an early termination?[4]	yes ☒ no ☐

[3] In case of a multi-country trial, if the national and global end of trial dates are different in a given Member State, the sponsor shall submit this form two times :

1) At the end of the trial in the individual Member State, section D1.1. shall be completed and submitted to the respective National Competent Authority.

2) At the global end of the trial, the sponsor shall complete section D.2.1. with the global trial end date and the completed form shall be submitted to all participating Member States in order to allow the sponsor to prepare the trial result summary within the 12-months (or 6-months in case of paediatric trials) timeframe.

If the national and global end dates coincide in a concerned Member State, the form shall be submitted only once to the National Competent Authority of this Member State with both sections D1.1. and D2.1 complete.

[4] Cf. Section 4.2. of the detailed guidance CT-1.

D.3.1 If yes, give date (YYYY/MM/DD): **2020/03/24**

D.3.2 Briefly describe in an annex (free text):

D.3.2.1 The justification for early termination of the trial;

Following the 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 enrolment in the MO-Ped study PVO-2A-201 was 14 years, all subjects in the MO-Ped study had treatment halted.

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.

The Sponsor has 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. This course of action was chosen 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.

D.3.2.2 Number of patients still receiving treatment at time of early termination in the MS concerned by the declaration and their proposed management;

There were no patients receiving treatment at the time of early termination. The total number of subjects enrolled in the Netherlands was 5.

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.

D.3.2.3 The consequences of early termination for the evaluation of the results and for overall risk benefit assessment of the investigational medicinal product.

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.

E SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

E.1 I hereby confirm on behalf of the sponsor that (delete which is not applicable):

- The above information given on this declaration is correct; and
- That the clinical trial summary report will be submitted within the applicable deadlines in accordance with the applicable guidance by the Commission.[5]

E.2	**APPLICANT TO THE COMPETENT AUTHORITY** (as stated in C.1)	☒
E.2.1	Date :	
E.2.2	Signature :	
E.2.3	Print name: 5.1.2.e [redacted]	

E.3	**APPLICANT TO THE ETHICS COMMITTEE** (as stated in C.2) **:**	☐

[5] Section 4.3. of the detailed guidance CT-1.

E.3.1	Date :
E.3.2	Signature :
E.3.3	Print name: