PPD

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.

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- 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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Appendices:

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