To: ccmo_bi[bi@ccmo.nl]
Cc: [redacted]@ppdi.com]
From: PPD Netherlands (SM)
Sent: Wed 26-8-2020 12:57:39
Subject: NL67312.028.18
Received: Wed 26-8-2020 12:57:56
B5. EudraCT Form Notification of Amendment.pdf
A1. Cover letter NL67312.028.18 dd 26Aug2020.pdf

Concerns:	**Submission Substantial Amendment #05 (SA#05) – local EoT, IB, IMPD**
Our reference:	**SA#05 – (FS)**
Protocol number:	**MO-Ped trial**
NL number:	**NL67312.028.18**
EudraCT number:	**2017-002751-28**

Dear members of the Central Committee on Research Involving Human Subjects,
With this letter we would like to ask the Competent Authority (Central Committee on Research Involving Human Subjects) to issue a certificate of no objection for the research entitled*: 'A Phase 2, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Palovarotene in Subjects with Multiple Osteochondromas'* which is registered under NL Number: NL67312.028.18. We would also like to notify the CCMO of the local End of Trial.
The modifications of this amendment are concerning:
☐ the addition of a new investigational medicinal product;
☐ a substantial modification of the current investigational medicinal product;
☒ otherwise, namely: Investigator Brochure Ed. 7 (substantial), IMPD (non-substantial)
Please find attached the full cover letter as well as supporting documents:

- A1. Cover letter NL67312.028.18 dd 26Aug2020
- B5. EudraCT Form Notification of Amendment

Please address any enquiries to undersigned.
Thank you for your review.
Met vriendelijke groet / Kind regards,

[redacted]
Site and Patient Access – Global Site Intelligence and Activation

PPD
Bornweg 12C 6721 AH Bennekom, NL
Phone +31 (0)31865[redacted]
Fax +31 (0)318 65[redacted]
[redacted]@ppdi.com
Upcoming OOO: 31Aug-04Sep

Substantial Amendment Notification Form (Cf. Section 3.7.b 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 A SUBSTANTIAL AMENDMENT TO A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE COMPETENT AUTHORITIES AND FOR OPINION OF THE ETHICS COMMITTEES IN THE EUROPEAN UNION

For official use:

Date of receiving the request :	Grounds for non acceptance/ negative opinion : ☐ Date :
Date of start of procedure:	Authorisation/ positive opinion : ☐ Date :
Competent authority registration number of the trial: Ethics committee registration number of the trial :	Withdrawal of amendment application ☐ Date :

To be filled in by the applicant:

This form is to be used both for a request to the Competent Authority for authorisation of a **substantial** amendment and to an Ethics Committee for its opinion on a **substantial** amendment. Please indicate the relevant purpose in Section A.

A TYPE OF NOTIFICATION

A.1 Member State in which the substantial amendment is being submitted:	**The Netherlands**
A.2 Notification for authorisation to the competent authority:	☒
A.3 Notification for an opinion to the ethics committee:	☐

B TRIAL IDENTIFICATION *(When the amendment concerns more than one trial, repeat this form as necessary.)*

B.1 Does the substantial amendment concern several trials involving the same IMP?[2] yes ☐ no ☒

B.1.1 If yes repeat this section as necessary.

B.2 Eudract number: 2017-002751-28

B.3 Full title of the trial : MO-Ped-Trial- A Phase 2, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Palovarotene in Subjects with Multiple Osteochondromas

B.4 Sponsor's protocol code number, version, and date: Protocol Amendment 2, 23-Apr-2019

C IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

C.1	**Sponsor**
C.1.1	Organisation: **Clementia Pharmaceuticals Inc**
C.1.2	Name of person to contact: [redacted]
C.1.3	Address: **1000, De La Gauchetière West, Suite 1200, Montreal, Quebec H3B 4W5, Canada**
C.1.4	Telephone number : **001** [redacted]
C.1.5	Fax number : **001** [redacted]
C.1.6	e-mail: [redacted] **@ipsen.com**

C.2	**Legal representative**[3] **of the sponsor in the European Union for the purpose of this trial (if different from the sponsor)**
C.2.1	Organisation: [redacted]
C.2.2	Name of person to contact: [redacted]
C.2.3	Address: [redacted]
C.2.4	Telephone number: [redacted]
C.2.5	Fax number:
C.2.6	e-mail: [redacted] **@ppdi.com**

D APPLICANT IDENTIFICATION (please tick the appropriate box)

---

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

2 Cf. Section 3.7. of the detailed guidance CT-1.

3 As stated in Article 19 of Directive 2001/20/EC.

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

D.2	Request for the Ethics Committee	
D.2.1	Sponsor	☐
D.2.2	Legal representative of the sponsor	☐
D.2.3	Person or organisation authorised by the sponsor to make the application.	☐
D.2.4	Investigator in charge of the application if applicable[4]:	
	• Co-ordinating investigator (for multicentre trial)	☐
	• Principal investigator (for single centre trial):	☐
D.2.5	Complete below	
D.2.5.1	Organisation:	
D.2.5.2	Name:	
D.2.5.3	Address:	
D.2.5.4	Telephone number:	
D.2.5.5	Fax number:	
D2.6	E-mail:	

E SUBSTANTIAL AMENDMENT IDENTIFICATION

E.1	**Sponsor's substantial amendment code number, version, date for the clinical trial concerned:** SA#05: Investigator Brochure

E.2	Type of substantial amendment	
E.2.1	**Amendment to information in the CT application form**	yes ☐ no ☒
E.2.2	**Amendment to the protocol**	yes ☐ no ☒
E.2.3	**Amendment to other documents appended to the initial application form**	yes ☒ no ☐
E.2.3.1	If yes specify: Investigator Brochure	
E.2.4	**Amendment to other documents or information:**	yes ☐ no ☒
E.2.4.1	If yes specify:	
E.2.5	**This amendment concerns mainly urgent safety measures already implemented**[5]	yes ☐ no ☒
E.2.6	**This amendment is to notify a temporary halt of the trial**[6]	yes ☐ no ☒
E.2.7	**This amendment is to request the restart of the trial**[7]	yes ☐ no ☒

4 According to national legislation.
5 Cf. Section 3.9. of the detailed guidance CT-1.
6 Cf. Section 3.10. of the detailed guidance CT-1.
7 Cf. Section 3.10. of the detailed guidance CT-1.

E.3	Reasons for the substantial amendment:	
E.3.1	**Changes in safety or integrity of trial subjects**	**yes ☒ no ☐**
E.3.2	**Changes in interpretation of scientific documents/value of the trial**	**yes ☒ no ☐**
E.3.3	**Changes in quality of IMP(s)**	**yes ☐ no ☒**
E.3.4	**Changes in conduct or management of the trial**	**yes ☐ no ☒**
E.3.5	**Change or addition of principal investigator(s), co-ordinating investigator**	**yes ☐ no ☒**
E.3.6	**Change/addition of site(s)**	**yes ☐ no ☒**
E.3.7	**Other change**	**yes ☐ no ☒**
E.3.7.1	**If yes, specify:**	
E.3.8	**Other case**	**yes ☐ no ☒**
E.3.7.1	**If yes, specify**	

E.4	Information on temporary halt of trial[8]	
E.4.1	**Date of temporary halt** (YYYY/MM/DD)	
E.4.2	**Recruitment has been stopped**	**yes ☐ no ☒**
E.4.3	**Treatment has been stopped**	**yes ☐ no ☒**
E.4.4	Number of patients still receiving treatment at time of the temporary halt in the MS concerned by the amendment ( )	
E.4.5	**Briefly describe (free text)**:	

- Justification for a temporary halt of the trial
- The proposed management of patients receiving treatment at time of the halt *(free text).*

The consequences of the temporary halt for the evaluation of the results and for overall risk benefit assessment of the investigational medicinal product *(free text)*.

F DESCRIPTION OF EACH SUBSTANTIAL AMENDMENT[9] *(free text)***:**

Previous and new wording in track change modus	New wording	Comments/explanation/reasons for substantial amendment
Please refer to the changes listed in the section "Summary of Significant Changes" of Investigator`s Brochure v7.0 (page 3) and track changes version document from previous	See Investigator`s Brochure V7 dated 15Jul2020 that has been submitted to the reviewing EC.	The changes in the updated IB: do affect the Reference Safety Information (RSI) of palovarotene (section 7.4): As of the IBV7 (date 15Jul2020, premature physeal closures (MedDRA Preferred Term Epiphyses premature fusion) are now an expected serious adverse event and are no longer considered Suspected Unexpected Serious Adverse Reactions. do affect patient safety: Due to 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 including the MO-Ped study PVO-2A-201. At the time of IBv7 release (date 15Jul2020), no subjects in study PVO-2A-201 were on treatment. do not affect the Study ICF or Study protocol because a decision to terminate the MO-Ped trial was taken. The accumulated data is

[8] Cf. Section 3.10. of the detailed guidance CT-1.

[9] Cf. Section 3.7.c. of the detailed guidance CT-1. The sponsor may submit this documentation on a separate sheet.

		being analysed to better inform on the efficacy, safety and future of palovarotene in the treatment of MO. The decision to terminate the study was taken as the study had been paused for such a length of time to the partial clinical hold that it would have affected the integrity of the data as few subjects had reached the trial midpoint. The termination was communicated to the CCMO on 07Apr2020. The last study visit (LPLV) is being scheduled 6 months after end of treatment and has taken place on 02Jul2020. The development into the indication of MO has now been terminated due to the lack of efficacy signals in the analysis of the MO-Ped trial. The final CSR will be submitted within 6 months of the LPLV.

G CHANGE OF CLINICAL TRIAL SITE(S)/INVESTIGATOR(S) IN THE MEMBER STATE CONCERNED BY THIS AMENDMENT

G.1 Type of change

G.1.1 **Addition of a new site**
G.1.1.1 **Principal investigator** (provide details below)
G.1.1.1.1 Given name
G.1.1.1.2 Middle name (if applicable)
G.1.1.1.3 Family name
G.1.1.1.4 Qualifications (MD……..)
G.1.1.1.5 Professional address
G.1.2 **Removal of an existing site**
G.1.2.1 **Principal investigator** (provide details below)
G.1.2.1.1 Given name
G.1.2.1.2 Middle name (if applicable)
G.1.2.1.3 Family name
G.1.2.1.4 Qualifications (MD……..)
G.1.2.1.5 Professional address
G.1.3 **Change of co-ordinating investigator** (provide details below of the new coordinating investigator)
G.1.3.1 Given name
G.1.3.2 Middle name
G.1.3.3 Family name
G.1.3.4 Qualification (MD…….)
G.1.3.5 Professional address
G.1.3.6 Indicate the name of the previous co-ordinating investigator:
G.1.4 **Change of principal investigator at an existing site** (provide details below of the new principal investigator)
G.1.4.1 Given name
G.1.4.2 Middle name
G.1.4.3 Family name
G.1.4.4 Qualifications (MD……..)
G.1.4.5 Professional address
G.1.4.6 Indicate the name of the previous principal investigator:

H CHANGE OF INSTRUCTIONS TO CA FOR FEEDBACK TO SPONSOR

H.1 Change of e-mail contact for feedback on application*

H.2 Change to request to receive an .xml copy of CTA data ☐ yes ☒ no
H.2.1 Do you want a .xml file copy of the CTA form data saved on EudraCT? ☐ yes ☐ no
H.2.1.1 If yes provide the e-mail address(es) to which it should be sent (up to 5 addresses):
H.2.2 Do you want to receive this via password protected link(s)[10]? ☐ yes ☐ no

If you answer no to question H.2.2 the .xml file will be transmitted by less secure e-mail link(s)

[10] This requires a EudraLink account. (See https://eudract.ema.europa.eu/ for details)

H.2.3 Do you want to stop messages to an email for which they were previously requested? ☐ yes ☐ no
H.2.3.1 If yes provide the e-mail address(es) to which feedback should no longer be sent:

(*This will only come into effect from the time at which the request is processed in EudraCT).

I LIST OF THE DOCUMENTS APPENDED TO THE NOTIFICATION FORM (cf. Section 3.7 of detailed guidance CT-1)

Please submit only relevant documents and/or when applicable make clear references to the ones already submitted. Make clear references to any changes of separate pages and submit old and new texts. Tick the appropriate box(es).

I.1 Cover letter	☒
I.2 Extract from the amended document in accordance with Section 3.7.c. of detailed guidance CT-1 (if not contained in Part F of this form)	☐
I.3 Entire new version of the document[11]	☐
I.4 Supporting information	☐
I.5 Revised .xml file and copy of initial application form with amended data highlighted	☐
I.6 Comments on any novel aspect of the amendment if any :	

J SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

J.1 I hereby confirm on behalf of the sponsor that

- The above information given on this request is correct;
- The trial will be conducted according to the protocol, national regulation and the principles of good clinical practice; and
- It is reasonable for the proposed amendment to be undertaken.

J.2 APPLICANT OF THE REQUEST FOR THE COMPETENT AUTHORITY (as stated in section D.1): ☒

J.2.1 Signature [12]:
J.2.2 Print name :
J.2.3 Date :

J.3 APPLICANT OF THE REQUEST FOR THE ETHICS COMMITTEE (as stated in section D.2): : ☐

J.3.1 Signature [13]:

J.3.2 Print name:
J.3.3 Date :

[11] Cf. Section 3.7.c. of the detailed guidance CT-1.
[12] On an application to the Competent Authority only, the applicant to the Competent Authority needs to sign.
[13] On an application to the Ethics Committee only, the applicant to the Ethics Committee needs to sign.

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

Bennekom, 26 August 2020

Concerns:	**Submission Substantial Amendment #05 (SA#05) – local EoT, IB, IMPD**
Our reference:	**SA#05 – (FS)**
Protocol number:	**MO-Ped trial**
NL number:	**NL67312.028.18**
EudraCT number:	**2017-002751-28**

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

With this letter we would like to ask the Competent Authority (Central Committee on Research Involving Human Subjects) to issue a certificate of no objection for the research entitled*: 'A Phase 2, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Palovarotene in Subjects with Multiple Osteochondromas'* which is registered under NL Number: NL67312.028.18. We would also like to notify the CCMO of the local End of Trial.

The modifications of this amendment are concerning:
☐ the addition of a new investigational medicinal product;
☐ a substantial modification of the current investigational medicinal product;
☒ otherwise, namely: Investigator Brochure Ed. 7 (substantial), IMPD (non-substantial)

Investigator Brochure V7.0 dated 15Jul2020 (substantial for approval)
The updated Investigator Brochure (IB) has been classified as "substantial" by the Sponsor. The changes are listed in the section "Summary of Significant Changes" in the updated Investigator's Brochure on page 3 of the document that has been submitted to the reviewing EC. The changes in the IB:

- do affect the Reference Safety Information (RSI) of palovarotene (section 7.4): As of the IBV7 (date 15Jul2020, premature physeal closures (MedDRA Preferred Term Epiphyses premature fusion) are now an expected serious adverse event and are no longer considered Suspected Unexpected Serious Adverse Reactions.

- do affect patient safety: Due to the occurrence of premature physeal closure (early growth plate closure) in the FOP program and subsequent discussions with the U.S. FDA initiated on 04 December 2019, a global partial clinical hold was placed on the ongoing palovarotene trials for subjects under 14 years of age including the MO-Ped study PVO-2A-201. At the time of IBv7 release (date 15Jul2020), no subjects in study PVO-2A-201 were on treatment.

- do **not** affect the Study ICF or Study protocol because a decision to terminate the MO-Ped trial was taken. The accumulated data is being analysed to better inform on the efficacy, safety and future of palovarotene in the treatment of MO. The decision to terminate the study was taken as the study had been paused for such a length of time to the partial clinical hold that it would have affected the integrity of the data as few subjects had reached the trial midpoint. The termination was communicated to the CCMO on 07Apr2020. The last study visit (LPLV) has been scheduled 6 months after end of treatment and has taken place on 02Jul2020. The development into the indication of MO has now been terminated due to the lack of efficacy signals in the analysis of the MO-Ped trial. The final CSR will be submitted within 6 months of the LPLV.

The IB was also updated to include nonclinical data, results of studies PVO-1A-102 / PVO-1A-103, clinical efficacy data in FOP patients, clinical safety data from healthy volunteers, FOP and MO patients, and updated clinical PK data. Updates to the Guidance for Investigator section based on safety data were also made. The annual DSUR submission has been completed on 26Jun2020.

In addition to the above modifications, this submission includes the following non-substantial changes:

IMPD dated 15Nov2019

The Palovarotene IMPD has again been updated following the optimization of the dissolution testing method. All changes are highlighted in the tracked-changes version of the IMPD that has been submitted to the reviewing EC and are summarized in the Summary of IMPD modifications (Please refer to pages 16 - 17 of the IMPD that has been submitted to the reviewing EC).
The modifications have been evaluated as “non-substantial” as they are unlikely to have an impact on the quality and safety of the IMP.

Letter to investigators dated 03Aug2020

This letter has been sent out to investigators to inform them on the closure of the multiple osteochondromas (MO) clinical development program for palovarotene. The letter has been enclosed in the submission to the reviewing EC.

Local EoT

The local EoT, last patient last visit, has taken place on 02Jul2020.

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).

Please note that due to the current COVID-19 regulations, it is currently not possible to sign this letter with a wet-ink signature, thus a digital signature was used.

Yours sincerely,

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PPD Netherlands BV
Bornweg 12c
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Phone: +31 (0)318 65 5.1.2.e
Fax: +31 (0)318 65 5.1.2.e
Email: 5.1.2.e@ppdi.com

Appendices:

- A1. Cover letter NL67312.028.18 dd 26Aug2020
- B5. EudraCT Form Notification of Amendment