STATISTICAL ANALYSIS PLAN

ROLLOVER STUDY; MULTICENTRE, PHASE III, OPEN-LABEL STUDY TO FURTHER EVALUATE THE SAFETY AND EFFICACY OF PALOVAROTENE CAPSULES IN MALE AND FEMALE PARTICIPANTS AGED ≥14 YEARS WITH FIBRODYSPLASIA OSSIFICANS PROGRESSIVA (FOP) WHO HAVE COMPLETED STUDY PVO-1A-301 OR PVO-1A-202/PVO-1A-204 AND MAY BENEFIT FROM PALOVAROTENE THERAPY

[CLIN-60120-452]

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HISTORY OF CHANGES

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	Wording Definition
ADL	Activities of Daily Living
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Class
C	Concomitant
CAJIS	Cumulative Analogue Joint Involvement Scale
CI	Confidence Interval
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DLCO	Diffusion Capacity of the Lung for Carbon Monoxide
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOS	End of Study
EudraCT	European Clinical Trials Database
EW	Early Withdrawal
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in One Second
FOP	Fibrodysplasia Ossificans Progressiva
FOP-PFQ	FOP Physical Function Questionnaire
FVC	Forced Vital Capacity
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
MedDRA	Medical Dictionary for Regulatory Activities
P	Prior
PC	Prior and Concomitant
PCSA	Potentially Clinically Significant Abnormalities

ABBREVIATION	Wording Definition
PN	Preferred Name
PP	Per Protocol
PROMIS	Patient Reported Outcomes Measurement Information System
PT	Preferred Term
RARγ	Retinoic Acid Receptor Gamma
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SI Unit	International System of Units
SoA	Schedule of Activities
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Events
TFLs	Tables, Figures and Listings
ULN	Upper Limit of Normal
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION

The purpose of this SAP is to outline the planned analyses to be completed to support the completion of the Clinical Study Report (CSR) for protocol CLIN-60120-452. It describes the rules and conventions to be used in the analysis and presentation of data, the data to be summarised and analysed, including specificities of the statistical analyses to be performed.

A separate shell will be provided for tables, figures and listings.

The SAP is to be finalised prior to database lock (DBL). Any deviations from the SAP after database lock will be documented in the CSR (section 9.8 "Changes in the conduct of the study or planned analyses" as per International Conference on Harmonisation (ICH) E3).

2 PROTOCOL OVERVIEW

The aim of Study CLIN-60120-452 is to provide continued access to palovarotene once the ongoing clinical studies have ended. More specifically, the aim is to provide treatment continuity to participants who have completed one of the parent studies (Study PVO-1A-301 or PVO-1A-202 (Parts C and D correspond to Study PVO-1A-204 in France)) and, in the investigator's judgement, may benefit from palovarotene therapy until palovarotene is reimbursed in the country where the study is being conducted, or another access programme becomes available, or until the study end date of November 2024 is reached, whichever occurs first.

2.1 Study Objectives and Hypotheses

The objectives of the study are as per the table below:

Objectives	Endpoints
Primary	
• To further evaluate the safety of palovarotene in adult and paediatric participants with FOP.	• Incidence and description of all treatment-emergent adverse events (TEAEs) whether or not they are considered as related to the study intervention; • Incidence and description of all serious and nonserious treatment-related TEAEs; • Incidence and description of all serious TEAEs, whether or not they are considered as related to the study intervention; • Incidence and description of all nonserious TEAEs whether or not they are considered as related to the study intervention.
Secondary	
• To describe range of motion, as assessed by the Cumulative Analogue Joint Involvement Scale (CAJIS) for FOP, at the Inclusion Visit and over time under palovarotene treatment;	• Raw values and change from the Inclusion Visit in CAJIS total score at each Follow-up Visit;
• To describe the use of assistive devices and adaptations for daily living by FOP participants, at the Inclusion Visit and over time under palovarotene treatment;	• Raw values and shift from the Inclusion Visit in the use of assistive devices and adaptations for daily living at each Follow-up Visit;
• To describe physical function, using the adult form of the FOP Physical Function Questionnaire (FOP-PFQ), at the Inclusion Visit and over time under palovarotene treatment;	• Raw values and change from the Inclusion Visit in % of worst score for total score, upper extremities subscore and mobility subscore using the adult form of the FOP-PFQ for all participants, at each Follow-up Visit;

• To describe the FOP healthcare utilization in patients with FOP	• Type and frequency of healthcare utilization
• To describe the parameters of lung function (observed and % predicted forced vital capacity (FVC), observed and % predicted forced expiratory volume in one second (FEV_1), absolute and predicted FEV_1/FVC ratio, observed and % predicted diffusion capacity of the lung for carbon monoxide (DLCO)) at the Inclusion Visit and over time under palovarotene treatment;	• Raw values and change from the Inclusion Visit in observed and % predicted FVC at each Follow-up Visit; • Raw values and change from the Inclusion Visit in observed and % predicted FEV_1 at each Follow-up Visit; • Raw values and change from the Inclusion Visit in absolute and predicted FEV_1/FVC ratio at each Follow-up Visit; • Raw values and change from the Inclusion Visit in observed and % predicted DLCO at each Follow-up Visit;
• To describe physical and mental health, using the adult form of the Patient Reported Outcomes Measurement Information System (PROMIS) Global Health Scale, at the Inclusion Visit and over time under palovarotene treatment;	• Raw values and change from the Inclusion Visit in physical and mental function (mean global physical and mental health score converted into T-scores), using the adult form of the PROMIS Global Health Scale for all participants, at each Follow-up Visit;
• To describe the number of investigator-reported flare-ups, flare-up outcomes (extra bone growth, restricted movement) and flare-up duration by body location and overall;	• Raw values and change from the Inclusion Visit in number of investigator-reported flare-ups, flare-up outcomes (extra bone growth, restricted movement) and flare-up duration at each Follow-up Visit by body location and overall; • Percentage of participants with extra bone growth associated or not with a flare-up status at each Follow-up Visit;
In relation to FOP (via interviews): • To further understand and describe participants' experiences with FOP symptoms (e.g. flare-ups, joints being locked); • To describe the overall impact of the disease on participants living with FOP (e.g. physical functioning, emotional health, social functioning, work/school/daily life impacts); • To identify and rank the critical joints from a participant's perspective; In relation to patient experiences with palovarotene in the parent study : • To further understand and describe participant experience with palovarotene (e.g. decrease in number of flares up, delay in physical disability, overall satisfaction) • To describe the emotional benefit for participants of using palovarotene as a treatment for FOP; • To assess participants' perceptions of benefits and risks of palovarotene.	• Not applicable.

2.2 Overall Study Design and Investigational Plan

Study CLIN-60120-452 is a multicentre, noncomparative rollover study with the aim of continuing to provide palovarotene to participants with FOP who have completed one of the

parent studies (Study PVO-1A-301 or PVO 1A 202/PVO 1A 204) and, in the investigator's judgement, may benefit from palovarotene therapy. Participants who have completed the parent study are defined as those who have completed the parent End of Study (EOS) or End of Treatment Visit.

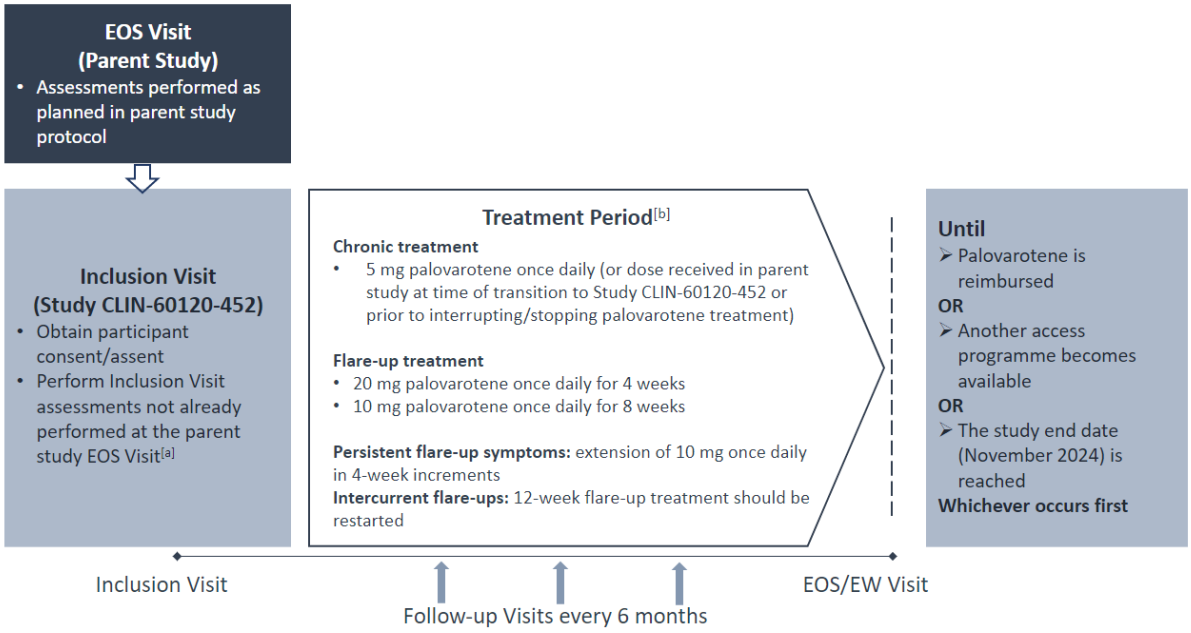
The study is designed primarily to further evaluate the safety of palovarotene and secondly, to collect efficacy data in male and female participants aged ≥14 years (qualifying as skeletally mature or, based on investigator's assessment, have reached final adult height) with FOP treated with palovarotene.

Participants are eligible for the study whether they are receiving chronic or flare-up treatment in the parent study at the time of transition. Participants who previously interrupted/stopped palovarotene treatment and are currently under parent study follow-up due to the premature physeal closure (PPC) related partial clinical hold in participants <14 years, are eligible for the study if they are ≥14 years of age and skeletally mature/have reached final adult height based on investigator's assessment. There must be a current parent study signed informed consent (ICF) form for the participant to be eligible for Study CLIN-60120-452.

A maximum of 87 participants from studies PVO-1A-301, PVO-1A-202/PVO-1A-204 are eligible to be enrolled and will receive palovarotene once daily at the dose received during their participation in the parent study at the time of transition to Study CLIN-60120-452 or prior to interrupting/stopping palovarotene treatment.

The study will consist of an Inclusion Visit (Day 1) (which ideally corresponds to the parent EOS Visit), a continuous dosing treatment period (including a Follow-up Visit every six months), and an EOS/Early Withdrawal (EW) Visit. The maximum duration is three years from enrolment to last study visit (November 2021 to November 2024). The study schema is below:

Figure 1 Study Schema



eCRF=electronic case report form; EOS=End of Study; EW=Early Withdrawal.

a. For any assessments already performed at the parent study EOS Visit, the study site will enter the data again in the Study CLIN-60120-452 eCRF. Participants who completed the paediatric versions of the questionnaires at the EOS Visit of the parent study are required to complete the adult versions of the questionnaires at the CLIN 60120 452 Inclusion Visit.
b. Treatment will be individualised for each participant and based on the regimen (chronic or flare-up treatment) and the dose received in the parent study at the time of transition to Study CLIN-60120-452 or prior to interrupting/stopping palovarotene treatment. Participants will be supplied with chronic treatment as well as the appropriate dose of palovarotene to initiate flare-up treatment when a flare-up or traumatic event is confirmed by the investigator. If a participant is instructed by the investigator to reduce the daily dose of palovarotene due to intolerable adverse reactions but does not have the appropriate dose in his/her possession, the study site will make immediate arrangements to ship the appropriate palovarotene dose to the participant.

Eligible participants will ideally enter the study directly after completing the EOS Visit of the parent study (Study PVO-1A-301 or PVO-1A-202/PVO-1A-204) and the ICF is signed. Any study assessments already performed at the parent EOS Visit will serve as the Inclusion Visit assessment for Study CLIN-60120-452 (maximum of one month allowed between the two visits). Treatment initiation for Study CLIN-60120-452 must concur with the EOS Visit and the study intervention administration schedule of the parent study in order to ensure palovarotene treatment continuity for both chronic and flare-up treatment.

The dose of palovarotene administered will be individualised for each participant and based on the regimen (chronic or flare-up treatment), the weight and the dose received during their participation in the parent study at the time of transition to Study CLIN-60120-452 or prior to interrupting/stopping palovarotene treatment (to allow for dose modifications made to the standard chronic/flare-up regimen during the parent study)

Chronic/flare-up regimen:

Chronic treatment: oral palovarotene once daily, 5 mg, or at the dose received during participation in the parent study at the time of transition Study CLIN-60120-452 or prior to interrupting/stopping palovarotene treatment.

Flare-up treatment: increase in dose at the time of a flare-up (or substantial high risk traumatic event likely to lead to a flare-up) to 20 mg once daily for 4 weeks (28 days), followed by 10 mg once daily for 8 weeks (56 days) for a total of 12 weeks (84 days) even if symptoms resolve earlier.

Participants receiving flare-up treatment at the time of transition to Study CLIN-60120-452 will continue and complete the flare-up treatment as was planned in the parent study.

Flare-up treatment should begin at the onset of the first symptom indicative of a FOP flare-up or substantial high risk traumatic event likely to lead to a flare-up. Chronic treatment should cease at the time of initiation of flare-up treatment, re-initiation of the chronic daily treatment should occur after completion of the flare-up treatment.

Persistent flare-up symptoms: treatment may be extended in 4-week intervals with 10 mg palovarotene and continued until the flare-up symptoms resolve.

Intercurrent flare-up: if the participant experiences an intercurrent flare-up (new flare-up location or marked worsening of the original flare-up) at any time during the flare-up treatment, then the 12-week flare-up treatment should be restarted.

In the case of any intolerable adverse reactions, the daily dose of the chronic/flare-up regimen can be reduced.

2.3 Sample Size Determination and Power

No formal sample size calculations have been performed as the sample size is dependent on the number of participants in the parent studies who are eligible. A maximum of 87 participants from studies PVO-1A-301, PVO-1A-202/PVO-1A-204 are eligible to be enrolled.

2.4 Randomisation and Blinding

This is a non-randomised open-label study therefore no procedures for blinding are applicable.

2.5 Schedule of Assessments

The schedule of Activities (SoA) planned in this study are presented in Table 1.

Table 1 Schedule of Activities

Assessment/Procedure	Inclusion Visit[a] Day 1			Follow-Up Visits Every 6 months (±1 month)[b]/ EOS/EW Visit[c]	
	Procedures already performed at the parent EOS Visit that will be transferred from parent study database	Procedures already performed at the parent EOS Visit to be entered in CLIN-60120-452 eCRF by the study site	Procedures to be performed at the CLIN-60120-452 Inclusion Visit	In-clinic Visit	Remote visit
Informed consent[d]			X		
Inclusion/exclusion criteria			X		
Study intervention administration/accountability[e]			X	X	X
Baseline demographics			X		
Physical examination			X		
Participant interview[f]			X		
Pregnancy testing and childbearing potential [g]		X[a]*		X	X
Linear height and body weight [h]		X[a]*		X	X
Vital signs [i]		X[a]*		X	X
Spinal health assessment [j]		X [a]**		X	
Lung function assessments [k]			X	X	
Flare-up assessment [l]			X	X	X [m]
Additional Extra bone growth assessment (without associated flare-up)			X	X	X
CAJIS [n]	X*			X	X
C-SSRS [n] [o]			X	X	X
FOP-PFQ assessment[p] [q]	X*		X [q]***	X	X
PROMIS Global Health Scale [p][q]	X*		X [q]***	X	X
FOP assistive devices assessment [p]			X	X	X
Healthcare Utilization [p]			X	X	X
Biochemistry (amylase, lipase, AST, ALT) and triglycerides	X*				
Disease and flare-up history	X				
Prior medications	X				
Concomitant medications		X		X	X
Concomitant procedures [r]		X		X	X
AEs [s]		X		X	X

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CAJIS=Cumulative Analogue Joint Involvement Scale for FOP; COVID-19=coronavirus disease 2019; C-SSRS=Columbia-Suicide Severity Rating Scale; DLCO=diffusion capacity of the lung for carbon monoxide; eCRF=electronic case report form; EOS=End of Study; EW=Early Withdrawal; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; FOP=fibrodysplasia ossificans progressiva; FOP-PFQ=FOP Physical Function Questionnaire; PROMIS=Patient Reported Outcomes Measurement Information System.

a. The Inclusion Visit should be in-clinic and corresponds ideally to the EOS Visit of the parent study (Study PVO-1A-301 or PVO-1A-202/PVO-1A-204). A maximum of one month is allowed between the two visits. For any assessments from the parent EOS Visit performed outside this allowed time window, assessments will need to be performed again at the Study CLIN-60120-452 Inclusion Visit (flagged with *). However, to enable continued access to the Investigational Product and rollover of participants with impaired mobility [in the case(s) when per investigator's judgement this is considered as beneficial for the participant's medical conditions], the parent EOS Visit and consenting for CLIN-60120-452 and CLIN-60120-452 Inclusion Visit can be conducted remotely. In such case(s) both parts of remote consenting used by the site – i.e. Informing/Consenting discussion and ICF signature should be agreed with the IRB/EC, and the investigator's judgement should be sufficiently documented in the patient source notes.

   For the spinal health assessment, a time window of 3 months post parent visit is allowed (flagged with **).

b. Follow-up Visits will be either in-clinic or performed remotely (e.g. at the participant's home by qualified SP in-home services, and/or via video-conference or telephone contact from clinical site personnel).

c. The EOS/EW Visit will be ideally an in-clinic visit (or remotely when permitted by the IRB/IEC) and will occur at the time of last study intervention intake. The EOS Visit must take place before the participant transitions to commercial treatment.

d. For participants <18 years, assent and legal guardian's consent will also be required.

e. Palovarotene status (treated or not treated) and regimen (chronic or flare-up treatment) at the time of transition to Study CLIN-60120-452 will be collected at the Inclusion Visit. Participants will be supplied with chronic treatment as well as the appropriate dose of palovarotene to initiate flare-up treatment when a flare-up or traumatic event is confirmed by the investigator. Participants will be instructed to report potential flare-up symptoms to study site personnel, only one symptom is required to define a flare-up (see Section **Error! Reference source not found.** of the protocol). In the presence of persistent flare-up symptoms, treatment may be extended in 4-week intervals until the flare-up symptoms resolve. If the participant experiences an intercurrent flare-up, or substantial high-risk traumatic event likely to lead to a flare-up, at any time during the flare-up treatment, the 12-week flare-up treatment should be restarted.

f. Participant interviews will be conducted in person or by telephone by the PI/qualified site staff and can be carried out anytime within 1 year (ideally within 1 month) following the Inclusion Visit.

g. Participants will be assessed for child-bearing status and pregnancy prevention measures (females only). According to local practice, medically documented blood or urine pregnancy tests should be carried out prior to starting therapy, monthly as long as the participant receives palovarotene and one month after stopping (the results of pregnancy tests will be recorded in the eCRF). See Section 8.2.6 and 8.3.5 of the protocol for procedure in case of a positive pregnancy test during the study.

h. For linear height, data from the parent EOS Visit will be used for the Study CLIN-60120-452 Inclusion Visit when available. Height at 6 to 12 months prior to the Inclusion Visit will be transferred from parent study database.

i. Vital signs to be collected are respiratory rate, blood pressure and heart rate.

j. The spinal health assessment must be performed at the Study CLIN-60120-452 Inclusion Visit ONLY if not already performed within the time window allowed (ie,, 3 months post-parent EOS Visit). The spinal health assessment will then be performed annually. The spinal health assessment should be performed using radiological imaging (e.g., CT, x-ray, scintigraphy, etc). This assessment may be performed locally.

k. Includes spirometry and the DLCO test. Spirometry obtains the lung function parameters of observed and % predicted FVC and FEV_1 and the absolute and predicted FEV_1/FVC ratio. The DLCO test obtains observed and % predicted DLCO which provides information on the efficiency of gas transfer from alveolar air into the bloodstream.

l. Includes extra bone growth assessment when associated with a flare-up

m. During remote visit performed at home by the SP in-home services, the participant will be asked if any flare-ups occurred since last visit. If yes, the homecare clinician will attempt to facilitate a call between the participant and the site to provide details.

n. In case of remote visit, the CAJIS and C-SSRS will be assessed via video-conference if possible or feasible or telephone contact from clinical site personnel. The homecare clinician will facilitate the call between the participant and Investigator.

o. 'Baseline' version of C-SSRS will be used at the Study CLIN-60120-452 Inclusion visit. 'Since Last Visit' version of C-SSRS will be used at Follow-Up Visits.

p. In case of remote visit, the questionnaires will be provided by the SP in-home services and completed by the participants.

q. Paper patient-reported questionnaires. Questionnaires completed at the parent EOS Visit will be used for the Study CLIN-60120-452 Inclusion Visit. The adult form (developed for participants ≥15 years old) of the FOP-PFQ and PROMIS Global Health Scale will be used for all participants. At in-clinic visits when multiple assessments are to be performed, the FOP-PFQ and the PROMIS Global Health Scale should be completed first, and in that order, before any other assessments are completed. Participants who completed the paediatric versions of the questionnaires at the EOS Visit of the parent study are required to complete the adult versions of the questionnaires at the CLIN-60120-452 Inclusion Visit (flagged with ***).

r. Any vaccinations received during the study (including COVID-19) should be recorded as concomitant procedures.

s. AEs first occurring during participation in the parent study and ongoing at the time of the Study CLIN-60120-452 Inclusion Visit will be entered again in the Study CLIN-60120-452 eCRF.

2.6 Change from Statistical Section of the Protocol

As per section 9.4.1 of the protocol it stated that all analyses will be performed by parent study (PVO-1A-301 or PVO-1A-202/PVO-1A-204), by palovarotene status at the time of transition to Study CLIN-60120-452 (treated, not treated) and treatment regimen (chronic treatment only, flare-up treatment only, chronic & flare-up treatment) and overall.

However, all analyses will only be performed overall and by treatment regimen (chronic treatment only, flare-up treatment only, chronic & flare-up treatment).

3 PLANNED ANALYSES

3.1 Data Monitoring

Participant safety will be regularly monitored by an external Independent Data Monitoring Committee (IDMC), which includes safety signal detection at any time during the study. Three IDMC meetings are planned to take place over the maximum three-year duration of the study.

Details related to IDMC membership, responsibilities, procedures and roles are described in the IDMC charter and the statistical analysis is described in the IDMC SAP.

3.2 Interim Analysis

No formal interim analysis will be performed. A stand-alone final report for the qualitative participant interviews will be made available once enrolment and all interviews have been completed within 1 year following the Inclusion Visit.

3.3 Final Analysis

The final analysis will be completed after database lock when all participants have completed the study.

4 ANALYSIS SETS

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Screened Set	All participants who signed the ICF
Enrolled Set	The Enrolled Set will contain all participants who were assigned to receive palovarotene in Study CLIN-60120-452. Participants will be included based upon the “Is participant included in the study?” question within the eCRF.
Full Analysis Set (FAS)/Safety Analysis Set (SAS)	The FAS/SAS will contain all participants who received at least one dose of palovarotene during Study CLIN-60120-452.
Per Protocol (PP) Set	The PP set will contain all participants from the FAS who did not experience any major protocol deviations that may interfere with safety/efficacy evaluations. Please refer to section 5.3 for details regarding the management of deviations.

5 STATISTICAL METHODS/ANALYSES

The statistical analyses will be performed in accordance with ICH E9 guidelines.

5.1 General Considerations

No formal statistical testing will be performed. All the analyses will be primarily descriptive in nature. If p-values are presented, they will be for exploratory purposes only. Confidence intervals will be 95%, unless otherwise specified in the description of the analyses.

With the exception of the QoL questionnaires, where missing data will be handled based upon the calculation of the derived scores, missing data will not be replaced but will be displayed in all relevant tables.

All analyses will be performed overall and by treatment regimen (chronic treatment only, flare-up treatment only, chronic & flare-up treatment).

All listings will be presented on the screened set.

All statistical analyses will be performed using the Statistical Analysis System® software version 9.4.

5.1.1 Outputs Presentation

5.1.1.1 Tables Header

All summary tables will be presented overall and by treatment regimen.

5.1.1.2 Presentation of Groups

Tables, Figures and Listings (TFLs) will be displayed using the following group labels, in the order presented:

Overall

- Overall

Overall includes all participants.

Treatment Regimen

- Chronic Treatment Only
- Flare-up Treatment Only
- Chronic and Flare-up Treatment
- Not Treated (Only required on outputs not using FAS/SAS)

The treatment regimen will be derived from the dosing form collected in CLIN-60120-452 study. All dosing records will be used. Cases where the treatment regimen is not available from the CRF will be discussed with the IPSEN team on a case-by-case basis.

5.1.1.3 Presentation of Visits / Timepoints

Summaries by visit will be presented using the derived window visits (See Section 6.1). Visits in the TFLs will be presented as follows and in the following order:

Visit Name
Baseline
Month 6
Month 12
Month 18
Month 24
Month 30
Month 36

5.1.1.4 Subgroups

As per section 5.1.1.1 all summaries will be performed by treatment regimen (chronic treatment only, flare-up treatment only, chronic & flare-up treatment).

5.1.2 Descriptive Statistics

All raw and derived variables will be listed and described using summary statistics.

For descriptive analyses, summary statistics will be presented at each scheduled visit and will include sample size, number of available observations (n), number of missing observations

(missing), mean, 95% CIs of the mean/median, standard deviation (SD), median and range for continuous variables. For categorical or discrete variables, the absolute and relative (percentage) numbers based on the non-missing number of observations for each category will be presented, including 95% CIs.

5.1.3 Baseline value

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior on the day of first Investigational Medicinal Product (IMP) administration in study CLIN-60120-452. This includes data collected at the Inclusion Visit and data transferred from the final parent study databases (either programmatically or entered by site). See the schedule of assessments in section 2.5 for the method of collection of data for the Inclusion Visit.

5.1.4 Reference Start Date and Study Day

Reference start date is defined as the day of the first IMP administration of palovarotene (Day 1) in Study CLIN-60120-452. Study day will be calculated as:

- The difference between the event date and the reference date plus one day, if the event is on or after the reference date.

- The difference between the event date and the reference date, if the date of event is prior to the reference date.

Study day will appear in any listings where an assessment date or event date appears.

In case of partial or missing event date, study day will appear missing while any associated durations will be presented based on the imputations described in appendix A3.

5.2 Disposition and Analysis Sets

The following disposition summaries and listings will be provided:

- Summary table with the number and percentages of enrolled participants per country, site on the screened set
- Summary table with the number and percentage of participants screened, enrolled, treated, completed, withdrawn and reason for withdrawal on the screened set
- Summary table with the number and percentage of participants per visit on the enrolled set
- Summary table on duration of participant participation in the study on the enrolled set. The definition of the duration of participant participation is from date of consent to the last study visit or date of completion/discontinuation, whichever comes later.
- Listing of dates of visit including duration of participant participation
- Listing of withdrawal participants

In addition, the below summaries and listings will be provided:

- Summary of the number of participants within each treatment regimen subgroup
- Summary of the number and percentages of participants included in each analysis set with reasons for exclusion from each analysis set
- Listing including flag for each analysis set and reason for exclusion from each set

5.3 Protocol Deviations

An exhaustive list of major/important protocol deviations that may occur during the course of the study and any action to be taken regarding exclusion of participants from the PP set is defined in Protocol Deviation Plan. Major protocol deviations will be determined and finalised during the data review for the final analysis and documented.

The following protocol deviation summary and listing will be provided on the enrolled set:

- Number and percentage of participants with major protocol deviations by deviation category
- A listing of major protocol deviations.
- A listing of all protocol deviations

5.4 Demography and Other baseline characteristics

All demographic and baseline characteristics summaries and listings will be provided for the FAS/SAS. The summary will be repeated on the PP set if ≥10% of participants are excluded from the FAS/SAS. [Note: Demographic variables of age and sex will be collected in Study CLIN-60120-452, all other variables will be transferred from the parent study database]

Following descriptive summaries will be provided:

- Demographic variables (age, age categories [<15, 15-25 & >25] and EudraCT age categories, sex, race, ethnicity, height (cm), weight (kg) and BMI (kg/m^2)). See appendix A6 for defined EudraCT age categories
- Disease history (time since date of diagnosis by a physician (years), method of diagnosis and type of FOP genetic mutation)
- Flare-up history over the past 12 months prior to the Inclusion Visit (number of flare-ups, start and stop date of flare-ups, location of flare-ups, symptoms of flare-up, cause of flare-up and time since last flare-up (months)).
- Extra bone growth history over the past 6 months prior to the Inclusion visit (number of extra bone growths, locations, preceded by and symptoms)
- Bone maturity history, for participants aged <18 years at study inclusion, (bone age, difference between chronological age and bone age (months), hand/wrist and knee epiphyseal assessment and skeletally mature assessments)

Time since date of diagnosis is defined as (Date of the first IMP administration of palovarotene in Study CLIN-60120-452 - date of diagnosis).

Date of diagnosis is collected directly for study PVO-1A-301. For PVO-1A-202/PVO-1A-204, age at first confirmation of heterotopic ossification (years) will be considered equivalent to the age of diagnosis and as such in combination with the birth date used to derive the year of the equivalent date of diagnosis.

[Note: 1 year = 365.25 days and 1 month = 30.4375 days].

Difference between chronological age and bone age is defined as (bone age – estimated age at time of bone maturity assessment [age captured at the inclusion visit will be used to calculate the year of birth, from which age at time of bone maturity assessment will be estimated by imputing the day and month as 30th June].

Listings will also be provided for all the summaries listed above.

5.5 Non-drug therapies, medications and surgical procedures

Non-drug therapies and surgical procedures will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) in effect within IPSEN at the time of database lock. Medications will be coded using the latest version of World Health Organization-Drug dictionary at the time of database lock. [Note: Prior medications will not be collected in Study CLIN-60120-452 but transferred from the final parent study database]

Medication, non-drug therapies and surgical procedures start and stop dates will be compared to the date of the first IMP administration of palovarotene in Study CLIN-60120-452 to allow classification as either Prior only, Prior and Concomitant, or Concomitant only:

Prior (P)	Start and stop dates prior to the date of the first IMP administration of palovarotene in Study CLIN-60120-452.
Prior and Concomitant (PC)	Start date before the date of the first IMP administration and stop date on or after the date of the first IMP administration of palovarotene in Study CLIN-60120-452.
Concomitant (C)	Start date on or after the date of first IMP administration of palovarotene in Study CLIN-60120-452.

Summary tables on prior medications/will include "P" only, summary tables on concomitant medications/non-drug therapies/surgical procedures will include "C" and "PC". See detailed rules in appendix A3 for classification of prior and concomitant medication/non-drug therapies, surgical procedures in case of partial/missing date.

Following summaries, presenting count and percentages of participants will be provided on the enrolled set:

- Prior medications (P) by ATC class level 2 and Preferred Name,
- Concomitant medications (PC, C) by ATC class level 2 and Preferred Name
- Concomitant procedures (PC, C) by primary SOC and Preferred Term,

Listings will be provided for all the summaries listed above. These listings should include a flag indicating the category (P, PC and C) as described in the table above.

5.6 Compliance

Compliance is defined as (total actual doses taken/total expected doses taken) x 100.

The total actual dose taken will be calculated as (total [capsules dispensed to the participant x respective dosage] – total [capsules returned x respective dosage]) by the participant across all medication kits dispensed.

If the number of returned capsules is missing from any kit, the number of returned capsules for that kit will be imputed by multiplying the number of capsules dispensed by the mean compliance observed in the MOVE study. For chronic kits (or weight-adjusted/de-escalate equivalent) <=5mg, a compliance of 80% will be used estimate the number of capsules returned. For flare-up kits (or weight-adjusted/de-escalate equivalent) >5mg, a compliance of 87% will be used to estimate the number of capsules taken for that kit. These imputed values will then be used to determine the overall dose taken across the duration of the study.

The total expected dose taken will be calculated by multiplying the duration of treatment in days for each treatment regimen, across all cycles of that regimen, (see derivation under section 5.6.6) by the planned dose for each regimen and finally totalling the expected dose across all regimens.

The expected duration of treatment is calculated as following for each treatment regimen:

Total of expected regimen cycle dosing periods across all regimen cycles. Each expected regimen cycle dosing period is defined as (last regimen cycle dose date – first regimen cycle dose date + 1).

Compliance will be summarised for the FAS/SAS set with descriptive statistics. Compliance in each category (<80%, ≥80% - ≤120%, >120%) will also be summarised for counts and percentages of participants.

A listing of treatment compliance, including all derived parameters will be provided.

5.7 Primary and Secondary Analysis

5.7.1 General Considerations

The FAS/SAS will be used for the analysis of the primary and secondary endpoints. Analyses of the secondary endpoints will be repeated on the Per Protocol (PP) Set if ≥10% of participants are excluded from the FAS/SAS Set.

All analyses will be performed overall and by treatment regimen (chronic treatment only, flare-up treatment only, chronic and flare-up treatment).

5.7.1.1 Significance Testing and Estimations

The statistical analysis is only descriptive therefore no formal statistical significance testing will be performed.

5.7.1.2 Handling of Dropouts and missing data

Diligent attempts will be made to limit the amount of missing data and to follow-up all enrolled participants to collect the primary and secondary efficacy endpoints for the statistical analysis.

With the exception of the QoL questionnaires, where missing data will be handled based upon the calculation of the derived scores, missing data will not be replaced but will be displayed in all relevant tables.

5.7.1.3 Statistical/analytical issues

Given all analysis is descriptive, adjustment for multiplicity is not applicable to this study.

5.7.2 Analysis of Primary Endpoint

5.7.2.1 Endpoints

The primary endpoints of the study are:

- Incidence and description of all treatment emergent adverse events (TEAEs) whether or not they are considered as related to the study intervention;
- Incidence and description of all serious and nonserious treatment-related TEAEs;
- Incidence and description of all serious TEAEs, whether or not they are considered as related to the study intervention;
- Incidence and description of all nonserious TEAEs whether or not they are considered as related to the study intervention.

5.7.2.2 Primary Analysis – Adverse Events

All adverse events (AEs) recorded in the eCRF will be coded using the latest version of MedDRA dictionary at the time of the database lock and will be classified by System Organ Class (SOC) and Preferred Term (PT). [Note: All ongoing AEs at the time of participant transition will be transferred from the parent study database]

AEs will be classified as Treatment-Emergent AEs (TEAEs) according to the rules below:

- Events with start date on or after the date of first IMP administration and up to 30 days after date of last dose of treatment of palovarotene in Study CLIN-60120-452 (or date of last contact if not available).

- Ongoing AEs from the parent study with a worsening in intensity or relationship (see relationship and intensity order below) to the study intervention following transition to Study CLIN-60120-452. New AEs during Study CLIN-60120-452 will be compared by SOC and PT to all previous study ongoing AEs for comparison of the intensity and relationship.

Ongoing AEs from the parent study with no change in intensity or relationship to the study intervention following transition to Study CLIN-60120-452 will therefore be an AE (non-TEAE).

In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the most conservative case; i.e. treatment emergent.

The below summaries will be provided:

- An overview table summarising the:
  - number and percentage of participants with at least one of the following AEs: any AE; any TEAE; maximum intensity of TEAEs; causality of TEAEs, worst causality and intensity of TEAEs (worst case); TEAE leading to a dose change; TEAE leading to withdrawal; TEAE leading to death; Serious Adverse Events (SAEs); Serious TEAE;
  - corresponding number of events for each of the AE categories listed above
- A summary of the number and percentage of participants reporting an AE by SOC and PT
- A summary of the number and percentage of participants reporting a TEAE by SOC and PT
- A summary of the number and percentage of participants reporting a TEAE by maximum intensity, SOC and PT
- A summary of the number and percentage of participants reporting a TEAE by worst causality, SOC and PT
- A summary of the number and percentage of participants reporting a related TEAE by SOC and PT
- A summary of the number and percentage of participants reporting a TEAE by intensity, causality, SOC and PT
- A summary of the number and percentage of participants reporting a non-Serious TEAE by SOC and PT
- A summary of the number and percentage of participants reporting a non-Serious related TEAE by SOC and PT
- A summary of the number and percentage of participants reporting a TEAE leading to treatment discontinuation by SOC and PT
- A summary of the number and percentage of participants reporting a TEAE leading to dose change (increase or decrease) by SOC and PT

The below summaries will also be provided by treatment dose at time of AE onset (5mg, 10/20mg and all palovarotene):

- Overall summary of Adverse events
- A summary of the number and percentage of participants reporting a TEAE by SOC and PT

- A summary of the number and percentage of participants reporting a TEAE by maximum intensity, SOC and PT
- A summary of the number and percentage of participants reporting a TEAE by worst causality, SOC and PT
- A summary of the number and percentage of participants reporting a TEAE leading to treatment discontinuation by SOC and PT
- A summary of the number and percentage of participants reporting a TEAE leading to dose change (increase or decrease) by SOC and PT

To calculate the treatment regimen at time of AE onset, the start date of each AE will be merged with each participant dosing log. Given dosing end dates are not captured the latest dosing record prior to the AE start date will be identified. If the dosing record is either 0 mg or after treatment discontinuation the regimen will be set to "off treatment".

AEs will be counted as follows:

- AEs summaries will be ordered in terms of decreasing frequency for SOC and PT within the overall column of each output.
- Participants with more than one AE within a particular SOC are counted only once for that SOC. Similarly, participants with more than one AE within a particular PT are counted only once for that PT.
- Participants reporting a TEAE more than once within that SOC/ PT, the TEAE with the worst-case intensity (intensity order: severe > missing > moderate > mild) will be used in the corresponding intensity summaries.
- Participants reporting a TEAE more than once within that SOC/ PT, the TEAE with the worst-case causality to study medication (order: related > missing > not related) will be used in the corresponding relationship summaries;
- If the intensity/relationship is missing for a TEAE, it will be considered as missing in the summary tables; Summaries by intensity/relationship will be presented (in the same order as above).
- The non-serious TEAEs table should include a specific row "any non-serious TEAE above x%"

A listing with all AEs data will be listed including non-TEAEs, Treatment-emergence status will be flagged in the listing. In addition listings for participants with a pregnancy or overdose will be presented (a table will be provided if more than 3 cases are observed in either category).

Deaths and SAEs

The below summaries will be provided:

- A summary of the number and percentage of participants reporting a serious TEAE
- A summary of the number and percentage of participants reporting a serious related TEAE
- A summary of the number and percentage of participants reporting a TEAE leading to death
- A summary of the number and percentage of participants reporting a serious TEAE by treatment dose at AE onset (5mg, 10/20mg and all palovarotene)

The below listings will be also provided:

- All SAEs

- All TEAEs leading to treatment discontinuation
- All Deaths

5.7.3 Analysis of Secondary Endpoints

All secondary endpoints (including derived parameters) will be listed.

5.7.3.1 FOP Physical Function Questionnaire (FOP-PFQ)

The FOP-PFQ is a disease-specific patient-reported outcome measure of physical impairment which includes questions related to ADL and physical performance. The adult form (developed for participants ≥15 years old) will be used for all participants.

The adult FOP-PFQ consists of 28 questions which are scored on a scale of 1 to 5, with lower scores indicating that the participant has more difficulty completing those tasks. A total score, upper extremities subscore and a mobility subscore will be calculated.

- The total score: the sum of the scores from each question which will range from 28 × 1 = 28 to 28 × 5 = 140
- Upper extremities subscore: the sum of the scores from 15 questions (Questions 1-12, 14, 25 and 26) which will range from 15 × 1 = 15 to 15 × 5 = 75
- Mobility subscore: the sum of the scores from 13 questions (Questions 13, 15-24, 27 and 28) which will range from 13 × 1 = 13 to 13 × 5 = 65

Missing scores for individual questions will not be imputed, but they will be taken into account according to the rules described below:

(1) If more than 20% of the questions contributing to the total score, upper extremities subscore or mobility subscore are missing, the corresponding total score will not be calculated. It will be considered as missing

(2) If less than 20% of the questions contributing to the total score, upper extremities subscore or mobility subscore are missing, the score will be calculated by summing all observed question scores, divided by the number of questions that were answered and by multiplying this average score by the total number of questions that were meant to be answered (i.e. × 28 for the total score).

The scores will be transformed to reflect a percentage of worst score. The percentage of worst score ranges from 0% to 100% with 0% indicating the best possible function and 100% indicating the worst possible function. The table below illustrates some sample derivations of the percentage of worst scores for upper extremities:

Sample Participant	Observed FOP-PFQ Score	Lowest Possible Score	Highest Possible Score	Range of Possible Scores	Distance = Highest - Observed	Distance/ Range	Percentage of Worst Score
1	45	15	75	60	30	0.500	50.0%
2	40	15	75	60	35	0.583	58.3 %
3	35	15	75	60	40	0.667	66.7%
4	30	15	75	60	45	0.750	75.0%
5	25	15	75	60	50	0.833	83.3%

The percentage of worst scores (for total score, upper extremities subscore and mobility subscore) and changes from the inclusion visit of each subscore will be summarised at each scheduled visit with descriptive statistic on the FAS/SAS.

5.7.3.2 PROMIS Global Health Scale

The PROMIS Global Health Scale is a patient-reported outcome measure of physical and mental function. The adult form (developed for participants ≥15 years old) will be used for all participants. The PROMIS Global Health Scale consists of 10 questions from which two scores are calculated: the global physical health score and the global mental health score, both ranging from 4 (worse health) to 20 (better health) and are calculated as follows:

- Global physical health score: the sum of scores from Questions 3, 6, 7 and 8
- Global mental health score: the sum of scores from Questions 2, 4, 5 and 10

In the calculation of the Global Physical Health and Global Mental Health scores, the following questions will be rescaled as shown in the table below:

Questions	Raw Score	Rescaled Score
7	0	5
	1-3	4
	4-6	3
	7-9	2
	10	1
8 and 10	1	5
	2	4
	3	3
	4	2
	5	1

PROMIS=Patient Reported Outcomes Measurement Information System.

If a participant is missing any of the contributing raw scores, the corresponding score (global physical health or global mental health score) will not be calculated for that participant.

Global Physical Health scores and Global Mental Health scores will also be converted to T-scores as described in detail in Section 7.1. T-score distributions are standardised such that a value of 50 represents the average (mean) for the general population and increments of ±10 points represent ±1 SD away from the norm. Higher T-scores indicate better physical/mental health. A T-score <50 indicates worse health than the general population, while a T-score >50 indicates better health.

PROMIS Global Physical Health and Global Mental Health T-scores and changes from the inclusion visit will be summarised at each scheduled visit with descriptive statistics on the FAS/SAS.

In additional the raw scores and changes from the inclusion visit for questions 1 and 9 will be summarised separately at each scheduled visit with descriptive statistics on the FAS/SAS.

5.7.3.3 Cumulative Analogue Joint Involvement Scale (CAJIS)

Range of motion across the whole body will also be assessed using the CAJIS. This scale, assesses functional disability by categorising range of motion across 12 joints (both right and left shoulder, elbow, wrist, hip, knee and ankle joints) and three body regions (neck, thoracic/lumbar spine and jaw), with each joint/region assessed as: 0=normal (<10% deficit); 1=partially impaired (10% to 90% deficit); 2=functionally ankylosed (>90% deficit).

The CAJIS total score is calculated as the sum of the scores of all joints/regions and ranges from 0 (no involvement) to 30 (maximally involved).

The CAJIS total score, each locations score and associated changes from the inclusion visit will be summarised at each scheduled visit with descriptive statistics on the FAS/SAS.

Ambulation will be summarised at each scheduled visit with descriptive statistics for each category as below:

- Walks only
- Walks/Wheelchair [defined as both “Walks” and “Wheelchair” marked]
- Wheelchair only

Use of assistive devices/adaptions will also be summarised at each scheduled visit with descriptive statistics for each category as below:

- Independent [defined as neither “Needs some help” or “Needs complete help” are marked]
- Needs some help
- Needs complete help

In addition a shift table of each category from the inclusion visit to each post-inclusion visit will be presented.

5.7.3.4 FOP Assistive Devices

The use of assistive devices and adaptations for daily living will be collected using the FOP assistive devices assessment at each visit.

The number of assistive devices in each category (mobility aids, eating tools, personal care tools, bathroom aids and devices, bedroom aids and devices, home adaptions, work environment adaptions, technology adaptions, sports and recreation adaptions, school adaptions and medical therapies for daily living) and the total number of assistive devices and adaptations for daily living being used will be summarised at each scheduled visit with descriptive statistics.

In addition the change in the number of assistive devices of each category and the total number of assistive device and adaptations for daily living from the inclusion visit to each post-inclusion visit will be presented.

5.7.3.5 Healthcare Utilisation

The use of health care services (yes/no) and their frequency in the past 6 months will be summarised at each scheduled visit with descriptive statistics. The below health services will be assessed:

- General Practitioner
- Homeopathic/Naturopathic provider
- Podiatrist
- Dentist – Orthodontist
- Occupational therapist
- Physiotherapist
- Speech therapist
- Ear, nose and throat doctor
- Psychologist/psychiatrist/counsellor
- Orthopaedic specialist
- Gastroenterologist
- Obstetrician-Gynecologist
- Dermatologist
- Pulmonologist
- Pain specialist
- Cardiologist

- Urologist
- Rheumatologist
- Neurologist
- Wound care specialist

In addition, the overall annualized rate for each healthcare service (and total healthcare services) will be summarised with descriptive statistics. The overall annualized rate will be calculated as (number of utilization during the study / duration of participant participation in the study in days) * 365.25.

5.7.3.6 Lung Function Parameters

*Lung function parameters (*observed and % predicted FVC, observed and % predicted FEV1, absolute and predicted FEV1/FVC ratio and observed and % predicted DLCO*)* and changes from the inclusion visit will be presented for all scheduled visit with descriptive statistics.

The DLCO value will be reported in either traditional units (mL/min/mmHg) or SI units (mmol/min/kPa). Values in SI units can be multiplied by 2.987 to obtain values in traditional units (Graham et al., 2017).

5.7.3.7 Flare-ups

The number of flare-ups since the last visit (for post-inclusion visits) as well as the number of participants with investigator-reported flare-ups, number of intercurrent flare-ups, location of flare-ups, flare-up causes, flare-up symptoms, flare-up outcomes (restricted movement and bone formation) and flare-up duration will be presented for each scheduled visit by body location and overall with descriptive statistics. For the summary of flare-ups, percentages will be calculated using the number of participants with at least a flare-up at each visit as the denominator. The following body locations will be presented:

- Shoulder (Includes left and right shoulder)
- Elbow (Includes left and right shoulder)
- Wrist or Hand (Includes left wrist or hand and right wrist or hand)
- Hip (Includes left hip and right hip)
- Knee (Includes left hips and right hip)
- Ankle or Foot (Includes left ankle or foot and right ankle or foot)
- Back (Includes upper back and lower back)
- Chest
- Abdomen
- Head and Anterior neck
- Jaw and Submandibular Area
- Spine (Includes Cervical Spine, Thoracic Spine and Lumbar Spine)
- Other (Includes all other locations)

The number of flare-ups since the last visit will be calculated by totalling the number of distinct flare-ups (based upon the flare-up start dates, not including intercurrent flare-ups) using the visit windows as defined in section 6.1.

Duration of flare-up will be defined as (date of end of flare-up – date of start of flare-up + 1) and will be calculated for each distinct flare-up before summing across each participant.

An intercurrent flare-up is defined as a new flare-up or marked worsening of the original flare-up at any time during a flare-up based treatment cycle.

In addition, the total number of flare-ups across the study, the duration of study participation, the individual flare-up rate per month and the global flare-up rate (including the 95% confidence interval derived using a poisson model offset by the duration of study participation) across all participants per month will be summarised.

The individual flare-up rate per month will be defined as [(Number of flare-ups during study follow-up) / duration in the study (in months)]. This duration will be calculated as (end of study date – informed consent date +1) / 30.4375.

The global flare-up rate will be calculated as the sum of flare-ups across all participants / sum of durations in the study(months).

5.7.3.8 Extra Bone Growth

The percentage of participants with any extra bone growth (associated or not with a flare-up) since the previous visit will be presented for each visit with descriptive statistics. The number of extra bone growths since the previous visit will be calculated by totalling the number of distinct records (based upon the start date) within each of the visit windows as defined in section 6.1.

The location (and associated restricted movement if collected), the cause/proceed by, the number preceded by symptoms and the duration of bone growth will be presented in a listings

The duration of the bone growth will be defined as (date of end of bone growth – date of start of bone growth + 1).

5.7.4 Analysis of Exploratory Endpoints

No exploratory endpoints are defined for this study.

5.8 Safety

5.8.1 General Consideration

All safety summaries and analyses will be based upon the FAS/SAS.

All analyses will be performed overall and by treatment regimen (chronic treatment only, flare-up treatment only, chronic and flare-up treatment).

All safety data will be included in participant data listings (see listing detail conventions in Appendix A5).

5.8.2 Extent of exposure

Duration of total treatment, duration of flare-up treatment, mean duration of flare-up treatment and duration of chronic treatment will be summarised for the FAS/SAS with descriptive statistics. In the eCRF Dosing Form, for each treatment period, only the start date if completed (no end date). So, for each period, the end date will be considered as the start date of the following period (periods have to be sorted by start date) – 1. For the last record, it will be the date of last dose if collected, or if not the date of last contact. The date of last contact will be the latest date available across all assessments.

5.8.2.1 Total Duration of Treatment

Total duration of treatment is defined as (last dose date of IMP administration of palovarotene in Study CLIN-60120-452 - first dose date of IMP administration of palovarotene in Study CLIN-60120-452 + 1). The first dose date will be the start date of the first record in eCRF Dosing Form and the last dose date will be the date of last contact.

5.8.2.2 Duration of Flare-up Treatment

For participants receiving flare-up treatment, duration of flare-up treatment (days) is defined as total flare-up cycle dosing periods (days) across all flare-up cycles. This includes any days for which the participant is receiving persistent flare-up symptom or intercurrent flare-up treatment.

For a flare-up cycle, the flare-up cycle dosing period (days) is defined as days that participants received flare-up-based treatment and is calculated as (last dose date of the flare-up cycle – first date of the flare-up cycle – days where flare-up medications were not taken/interrupted during the flare-up cycle + 1).

The mean duration of flare up treatment is defined as the total duration of flare-up treatment (across all cycles) divided by the number of flare-up treatment cycles for each individual.

The duration of persistent flare-up symptom and intercurrent flare-up treatment will be calculated in a similar manner.

5.8.2.3 Duration of Chronic Treatment

Based on the study design, participants are assumed to be on non-flare-up-based treatment from the date they received the first non-flare-up treatment unless they receive flare-up-based treatment. Thus, duration of non-flare-up treatment (days) will be calculated as (last non-flare-up treatment date - first non-flare-up treatment date – duration of flare-up treatment (days) - days where non-flare-up medications were not taken/interrupted + 1).

5.8.3 Laboratory Data

Amylase, lipase, AST, ALT and fasting triglyceride levels from the EOS of parent studies and centrally measured (or locally measured of the inclusion visit is >1 month than the end of the parent study visit) will be used at the Inclusion Visit for screening purposes only. [Note: Amylase, lipase, AST, ALT and fasting triglyceride levels at the EOS of parent studies will be transferred from the parent study database.]

All laboratory data will be presented in the units of International System of Units (SI), summarised descriptively for the inclusion visit and listed.

5.8.4 C-SSRS

A summary of the number and percentage of participants with any type of suicidal ideation or behaviour (yes/no) will be presented at each visit. The number of questionnaires completed and the CSSRS suicidal ideation score will be also presented at each visit. Suicidal ideation includes the categories:

- Wish to be dead
- Non-specific active suicidal thoughts
- Active suicidal ideation with any methods (not plan) without intent to act
- Active suicidal ideation with some intent to act, without specific plan
- Active suicidal ideation with specific plan and intent

Whereas suicidal behaviour includes:

- Preparatory acts or behaviour
- Aborted attempt
- Interrupted attempt
- Non-fatal suicide attempt
- Completed suicide

In addition, a shift table from the inclusion visit to each post-inclusion visit of no suicidal ideation or behaviour, any suicidal ideation and any suicidal behaviour will be presented. Participants with both suicidal ideation and suicidal behaviour are included in the suicidal behaviour category.

Similarly, a shift table of maximum suicidal ideation assessments from the inclusion visit to each post-inclusion visit will be presented. Maximum refers to the maximum C-SSRS suicidal ideation score during treatment (0 = least severe, 5 = most severe) where 0=No Suicidal Ideation, 1=Wish to be Dead, 2=Non-specific Active Suicidal Thoughts, 3=Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act, 4=Active Suicidal Ideation with Some Intent to Act, without Specific Plan, and 5=Active Suicidal Ideation with Specific Plan and Intent.

All participants who report any type of suicidal ideations in the C-SSRS or any suicidal behaviour during the study will be presented in listings.

5.8.5 Linear Height and Body Weight

Actual values and mean changes from baseline in height/linear height (cm) and body weight (kg) will be presented descriptively at each visit for the FAS/SAS. For participants under the age of 18 years, the mean of triplicate height measurements will be used.

In addition, for participants aged <18 years at study inclusion, height velocity [cm/year] and linear height z-score actual values and changes from inclusion visit will be summarised descriptively at each visit for the FAS/SAS.

The calculation of height velocity will be performed as follows: ((Current Height – Previous Height)/(duration (days)=(current date – previous date))) * 365.25 = Annualized height velocity (cm/year). In addition to providing the calculated height velocities per time period for each participant at each visit, the data will also be categorized according to the following three categories: <4 cm/year; 4 to 5 cm/year; and >5 cm/year.

The linear height z-scores will be calculated using the reference population from the Centers for Disease Control and Prevention (CDC). See Appendix 7.2 for further details.

A listing of all linear height and body weight parameters will be presented.

5.8.6 Vital Signs

Vital signs include systolic blood pressure [mmHg], diastolic blood pressure [mmHg], heart rate [beats/min] and respiratory rate [breathes/min].

A summary of all vital sign variables (vital sign raw values and changes from inclusion visit) will be calculated for each visit for the FAS/SAS with descriptive statistics.

Potentially clinically significant (PCS) values are predefined criteria/thresholds presented in Appendix A2.

New-onset PCS values are defined as values that were not PCS at baseline and were PCS post-baseline. New-onset PCS values post-baseline will be summarised with counts and percentages. In addition a shift table from inclusion visit to each post-inclusion visit will be presented by abnormality (low, normal, high) as defined by the below criteria:

In addition a shift table from inclusion visit to each post-inclusion visit will be presented by abnormality (low, normal, high) as defined by the below criteria:

	Low	Normal	High
Systolic blood pressure	<86 mmHg	86 – 180 mmHg	>180 mmHg

	Low	Normal	High
Diastolic blood pressure	<48 mmHg	48 – 110 mmHg	>110 mmHg
Heart rate	<45 bpm	45 – 125 bpm	>125 bpm
mmHg = millimeters of mercury, bpm = beats per minute.			

A listing of all vital sign data and PCS values will be presented.

5.8.7 Physical Examination

A summary of physical examination results (Normal, Abnormal non-clinically significant and abnormal clinically significant) will be provided by body system at the inclusion visit for the FAS/SAS with descriptive statistics.

A listing of physical examination data will be provided.

5.8.8 Spinal Health Assessment

A listing of Spinal health assessment data will be provided using the FAS/Safety Set.

6 DATA HANDLING

6.1 Visit window

The below time windows for visit/timepoints will be used for analyses:

Analysis Visit	Scheduled Day	Visit Window
Baseline	Up to Day 1	≤ Day 1 Last non-missing measurement taken prior to first Investigational Medicinal Product (IMP) administration in study CLIN-60120-452
Month 6	182	Day 2-274
Month 12	365	Day 275-456
Month 18	547	Day 457-639
Month 24	730	Day 640-821
Month 30	912	Day 822-1003
Month 36	1095	≥Day 1004

For post-baseline visit windows, the following applies when there are multiple assessments in a particular visit window, the closest to the scheduled day is chosen (if two assessments have the same distance, then the later one will be chosen).

6.2 Unscheduled Visits, Retest, Withdrawal Visit

All listings will include retests and unscheduled visits, while for the description by visit in the tables, only the scheduled visits according to the protocol will be described.

Unscheduled visit and retest measurements will be used to provide a measurement for a baseline data or endpoint value (e.g. worst value), if appropriate according to their definition. These measurements will also be used to determine PCS vital signs values.

If a value requires a retest (for vital signs) or there is an unscheduled visit the closest non-missing reliable value to the scheduled visit will be used in the summary tables.

7 DERIVED DATA

7.1 PROMIS T-Score Conversions

The following conversion tables allow a user to convert Global Physical Health, Global Mental Health, and Total scores into T-scores. T-score distributions are standardized such that a 50 represents the average (mean) for the US general population, and the standard deviation around

that mean is 10 points. A high score always represents more of the concept being measured. Thus, a participant who has a T-score of 60 is one standard deviation better (healthier) than the general population.

Global Physical Health			Global Mental Health		
Raw Score	**T-Score**	**Standard Error**	**Raw Score**	**T-Score**	**Standard Error**
4	16.2	4.8	4	21.2	4.6
5	19.9	4.7	5	25.1	4.1
6	23.5	4.5	6	28.4	3.9
7	26.7	4.3	7	31.3	3.7
8	29.6	4.2	8	33.8	3.7
9	32.4	4.2	9	36.3	3.7
10	34.9	4.1	10	38.8	3.6
11	37.4	4.1	11	41.1	3.6
12	39.8	4.1	12	43.5	3.6
13	42.3	4.2	13	45.8	3.6
14	44.9	4.3	14	48.3	3.7
15	47.7	4.4	15	50.8	3.7
16	50.8	4.6	16	53.3	3.7
17	54.1	4.7	17	56	3.8
18	57.7	4.9	18	59	3.9
19	61.9	5.2	19	62.5	4.2
20	67.7	5.9	20	67.6	5.3

PROMIS=Patient Reported Outcomes Measurement Information System.

7.2 Linear Height Z-scores

The linear height z-scores will be calculated using the reference population from the Centers for Disease Control and Prevention (CDC):

https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm.

The Z-scores will be derived by following the below steps:

(1) Download the reference file and SAS code from the above link

(2) Create a temporary dataset that contains the height (cm), sex (1 for males and 2 for females) and age (months) of each participant.

(3) The SAS code should be executed to generate the Z-score based upon the reference population.

8 REFERENCES

1. https://www.healthmeasures.net/explore-measurement-systems/promis/obtain-administer-measures

2. Graham BL, Brusasco V, Burgos F et al. 2017 ERS/ATS standards for single-breath carbonmonoxide uptake in the lung. Eur Respir J 2017;49(1):1600016.

9 APPENDICES

A1. SAS code

No predefined SAS code is required.

A2. List of PCSA criteria

PCSA for Vital Signs parameters:

	PCS Low	PCS High
Systolic blood pressure	<86 mmHg or a decrease of ≥25 mmHg from baseline	>180 mmHg or an increase of ≥25 mmHg from baseline
Diastolic blood pressure	<48 mmHg or a decrease of ≥20 mmHg from baseline	>110 mmHg or an increase of ≥20 mmHg from baseline
Heart rate	<45 bpm or a decrease of ≥20 bpm from baseline	(1) >105 bpm AND an increase of ≥20 bpm from baseline (2) >125 bpm
mmHg = millimeters of mercury, bpm = beats per minute.		

A3.Partial/Missing Date Convention

In all listings, missing or incomplete dates should be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used:

- The most conservative approach will be systematically considered (i.e. if the onset date of an AE/concomitant medication is missing / partial, it is assumed to have occurred during the study treatment phase (i.e. a TEAE for AEs) except if the partial onset date or the stop date indicates differently.
- Where this is possible, the derivations based on a partial date will be presented as superior inequalities (i.e.: for an AE started in FEB2004 after the first IMP administration performed on 31JAN2004, the days since last dose will be "≥2", similarly the duration of ongoing AEs or medication will be "≥xx" according to the start and last visit dates).

Algorithm for Prior/ Concomitant

In case of partial start and/or stop medication/ non-drug therapies/surgical procedures dates, imputation will be done to determine the classification:

- If a partial start date, the first day of the month will be imputed for missing day and January for missing month,
- If a partial stop date, the last day of the month will be imputed for missing days and December will be imputed for missing month.

In case incomplete start or stop date does not allow the classification, it will be classified as concomitant.

Algorithm for TEAE

The date imputation algorithm for incomplete adverse event start dates is described in the table below. Classification of adverse event according to its treatment-emergent status is then done using the imputed date.

In the following table, all dates are presented using an YYYY-MM-DD format. As an example, suppose First IMP administration = 2002-08-11 and several AEs have incomplete start dates.

Description of incomplete date	Imputed numeric date	Example	
		Character date	Imputed date
Day is missing			
YYYY-MM < YYYY-MM of [First IMP admin.]	YYYY-MM-01	2002-07-XX	2002-07-01
YYYY-MM = YYYY-MM of [First IMP admin.]	Min ([First IMP admin.], AE end date)	2002-08-XX	Min (2002-08-11, AE end date)
YYYY-MM > YYYY-MM of [First IMP admin.]	YYYY-MM-01	2002-09-XX	2002-09-01
Day and month are missing			
YYYY < YYYY OF [First IMP admin.]	YYYY-01-01	2001-XX-XX	2001-01-01
YYYY = YYYY OF [First IMP admin.]	Min ([First IMP admin.], AE end date)	2002-XX-XX	Min (2002-08-11, AE end date)

YYYY > YYYY OF [First IMP admin.]	YYYY-01-01	2003-XX-XX	2003-01-01
Day, month, and year are missing			
XXXX-XX-XX	Min ([First IMP admin.], AE end date)		Min (2002-08-11, AE end date)

YYYY = non-missing year, MM = non-missing month, DD = non-missing day, XX = missing field.

A4. Programming Convention for Outputs

All text fields must be left justified and numeric or numeric with some text specification (e.g.: not done, unknown, <4.5, …) must be decimal justified.

The mean, median, lower quartile, upper quartile, SD and standard errors (SE) of the mean/median 95% confidence interval values will be reported to one decimal place greater than the raw data recorded in the database.

The minimum and maximum values will be reported with the same number of decimal places as the raw data recorded in the database.

In general, the maximum number of decimal places reported should be four for any summary statistic.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentage will be calculated using n as denominator. The denominator n will be specified in a footnote for clarification if necessary. If sample sizes are small, the data displays will show the percentages, but in the CSR only frequency counts should be described.

All values below or above a limit of detection (e.g. <0.1 or >100) will be listed as such.

Dates will be presented in the format [ddmmmyyyy] and times in the format [hh:mm].

A5. Listings conventions

All listings will contain at least the following data: participant identifier, age and gender. When dates are presented, the associated study days should be included. All listing will be sorted by treatment regimen and participant identifier.

A6.EudraCT categories for age

For EudraCT results summaries, in addition to quantitative descriptive statistics of age, demographic tables should include presentation of age using the following EudraCT categories (as applicable):

In utero
Preterm newborn - gestational age < 37 weeks
Newborns (0-27 days)
Infants and toddlers (28 days-23 months)
Children (2-11 years)
Adolescents (12-17 years)
Adults:18-64 years
65 - 84 years
85 years and over