PASS Annual Progress Report 1	
Active substance	Selumetinib
Product reference	D1346R00004
Version number	1.0
Date	24 August 2023

Post-Authorisation Safety Study of Paediatric Patients Initiating Selumetinib: A Multiple-Country Prospective Cohort Study – Annual Progress Report 1

Marketing Authorisation Holder(s)

Marketing authorisation holder(s)	AstraZeneca AB, 151 85 Södertälje, Sweden
MAH contact person	PPD

KOSELUGO ™ is a trademark of the AstraZeneca group of companies.

This document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Approved by:

PPD

Date

PPD

Date

PASS INFORMATION

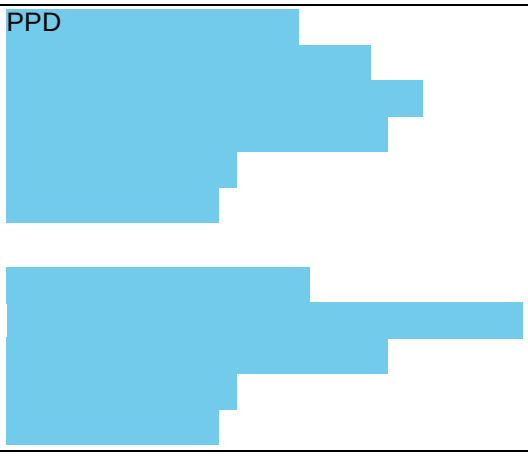
Title	Post-Authorisation Safety Study of Paediatric Patients Initiating Selumetinib: A Multiple-Country Prospective Cohort Study
Version identifier of the Annual Progress Report	1.0
Date of last version of the Annual Progress Report	NA
EU PAS register number	EUPAS45972
Active substance	Selumetinib
Medicinal product	Selumetinib (KOSELUGO®)
Product reference	EMEA/H/C/005244
Procedure number	EMEA/H/C/PSP/S/0095
Marketing authorisation holder(s)	AstraZeneca AB, 151 85 Södertälje, Sweden
Joint PASS	No
Research question and objectives	The primary objective of this study is: • To characterise the safety of selumetinib, including long-term safety, in paediatric patients with NF1-related symptomatic, inoperable PN, 8 to < 18 years old who have not reached Tanner Stage V at the start of selumetinib treatment. The secondary objective of this study is: • To describe the paediatric population 3 to < 18 years old with NF1-related symptomatic inoperable PN who start selumetinib in routine clinical practice.
Country (-ies) of study	Up to 12 European countries
Author	

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. ABSTRACT

Title

Title: Post-Authorisation Safety Study of Paediatric Patients Initiating Selumetinib: A Multiple-Country Prospective Cohort Study

Main Author: PPD

Date: 24 August 2023

Keywords

Selumetinib, Neurofibromatosis Type 1, Plexiform Neurofibromas, Paediatric, Post-authorisation Safety

Rationale and Background

Neurofibromatosis type 1 is a rare, autosomal dominant genetic disorder that is caused by germline mutations in the NF1 tumour suppressor gene, which encodes the tumour suppressor protein neurofibromin 1. Plexiform neurofibromas are histologically benign nerve sheath tumours, which typically grow along large nerves and plexi. Selumetinib monotherapy has been found to be well tolerated with a manageable safety profile in paediatric patients with NF1 PNs.

European Medicines Agency approval of selumetinib was based on the outcome of the pivotal Phase 2 Study D1532C00057. As part of the approval process, a RMP was developed and submitted to the EMA to summarise the safety concerns emerging from the clinical development program. The RMP included an additional pharmacovigilance plan for a non-interventional PASS to further characterise the safety of selumetinib in paediatric patients with NF1-related PN receiving treatment in routine clinical practice. This study will address gaps in knowledge identified by the EU RMP, including additional information on the important identified risk (LVEF reduction) and some of the important potential risks and missing information on long-term developmental toxicity in children.

Research Question and Objectives

The primary objective of this study is to characterise the occurrence of the safety outcomes of interest in the Nested Prospective Cohort. The secondary objective of this study is to describe the demographics and clinical characteristics of patients in the Base Cohort.

Study Design

Two cohorts will be enrolled: the Base Cohort will include all patients aged 3 to < 18 years and the Nested Prospective Cohort will include a subset of the base cohort of patients aged 8 to < 18 years who have not reached Tanner Stage V at the start of selumetinib treatment.

Setting

This study will be conducted in up to 36 specialist clinics for the treatment of paediatric patients with NF1 across up to 12 European countries.

Subjects and Study Size, Including Dropouts

The target population for this PASS is patients with NF1-associated symptomatic, inoperable PN in the EU and the UK, who have been prescribed at least one dose of selumetinib, and who are aged 3 to < 18 years at the start of selumetinib treatment. Patients who received treatment with other MEK inhibitors, and those currently participating in a randomised trial are not eligible for the study. The target enrolment for the Base Cohort is 125 patients. Of these, approximately 100 patients are expected to meet eligibility criteria for the Nested Prospective Cohort.

Variables and Data Sources

Baseline data for the Base Cohort will be retrospectively collected from medical records for one year prior to the index date (ie, date of first prescription of selumetinib). Follow-up will be up to 5 years from enrolment date of the first patient. Patients in the Nested Prospective Cohort who discontinue selumetinib will remain in the study for follow-up safety assessments. This PASS is ongoing and currently enrolling. The enrolment period will last 2 years from date of first patient enrolled (23 May 2022).

Results

Due to the current sample size, a full evaluation of the safety data against the primary objectives of this study is not yet possible. However, the following key safety results are presented:

- As of the DCO, 33 patients in the Base Cohort across 4 European countries were enrolled in the study. Patient age ranged from 3 to 18 years and approximately two thirds of patients were male.
- Ten of the 16 patients enrolled in the Nested Prospective Cohort reported at least one AE reported as possibly related to selumetinib. The majority of these AEs were gastrointestinal or skin disorders, which are known to be very common ADRs associated with selumetinib, as per the product label.
- No patients in the Nested Prospective Cohort reported an AE of CTCAE Grade 3 or higher or a SAE.

Discussion

This is the first PASS Annual Progress Report for selumetinib with a DCO of 21 July 2023. As of the DCO, recruitment was ongoing (33 patients out of a planned total of 125 patients in the Base Cohort were enrolled). Small patient numbers by country make generalisability of results to NF1 PN patients in the regions that have currently recruited patients difficult. The

Sponsor will continue to monitor the safety of patients in the study and will continue to submit Annual Progress and Interim Reports as per the planned milestones.

Marketing Authorisation Holder(s)

AstraZeneca AB, 151 85 Södertälje, Sweden

Names and Affiliations of Principal Investigators

There were 20 active sites with 20 Principal Investigators across 6 countries.

2. LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AZ	AstraZeneca
bd	twice daily
CPK	Creatine phosphokinase
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut-off
DES	Data entry site
EAP	Early Access Program
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EMEA	Europe, Middle East, and Africa
EU	European Union
ICF	Informed consent form
LVEF	Left ventricular ejection fraction
MEK	Mitogen-activated protein kinase inhibitor
NF1	Neurofibromatosis type 1
PASS	Post-authorisation Safety Study
PN	Plexiform neurofibroma
PRAC	Pharmacovigilance Risk Assessment Committee
Q	Quarter
RMP	Risk Management Plan
SAE	Serious adverse event
SAP	Statistical analysis plan
SOP	Standard operating procedure

Abbreviation or special term	Explanation
UK	United Kingdom

3. INVESTIGATORS

There were 20 active sites with 20 Principal Investigators across 6 countries. For full details (including names, degrees, and contact information), see Appendix B.

4. OTHER RESPONSIBLE PARTIES

AstraZeneca
PPD PPD

5. MILESTONES

See Table 1 for study milestones.

Table 1 Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	Q2 2022	23 May 2022	NA
End of data collection	Q2 2027	Not reached	NA
Registration in the EU PAS register	Before the start of data collection	03 March 2022	NA
Annual Progress Report 1	Q3 2023	24 August 2023 (date of this report)	NA
Annual Progress Report 2	Q3 2024	Not reached	NA
Annual Progress Report 3	Q3 2025	Not reached	NA
Annual Progress Report 4	Q3 2026	Not reached	NA
Interim Report 1	Q3 2024	Not reached	NA
Final Report of study results	31 March 2028	Not reached	NA

Abbreviations: EU PAS Register = European Union electronic Register of Post-Authorisation Studies; NA = Not applicable; Q = Quarter.

6. RATIONALE AND BACKGROUND

6.1 Background

Neurofibromatosis type 1 is a rare, autosomal dominant genetic disorder that is caused by germline mutations in the NF1 tumour suppressor gene, which encodes the tumour suppressor protein neurofibromin 1. Plexiform neurofibromas are histologically benign nerve sheath tumours, which typically grow along large nerves and plexi.

In the pivotal Phase 2 study (NCT01362803; SPRINT) that led to marketing authorisation in the United States, selumetinib was well tolerated in paediatric patients with NF1 and inoperable PN. The median total number of treatment cycles was 36, approximately 3 years at twice-daily doses of 25 mg/m^2 at the DCO of 2019. Approximately 2 years of additional safety and efficacy data published in 2023 showed that the most patients (n = 49 from 50) had ≥ one AE at least possibly related to treatment (97% Grade ≤ 2). The most common AEs were gastrointestinal symptoms, asymptomatic CPK increase, paronychia, and acneiform rash. Sixteen patients had ≥ one dose reduction; 5 of these had 2 dose reductions for toxicity. Three Grade 4 AEs possibly related to study drug were reported (CPK increase, hyperuricemia, and skin ulceration). Five patients were removed from treatment for an AE considered possibly related to selumetinib (Grade 4 skin ulceration, Grade 3 weight gain, Grade 3 paronychia, Grade 3 acute kidney injury, and Grade 3 diarrhoea).

No new or concerning safety signals were identified during the additional years of observation. As a class, MEK inhibitors are known to have rare but potentially serious ocular and cardiac side effects. Long-term safety follow-up analysis of both Phase 1 and Phase 2 Stratum 1 studies have shown that out of a total of 74 paediatric patients only one participant developed shallow asymptomatic bilateral central serous retinopathy (Grade 1). Several patients developed known AEs such as asymptomatic decreased LVEF in both Phase 1 and Phase 2 Stratum 1 studies (15 patients [14 patients with Grade 2 events and one patient with a Grade 3 event]). These findings highlight that though generally tolerated, treatment with selumetinib is not without potential toxicities, and that long-term monitoring for AEs, such as cardiac and ophthalmologic toxicities, is indicated. In summary, selumetinib monotherapy was well tolerated and had a manageable safety profile in these paediatric patients however long-term safety monitoring is ongoing (Gross et al 2020; Gross et al 2023).

6.2 Rationale

On 05 March 2020, a centralised Marketing Authorisation Application was submitted to the EMA, with approval received on 17 June 2021.

As part of the approval process, a RMP was developed and submitted to the EMA to summarise the safety concerns emerging from the clinical development program. The RMP

included plans for a non-interventional PASS to further characterise the safety of selumetinib in paediatric patients with NF1-related PN receiving treatment in routine clinical practice.

The RMP version 1.0 (succession 4) approved by EMA on 22 April 2021 had one important identified risk with selumetinib treatment:

- LVEF reduction

The RMP also identified 5 important potential risks with selumetinib treatment:

- Physeal dysplasia
- Ocular toxicity
- Myopathy
- Hepatotoxicity
- Choking on the capsule

Long-term exposure (including long-term safety data on developmental toxicity in children) was identified in the RMP as an area of missing information.

This study will address gaps in knowledge identified by the RMP, including the important identified risk and some of the potential risks and missing information on long-term developmental toxicity in children, by characterising the safety profile associated with selumetinib use among paediatric patients (ages 8 to < 18 years old) with a diagnosis of NF1 with symptomatic, inoperable PN. Conduct of this study is a specific obligation in the context of a conditional marketing authorisation for selumetinib (ie, Category 2 PASS). Study results will contribute to updating the safety profile of selumetinib in a relatively large population of patients with different personal characteristics across multiple health care systems and patterns of real-world clinical practice in the EU and in the UK.

7. RESEARCH QUESTION AND OBJECTIVES

The primary objective of this study is:

- To characterise the safety of selumetinib, including up to 5 years of long-term safety, in paediatric patients with NF1-related symptomatic, inoperable PN, 8 to < 18 years old who have not reached Tanner Stage V at the start of selumetinib treatment (Nested Prospective Cohort).

The secondary objective of this study is:

- To describe the demographic and clinical profile of the paediatric population 3 to < 18 years old with NF1-related symptomatic inoperable PN who start selumetinib in routine clinical practice (Base Cohort).

8. AMENDMENTS AND UPDATES

Amendment History

Table 2 shows the document history for the Selumetinib PASS Protocol. There were no substantial protocol amendments submitted to regulatory authorities before the start of data collection. For key amendments, updates, and clarifications made after the issue of Selumetinib PASS Protocol (version 2.0), see Table 3. For full details of amendment history, refer to Section 5 of the Selumetinib PASS Protocol (version 2.0).

Table 2 Selumetinib PASS Protocol Document History

Document	Date of issue
Selumetinib PASS Protocol (version 1.0)	05 August 2021
Selumetinib PASS Protocol (version 2.0)	05 November 2021
Selumetinib PASS Protocol (version 3.0) [a]	Submitted to the EMA PRAC August 2023

[a] Selumetinib PASS Protocol (version 3.0) was drafted to document the changes reflected in the Administrative Letters or the Administrative Change Letters which were distributed after Selumetinib PASS Protocol (version 2.0) was issued. The changes specified in these letters were implemented in the study as of their respective dates.

Abbreviations: EMA = European Medicines Agency; PASS = Post-authorisation Safety Study; PRAC = Pharmacovigilance Risk Assessment Committee.

Table 3 Key Amendments, Updates, and Clarifications After Issue of Selumetinib PASS Protocol (Version 2.0)

Number	Date	Section of study protocol	Amendment/update/clarification	Reason
Administrative Change Letter 2	11 March 2022	4.4, 9.1	Age range corrected to 3 to < 18 years.	Correction of typographical error.
		11	No AEs will be collected for patients in the Base Cohort 1 from Day -365 to Day -1 via medical chart review or summarised in any Interim Report(s) or in the Final Study Report.	Patients will not have been receiving selumetinib from Day -365 to Day -1.
Administrative Letter 1	10 May 2022	9.2.1.1	Updated inclusion criterion 2 to allow patients who have initiated with selumetinib up to 6 months (ie, 182 days) prior to enrolment into the study.	To define time window for 'newly prescribed'.

Number	Date	Section of study protocol	Amendment/update/clarification	Reason
Administrative Change Letter 2	11 March 2022	4.4, 9.1	Age range corrected to 3 to < 18 years.	Correction of typographical error.
		11	No AEs will be collected for patients in the Base Cohort 1 from Day -365 to Day -1 via medical chart review or summarised in any Interim Report(s) or in the Final Study Report.	Patients will not have been receiving selumetinib from Day -365 to Day -1.
Administrative Letter 2	21 September 2022	11	In relation to Administrative Letter 1 (10 May 2022) it was clarified that, for the Nested Prospective Cohort, safety data will be collected in the eCRF from the Index Date (first prescription of selumetinib) as per Section 11.4.2. of the Selumetinib PASS Protocol (version 2.0): "Adverse Events will be collected from the time of starting the medicinal product under study (patient index date [Day 1]) throughout the treatment period and during the study 5-year follow-up period." Reporting to the AZ Patient Safety data entry site will only start from the time patients enrol in the PASS ie, signature of ICF; AEs having a start date between the Index Date and the date of enrolment in the study will be reported via the Local AZ office according to local requirements.	To better clarify the requirements and processes for the management of AEs/ADRs.
Administrative Change Letter 5	16 August 2023	9.9	Text updated to clarify that the assessment of Tanner score is mandatory for the enrolment of patients into the Nested Prospective Cohort.	To ensure that patients are consistently assigned to the correct study cohort.

Abbreviations: ADR = adverse drug reactions; AE = adverse event; AZ = AstraZenca; eCRF = electronic case report form; ICF = informed consent form; PASS = Post-authorisation Safety Study.

Base Cohort Only (Data Collected in Error)

Per protocol, Investigators are not required to report AEs in the eCRF for patients assigned to the Base Cohort only as the AEs for this study population are to be reported as per local AE reporting requirements and procedures. All AEs are collected in the eCRF for patients in the Nested Prospective Cohort. Nevertheless, some sites incorrectly recorded AE information for patients assigned to the Base Cohort only. Data collected from patients in the Base Cohort only are presented separate to the Nested Prospective Cohort data in Section 10.7.

9. RESEARCH METHODS

9.1 Study Design

This is a cohort study of paediatric patients (aged 3 to < 18 years of age) with NF1 with symptomatic, inoperable PNs who begin selumetinib treatment at study sites across several European countries where selumetinib has been marketed for use.

Selumetinib treatment will remain a decision of the treating clinicians and is not mandated by this study protocol. All patients prescribed selumetinib at the study sites in the usual manner and according to the terms of the marketing authorisation will be invited to participate in the study. Patients who meet the eligibility criteria, including parental/legal guardian consent to participation, will be enrolled.

The patient enrolment period will begin once the first patient is enrolled and end 2 years after that date (estimated end of enrolment = Q2 2024). Patients may continue in the study until the study end date which is 5 years after the first patient enrolment date (estimated end of study = Q2 2027). Patient enrolment and follow-up periods have been updated in Selumetinib PASS Protocol (version 3.0) which was submitted to the EMA PRAC in August 2023. Each enrolled patient will be assigned an index date (Day 1) defined as the date of first prescription of selumetinib. Baseline data will be collected at enrolment through retrospective chart abstraction from Day -365 to Day -1.

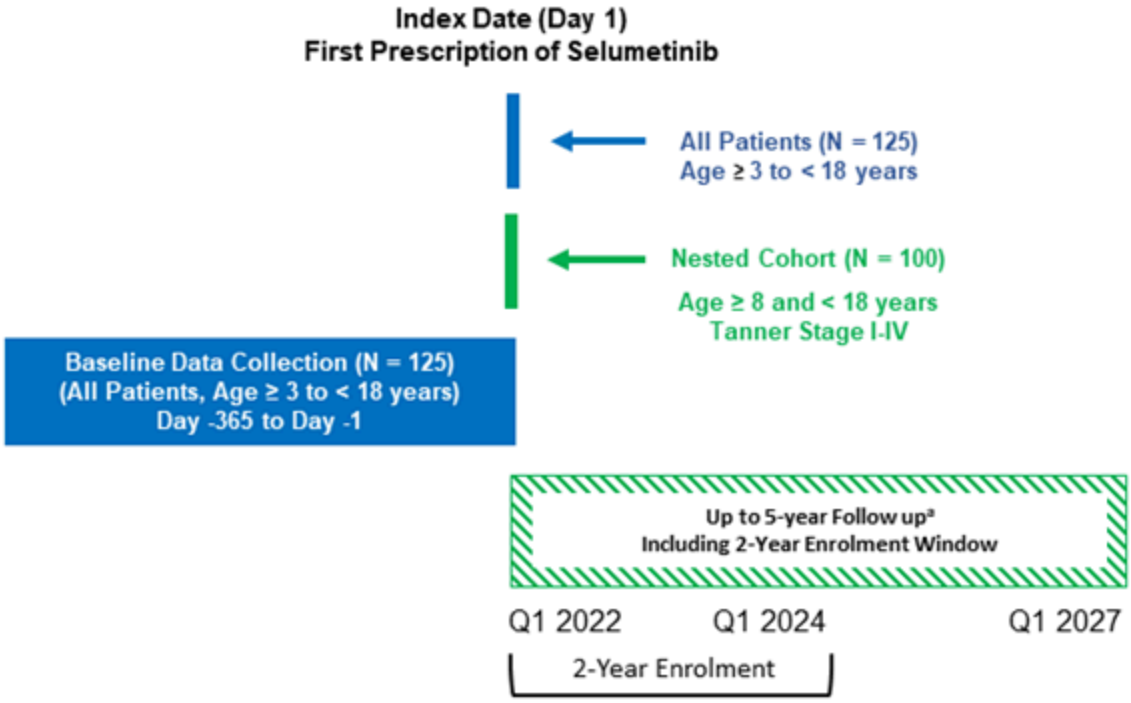
An eligible subset of patients (aged 8 to < 18 years who have not reached Tanner Stage V on the index date) will be enrolled in the Nested Prospective Cohort. Data will be collected following the first dose of selumetinib (Day 1) for the duration of the study and will focus on assessing the safety outcomes of interest.

Patients in the Nested Prospective Cohort will be followed from the index date to the censor date, defined as the earliest of the end of the 5-year study period, study withdrawal, loss to follow-up, or death. The 5-year study period is defined as a maximum of 5 years from the time the first patient is enrolled (estimated time period = Q2 2022 to Q2 2027). A proposal to extend the study/follow-up period is included in Selumetinib PASS Protocol (version 3.0) which was submitted to the EMA PRAC in August 2023.

Whether to treat the patient with selumetinib will be based on the decision of the prescribing physician under conditions of routine clinical care. Participating study sites will treat patients according to normal clinical practice and no intervention will be assigned.

The study schematic is shown below in Figure 1.

Figure 1 Study Schema



[a] Patients in the Nested Prospective Cohort will be followed from index date to the censor date, defined as the earliest of the end of the 5-year study period, study withdrawal, loss to follow-up, or death.

Abbreviations: Q = Quarter.

9.2 Setting

This study will be conducted in up to 36 specialist clinics for the treatment of paediatric patients with NF1 across up to 12 European countries.

The study observation period was anticipated to begin in Q2 2022, with some variation by country. Patients will be enrolled after commercial launch of selumetinib in each participating country, when patients/physicians have access to medicine as part of standard clinical practice.

The target population for this study is patients with NF1 in the EU with symptomatic, inoperable PN who have been prescribed at least one dose of selumetinib and who are aged 3 to < 18 years at the start of selumetinib treatment, except for those patients receiving treatment with a MEK before the index date.

The study will enrol 2 cohorts:

1 The Base Cohort includes all enrolled patients aged 3 to < 18 years.
2 The Nested Prospective Cohort includes the subset of Base Cohort patients aged 8 to < 18 years who have not reached Tanner Stage V on the index date.

Patient screening will be conducted throughout the enrolment period and baseline data for all patients will be abstracted from medical records. Those meeting the criteria for enrolment in the Nested Prospective Cohort will be followed up during their routine encounters with the treating clinician (expected to occur every 6 to 12 months) for up to 5 years.

A site may have multiple eligible patients and there will be a limit on the number of patients per site to ensure appropriate representation of patients, given that treatments administered may vary across sites and countries. For additional detail, refer to Section 9.2 of the Selumetinib PASS Protocol (version 2.0).

The study protocol will be adopted at each study site. A SAP will be prepared by the study Contract Research Organisation for AZ approval before performing the analysis.

9.3 Subjects

9.3.1 Eligibility Criteria

All patients meeting study inclusion and not meeting exclusion criteria will be eligible for the study.

9.3.1.1 Inclusion Criteria

Patients are eligible to be included in the study only if all the following criteria apply:

1 Have been diagnosed with NF1 with symptomatic, inoperable PN
2 Have initiated treatment with selumetinib up to 6 months (ie, 182 days) prior to enrolment into the study (ie, signature of ICF) [1, 2]

[1] Provided that, for patients enrolled in the Nested Prospective Cohort, key retrospective data are available (eg, baseline characteristics, any safety outcome measures, and AEs).

[2] This inclusion criterion was updated per Administrative Letter 1 (10 May 2022). This change has also formally been documented in Selumetinib PASS Protocol (version 3.0) (submitted to the EMA PRAC in August 2023).

3 Are aged 3 years and above, and are < 18 years of age on the index date

4 Parent or legal guardian, as required by country-specific regulation, have provided informed consent (unless a country-specific waiver is obtained)

Additional Criteria for Nested Prospective Cohort

5 Are at least 8 years old and

6 Are prior to attainment of Tanner Stage V on the index date

9.3.1.2 Exclusion Criteria

Patients are excluded from the study if the following criteria apply:

1 Have received treatment with a MEK before the index date

2 Are participating in a randomised controlled trial

9.3.2 Safety Management

Collection of safety data for patients in the Base Cohort versus patients in the Nested Prospective Cohort was clarified in Administrative Change Letter 2 (11 March 2022). This change has also formally been documented in Selumetinib PASS Protocol (version 3.0) (submitted to the EMA PRAC in August 2023).

9.3.2.1 Base Cohort

For all patients enrolled in the study, no AEs will be collected in the eCRF or reported to the AZ DES during the baseline period as patients will not be receiving treatment with selumetinib at that time (ie, from Day -365 to Day -1).

If any AE occurs from the index date onwards in patients assigned to the Base Cohort only (ie, ~25 patients), such events should be reported to the local AZ office according to local requirements and the reporting of any follow-up of these events will follow the same procedure via the local AZ office.

9.3.2.2 Nested Prospective Cohort – Secondary Use of Data and Primary Data Collection

Secondary Use of Data: From the index date (ie, start of selumetinib treatment/Day 1) until date of enrolment in the study (ie, signature of ICF), all AEs and special situations will be collected in the eCRF, but not reported to the AZ DES. For non-interventional study designs based on secondary use of data, reporting to the AZ DES and submission of individual AEs/ADR case reports are not required. Such events should be reported to the local AZ office

according to local requirements and the reporting of any follow-up of these events will follow the same procedure via the local AZ office.

Primary Data Collection: From the enrolment date onwards, all AEs and special situations must be managed as described in Section 11 of the Selumetinib PASS Protocol (version 3.0) (submitted to the EMA PRAC in August 2023).

9.4 Variables

9.4.1 Baseline Data

The following baseline data will be collected via medical chart abstraction for all patients in the Base Cohort, where baseline will include the most recent assessments made within 365 days before the index date. For repeated measurements during the baseline period, the value closest in time to the index date will be taken:

- **Demographics**: Age, sex, race, and ethnicity (where allowed by General Data Protection Regulation/privacy laws)
- **Clinical characteristics**: PN(s) (number, location, classification, and morbidities), prior medication and relevant procedures, concomitant medications, comorbidities, date of initial NF1 and PN diagnosis, NF1 origin (familial or spontaneous), and any genetic testing results

9.4.2 Outcomes – Nested Prospective Cohort

To monitor long-term safety, all patients in the Nested Prospective Cohort will be followed for up to 5 years under conditions of routine clinical care to collect data on the occurrence of the safety outcomes of interest. These safety outcomes have been chosen to characterise the important identified risk (LVEF reduction), the important potential risks (physeal dysplasia, ocular toxicity, myopathy, and hepatotoxicity), and the missing information on long-term exposure described in the RMP; to describe any developmental toxicity during selumetinib use in children; and to further characterise the frequency and severity of safety outcomes of interest and AEs occurring during selumetinib treatment in real-world clinical practice.

Patients who may discontinue selumetinib treatment are to continue in the study for long-term safety follow-up assessment, unless consent is withdrawn. Refer to Section 9.3 of the Selumetinib PASS Protocol (version 2.0) for additional detail.

9.4.3 Exposure

Exposure to selumetinib will be collected from the index date to the date of the last dose of selumetinib using a standardised eCRF that captures, eg, date(s), selumetinib dose (daily and cumulative), treatment cycles, treatment modification(s) (including interruption, dose reduction, and discontinuation), and associated reasons.

9.4.4 Other Variables and Covariates

See Section 9.3.4 of the Selumetinib PASS Protocol (version 2.0) for demographic and clinical characteristics, and site characteristics data that will be collected throughout follow-up.

9.5 Data Sources and Measurement

Baseline data will be abstracted from medical charts (either electronic or paper) by trained site staff and entered into a standard eCRF. All follow-up data will be entered directly into eCRFs provided to participating study physicians at each encounter, with a specific focus on safety outcomes of interest.

Data collection and validation procedures will be provided in the study manuals.

9.6 Bias

9.6.1 Information Bias

The present study is being carried out using data recorded during routine clinical care. Some records are expected to be incomplete. In addition, the availability of the information in a patient's health record may depend on the study site and/or countries.

This potential source of bias should be relatively minor with respect to these safety outcomes in the paediatric patient population. Refer to Section 9.7.6.1 of the Selumetinib PASS Protocol (version 2.0) for additional detail.

9.6.2 Selection Bias

This study encompasses a self-selected population of paediatric patients with consenting parents/legal guardians and clinicians who have expressed their interest to participate. Participating investigators may be more likely to adopt new treatment options and may somehow differ from investigators who elect not to participate in the study. Similarly, the paediatric patients may have a profile not fully representative of the selumetinib-treated population. However, several measures are introduced in the study design and analysis that can mitigate the potential for selection bias. First, the large number of study sites across numerous European countries can be anticipated to provide data representative of the treatment of NF1 patients with PN across Europe.

In addition, the enrolment of consecutive patients initiating selumetinib treatment at study sites, with inclusion and exclusion criteria that are well described (see Section 9.3.1), will ensure that eligible patients at a given site have an equal chance of selection into the study.

9.7 Study Size

The target enrolment for the Base Cohort is 125 patients. Of these, approximately 100 patients are expected to meet eligibility criteria for the Nested Prospective Cohort.

The 36 sites from the 12 European countries that expressed interest in participating in the non-interventional PASS indicated they could enrol 180 patients into the Base Cohort and 144 patients into the Nested Prospective Cohort. Assuming approximately 80% of sites ultimately participate and 70% of eligible patient numbers will enrol yields approximately 125 patients for the Base Cohort and approximately 100 patients for the Nested Prospective Cohort.

A range of cumulative incidence values is expected based on evidence from Study D1532C00057 (SPRINT Phase 2) and, in cases where the event was not observed in SPRINT, from other studies of MEK given as monotherapy (eg, trametinib). With 100 patients expected in the Nested Prospective Cohort patients, there is a 90% probability of observing at least one event with an underlying real-world incidence of 2.28%. Refer to Section 9.7.8 of the Selumetinib PASS Protocol (version 2.0) for further details.

9.8 Data Transformation

Routine procedures performed at each site will be recorded in electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality control checks of all eCRFs. Each site will maintain any patient-identifying information securely on site according to internal SOPs or guidance documents. For additional detail on data transformation refer to Section 9.6 of the Selumetinib PASS Protocol (version 2.0).

9.9 Statistical Methods

The Annual Progress Reports (Q3 2023, Q3 2024, Q3 2025, Q3 2026) were planned to include relevant information to document the progress of the study such as patient disposition and safety data.

The below were produced for this Annual Progress Report:

Patient Disposition (Listing and Summary by Country, Site, and Overall) and Analysis Sets

The number and percentage of patients satisfying each of the following were summarised for all enrolled patients:

- Enrolled
- Previously treated under the EAP (Yes/No)
- Discontinued treatment and associated reasons

- Ongoing in the study at the data cut off
- Completed the study
- Discontinued from the study and associated reasons

The number of patients in each of the analysis sets (ie, the Base and Nested Prospective Cohorts) were summarised for all enrolled patients.

Demography

Summaries and listings of demographic characteristics (see Section 5.2.2 of the SAP [version 1.0]).

Exposure

Exposure data (see Section 5.2.5.7 of the SAP [version 1.0]) was summarised.

Adverse Events

An overview table of the number and percentage of patients with at least one AE as well as the absolute counts of number of AEs were summarised.

An AE and SAE listing were also presented. Refer to Section 7.1 of the SAP (version 1.0) for detail of the categories presented.

9.9.1 Amendments to the Statistical Analysis Plan

There have been no documented updates to the final SAP (version 1.0) (dated 30 August 2022).

9.10 Quality Control

The study is being conducted in accordance with the relevant SOPs of the Sponsor or designee as appropriate and/or agreed.

These procedures include internal quality audits, rules for secure and confidential data storage, and methods to maintain and archive project documents. For full details of the study's quality control mechanisms see Section 9.8 of the Selumetinib PASS Protocol (version 2.0).

10. RESULTS

10.1 Participants

The disposition of the patients in the Base Cohort is summarised in Table 4.

As of the DCO, 33 patients across 4 European countries (Austria, France, Germany, and Portugal) were enrolled in the study, of which 16 were assigned to the Nested Prospective Cohort. Of note, one patient (Patient E2310001) in France was erroneously not assigned to the

Nested Prospective Cohort in the eCRF at the time of the DCO, bringing the total in the Nested Prospective Cohort to 17 patients. Therefore, to align with source data at the time of the DCO, Patient E2310001 was not included in the analysis for the Nested Prospective Cohort. Most patients (32 [97.0%] patients) enrolled met eligibility criteria for the study cohorts.

Of the 33 patients enrolled in the study, none were previously treated under the EAP. Of the 33 patients enrolled in the Base Cohort, 28 (84.8%) patients received treatment with selumetinib. Eight (24.2%) patients were reported as having discontinued from the study (see Listing 10.2.1, Appendix C). However, the disposition status for Patient E2308003, assigned to the Nested Prospective Cohort, was erroneously assigned as 'other' on the eCRF at the time of the DCO. Patient E2308003 was not discontinued in the study. Noting this data entry error, a total of 7 patients in the Base Cohort discontinued from the study; no patients in the Nested Prospective Cohort discontinued from the study. Four (12.1%) patients discontinued treatment.

Table 4 Patient Disposition (Base Cohort)

Overall	Number (%) of patients
Patients enrolled [a]	33
Patients previously treated under the EAP	0
Patients who received treatment	28 (84.8)
Patients who discontinued treatment	4 (12.1)
Adverse event	0
Patient decision	1 (3.0)
Patient forgot to take dose	0
Patient not able to swallow tablet	0
Response-related dose change	0
Other	0
Missing	3 (9.1)
Patients ongoing in the study at the data cut-off	25 (75.8)
Patients discontinued from study	8 (24.2)
Withdrawal by parent/guardian	0
Completed	6 (18.2)
Death	0
Lost to follow-up	0
Withdrawal by patient	0
Other	2 (6.1)
Patients included in Nested Prospective Cohort	16 (48.5)

Table 4 Patient Disposition (Base Cohort)

Overall	Number (%) of patients
Patients who met all eligibility criteria	32 (97.0)
Patients who did not meet all eligibility criteria	1 (3.0)
Exclusion criterion 1 [b]	1 (3.0)

[a] Informed consent/assent received.

[b] Exclusion criterion 1: Have received treatment with a MEK before the index date (Section 9.3.1.2).

The disposition status for Patient E2308003 was erroneously entered as 'other' in the eCRF at the time of the DCO; the patient was not discontinued from the study as of the DCO.

One patient in France (Patient E2310001) was erroneously not assigned to the Nested Prospective Cohort in the eCRF at the time of the DCO.

Abbreviations: DCO = data cut-off; EAP = Early Access Program; eCRF = electronic case report form; MEK = mitogen-activated kinase.

Source: Table 10.1.1.

The 33 patients in the Base Cohort were distributed across 11 sites in 4 European countries. Of these 33 patients, the 16 patients in the Nested Prospective Cohort were distributed across 6 sites in 3 European countries (Table 5).

Table 5 Patient Enrolment by Country and Site (Base Cohort and Nested Prospective Cohort)

		Number (%) of patients	
		Base Cohort	Nested Prospective Cohort
Country	Site	Overall (N = 33)	Overall (N = 16) [a]
France	**Total**	**16 (48.5)**	**11 (68.8)**
	02302	7 (21.2)	6 (37.5)
	02308	4 (12.1)	3 (18.8)
	02305	2 (6.1)	0
	02307	1 (3.0)	1 (6.3)
	02306	1 (3.0)	1 (6.3)
	02310	1 (3.0)	0
Portugal	**Total**	**9 (27.3)**	**4 (25.0)**
	05801	9 (27.3)	4 (25.0)
Germany	**Total**	**6 (18.2)**	**1 (6.3)**
	02601	4 (12.1)	0
	02603	1 (3.0)	0
	02604	1 (3.0)	1 (6.3)

Table 5 Patient Enrolment by Country and Site (Base Cohort and Nested Prospective Cohort)

Country	Site	Number (%) of patients	
		Base Cohort	Nested Prospective Cohort
		Overall (N = 33)	Overall (N = 16) [a]
Austria	**Total**	**2 (6.1)**	**0**
	00401	2 (6.1)	0

[a] One patient in France (Patient E2310001) was erroneously not assigned to the Nested Prospective Cohort in the eCRF at the time of the DCO.

Abbreviations: DCO = data cut-off; eCRF = electronic case report form; N = number of patients in cohort group.

Source: Table 10.1.2.1 and Table 10.1.2.2.

10.2 Descriptive Data

The demographics were representative of the intended patient population (Table 6). For demographic and anthropometric baseline characteristics of study patients, see Listing 10.2.2.1, Appendix C.

Age and sex were reported for all 33 patients in the Base Cohort. Patient age ranged from 3 to 18 years. Of note, at the time of the DCO the eCRF asked for age at time of enrolment (ie, date informed consent was signed) rather than age at time of selumetinib initiation. One patient who started selumetinib as a 17-year-old (as per eligibility criterion < 18 years) was enrolled in the study after turning 18 years of age. The eCRF was modified after DCO to collect age at time of selumetinib initiation. With respect to the distribution of recorded sex there were 21 males (~64%) and 12 females (~36%) at DCO (Base Cohort). Of these, 11 males (~69%) and 5 females (~31%) were assigned to the Nested Prospective Cohort. The distribution of sex in the older age group restricted to the Nested Prospective Cohort (ie, age 8 to < 18 years) showed that approximately two thirds of the population were male.

Table 6 Demographic Characteristics (Base Cohort and Nested Prospective Cohort)

Demographic characteristic		Base Cohort	Nested Prospective Cohort
		Overall (N = 33)	Overall (N = 16) [a]
Age (years) [b]	n	33	16
	Mean (SD)	12.3 (4.08)	11.9 (2.13)
	Median (min, max)	13.0 (3, 18)	12.0 (8, 15)
Age group (years) [b], n (%)	< 12	13 (39.4)	7 (43.8)

Table 6 Demographic Characteristics (Base Cohort and Nested Prospective Cohort)

Demographic characteristic		Base Cohort	Nested Prospective Cohort
		Overall (N = 33)	Overall (N = 16) [a]
	≥ 12	20 (60.6)	9 (56.3)
Sex, n (%)	Male	21 (63.6)	11 (68.8)
	Female	12 (36.4)	5 (31.3)
Race, n (%)	White	6 (18.2)	1 (6.3)
	Black or African American	2 (6.1)	1 (6.3)
	Asian	0	0
	Native Hawaiian or Other Pacific Islander	0	0
	American Indian or Alaskan Native	0	0
	Other	1 (3.0)	0
	Not Reported	23 (69.7)	13 (81.3)
	Multiple	0	0
	Missing	1 (3.0)	1 (6.3)
Ethnic group, n (%)	Hispanic or Latino	11 (33.3)	6 (37.5)
	Not Hispanic or Latino	9 (27.3)	2 (12.5)
	Missing	13 (39.4)	8 (50.0)
Country, n (%)	Austria	2 (6.1)	0
	France	16 (48.5)	11 (68.8)
	Germany	6 (18.2)	1 (6.3)
	Portugal	9 (27.3)	4 (25.0)

[a] See Section 10.1 for more detail on cohort assignment errors.

[b] Age at date of ICF as collected in the eCRF.

Abbreviations: eCRF = electronic case report form; ICF = informed consent form; max = maximum; min = minimum; N = number of patients in cohort group, n = number of patients included in analysis; SD = standard deviation.

Source: Table 10.2.1.1 and Table 10.2.1.2.

10.3 Exposure

As of the DCO date, data on exposure to selumetinib was recorded in the eCRF for 28 of the 33 patients enrolled (Base Cohort); queries to investigative sites regarding missing exposure data for 5 patients remained unresolved as of the DCO. Selumetinib start dates for these

28 patients ranged from 20 January 2020 to 05 April 2023 (see Listing 10.5.1, Appendix C). Note that the start date of 20 January 2020 was incorrectly recorded for a patient in the Nested Prospective Cohort. Taking into consideration a corrected start date for one patient (corrected after DCO), the start dates ranged from 02 June 2022 to 05 April 2023 for patients in the Nested Prospective Cohort (see Table 7 footnote [f] for further details).

For the Nested Prospective Cohort, see Table 7 for duration of exposure to selumetinib. Taking into consideration a corrected start for one subject after DCO, the corrected mean values for duration of total exposure and actual cumulative exposure to selumetinib were ~7.9 months (range: 0.3 to 13.6 months) and ~7.6 months (range: 0.3 to 12.8 months), respectively. Furthermore, the aforementioned correction of start date resulted in actual values for total cumulative dose (mg) as follows: mean (standard deviation) 14101.9 (9703.3), median (minimum, maximum) 13175.0 (450, 29890) (AstraZeneca data on file).

Table 7 Duration of Exposure to Selumetinib (Nested Prospective Cohort)

Characteristic	Statistic	Overall (N = 16) [a]
Duration of total exposure (months) [b]	n	16
	Mean (SD)	10.14 (9.55)
	Median (min, max)	9.32 (0.3, 42.0)
Duration of actual cumulative exposure (months) [c]	n	16
	Mean (SD)	9.87 (9.52)
	Median (min, max)	8.84 (0.3, 42.0)
Total cumulative dose (mg) [d]	n	16
	Mean (SD)	17526.9 (15673.59)
	Median (min, max)	14770.0 (450, 63950)
Dosage (mg/month) [e]	n	16
	Mean (SD)	1712.56 (397.18)
	Median (min, max)	1601.76 (1065.5, 2452.0)
Year of initiation of selumetinib, n (%)	2020 [f]	1 (6.3)
	2022	12 (75.0)
	2023	3 (18.8)

[a] See Section 10.1 for more detail on cohort assignment errors.

[b] Total (or intended) exposure = [min (last dose date where dose > 0 [mg], date of death, date of DCO) – first dose date +1] / (365.25 / 12).

[c] Actual cumulative exposure = Total (or intended) exposure, excluding dose interruptions.

[d] Total cumulative dose was the total dose received during the total exposure of selumetinib.

[e] Dosage (mg/month) = total cumulative dose received (mg)/ (Number of days receiving study drug) / (365.25 / 12).

[f] Date of first exposure to selumetinib for Patient E2307001 was corrected from 20 January 2020 to 20 January 2023 in the eCRF after DCO; patient-specific values and summary characteristics for selumetinib exposure were affected.

Abbreviations: DCO = data cut-off; eCRF = electronic case report form; max = maximum; min = minimum; N = number of patients in cohort group; n = number of patients included in analysis; SD = standard deviation.

Source: Table 10.4.2.

The total daily dose at time of treatment start (ie, at baseline) ranged from 30 mg to 100 mg for the Base Cohort and from 35 mg to 90 mg for the Nested Prospective Cohort (Table 8).

Table 8 Total Daily Selumetinib Dose at Baseline (Base Cohort and Nested Prospective Cohort)

Characteristic	Statistic	Base Cohort	Nested Prospective Cohort
		Overall (N = 33)	Overall (N = 16) [a]
Total daily selumetinib dose at baseline (mg)	n	28	16
	Mean (SD)	62.0 (17.97)	56.6 (14.46)
	Median (min, max)	65.0 (30, 100)	50.0 (35, 90)

[a] See Section 10.1 for more detail on cohort assignment errors.

Abbreviations: max = maximum; min = minimum; N = number of patients in cohort group; n = number of patients included in analysis; SD = standard deviation.

Source: Table 10.4.3.1 and Table 10.4.3.2.

In the Nested Prospective Cohort there were a total of 10 treatment interruptions in 6 patients, of which 2 interruptions were reported as having been due to an AE. One patient in the Nested Prospective Cohort permanently discontinued treatment as of the DCO (Table 9). No patients in the Nested Prospective Cohort discontinued from the study (see Section 10.1 for more detail).

Table 9 Selumetinib Discontinuation, Interruption, Dose Increase, and Dose Reduction During Follow-up (Nested Prospective Cohort)

	Number (%) of patients
	Overall (N = 16) [a]
Number of patients with at least one treatment interruption	6 (37.5)
Number of patients with 2 or more treatment interruptions	3 (18.8)
Number of treatment interruptions [b]	10 (62.5)
Reasons for treatment interruption	
Adverse event	2 (20.0) [c]

Table 9 Selumetinib Discontinuation, Interruption, Dose Increase, and Dose Reduction During Follow-up (Nested Prospective Cohort)

	Number (%) of patients
	Overall (N = 16) [a]
Response-related dose change	0
Patient forgot to take dose	0
Patient decision	2 (20.0) [c]
Patient not able to swallow tablet	0
Other	6 (60.0) [c]
Number of patients with at least one dose reduction	1 (6.3)
Number of patients with at least one dose increase	2 (12.5)
Number of patients who permanently discontinued treatment	1 (6.3) [d]

[a] See Section 10.1 for more detail on cohort assignment errors.
[b] Patients may have had more than one treatment interruption during the study.
[c] Percentages were based on the number of all treatment interruptions.
[d] See Section 10.1 for more detail on cohort discontinuation status errors.
Abbreviations: N = number of patients in cohort group.
Source: Table 10.4.4.

10.4 Outcome Data

Not within the scope of this Annual Progress Report.

10.5 Main Results

Not within the scope of this Annual Progress Report.

10.6 Other Analyses

Not within the scope of this Annual Progress Report.

10.7 Adverse Events/Adverse Reactions

10.7.1 Categories of Adverse Events

Nested Prospective Cohort

See Table 10 for details of AEs by Any Category for the Nested Prospective Cohort.

Eleven (68.8%) of the 16 patients enrolled in the Nested Prospective Cohort experienced at least one AE, of which 10 (62.5%) patients reported 31 AEs that were considered to be possibly related to selumetinib. The majority of these AEs were gastrointestinal or skin disorders, which are known to be very common ADRs associated with selumetinib, as per the

product label (see Listing 10.6.1, Appendix C). No patients in the Nested Prospective Cohort reported an AE of CTCAE of Grade 3 or higher or a SAE; there were no deaths. There were no AEs leading to permanent dose discontinuation. Adverse events leading to dose reduction occurred in one (6.3%) patient and AEs leading to dose interruption of selumetinib were reported in 2 (12.5%) patients. One (6.3%) patient in the Nested Prospective Cohort experienced an AESI (Table 10).

Base Cohort Only (Data Collected in Error)

Of the patients enrolled in the Base Cohort only and from whom safety data was collected, 9 patients experienced at least one AE with 8 patients reporting 36 AEs which were considered to be possibly related to selumetinib. Three patients in the Base Cohort only experienced an AE of CTCAE of Grade 3 or higher and 2 patients experienced a SAE; there were no deaths. Adverse events leading to permanent dose discontinuation, dose reduction, and dose interruption of selumetinib were each reported in ≤ 2 patients (see Listing 10.6.1, Appendix C).

Table 10 Overview: Adverse Events in Any Category (Nested Prospective Cohort)

Characteristic	Overall (N = 16) [a]	
	Number (%) of patients [b]	Events [c]
Any AE	11 (68.8)	42
Any AE with a reasonable possibility caused by selumetinib	10 (62.5)	31
Any AE with outcome of death	0	0
Any AEs of CTCAE Grade 3 or higher	0	0
Any AEs of CTCAE Grade 3 or higher with a reasonable possibility caused by selumetinib	0	0
Any SAEs (including events with outcome of death)	0	0
Any SAEs leading to permanent treatment discontinuation	0	0
Any SAEs with a reasonable possibility caused by selumetinib	0	0
Any AEs leading to permanent treatment discontinuation	0	0
Any AEs leading to dose increase of selumetinib	0	0
Any AEs leading to dose reduction of selumetinib	1 (6.3)	2
Any AEs leading to dose interruption of selumetinib	2 (12.5)	3

Table 10 Overview: Adverse Events in Any Category (Nested Prospective Cohort)

Characteristic	Overall (N = 16) [a]	
	Number (%) of patients [b]	Events [c]
Any AESI	1 (6.3)	3
Any AESI of CTCAE Grade 3 or higher	0	0
Any AESI with a reasonable possibility caused by selumetinib	1 (6.3)	3

[a] See Section 10.1 for more detail on cohort assignment errors.

[b] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category with multiple events were counted once in each of those categories.

[c] Multiple events in the same category were counted multiple times in that category. Multiple events belonging to more than one category were counted multiple times in each of those categories.

Common Terminology Criteria for Adverse Events: version 5.0.

Medical concepts for AESIs in this study are: cardiac toxicity, muscular toxicity, hepatotoxicity, ocular toxicity, and, in the paediatric population only: physeal dysplasia and choking on capsule.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CTCAE = Common Terminology Criteria for Adverse Events; N = Number of patients in cohort group; SAE = serious adverse event.

Source: Table 10.6.1.2.

10.7.2 Serious Adverse Events

Nested Prospective Cohort

No patients in the Nested Prospective Cohort experienced a SAE (see Table 10.6.13.2, Appendix C).

Base Cohort Only (Data Collected in Error)

Two patients in the Base Cohort only experienced a SAE. One patient reported a SAE of pain, which, as of the DCO, was reported as unresolved and one patient experienced a SAE of toxicity to various agents, which, as of the DCO, was reported as resolved. Neither SAE was considered to be related to selumetinib (see Listing 10.6.1, Appendix C).

Narratives for these patients are provided in Appendix D.

10.7.3 Deaths

Nested Prospective Cohort

As of the DCO (21 July 2023), no deaths were reported in the Nested Prospective Cohort (see Table 16.6.18, Appendix C).

Base Cohort Only (Data Collected in Error)

As of the DCO (21 July 2023), no deaths were reported in patients in the Base Cohort only (see Listing 10.6.1, Appendix C).

11. DISCUSSION

11.1 Key Results

Due to the current sample size, a full evaluation of the safety data against the primary objectives of this study is not yet possible. However, the following key safety results are presented:

- As of the DCO, 33 patients in the Base Cohort across 4 European countries were enrolled in the study. Patient age ranged from 3 to 18 years and approximately two thirds of patients were male.
- Ten of the 16 patients enrolled in the Nested Prospective Cohort reported at least one AE reported as possibly related to selumetinib. The majority of these AEs were gastrointestinal or skin disorders, which are known to be very common ADRs associated with selumetinib, as per the product label.
- No patients in the Nested Prospective Cohort reported an AE of CTCAE Grade 3 or higher or a SAE.

11.2 Limitations

There are potential challenges with enrolment in a prospective data collection study with consideration of each participating site's capacity and need for patient/legal guardian consent. Originally, a previously conducted feasibility assessment had identified treating centres in most European countries and found that recruitment of the target number of patients required would be possible in the specified time period. This, however, is no longer the case and a proposal to extend the study/follow-up period is included in Selumetinib PASS Protocol (version 3.0) which was submitted to the EMA PRAC in August 2023.

The prospective data collection study will include a self-selected sample, potentially creating selection bias with patients having demographic and clinical characteristics that may differ from the broader population of NF1 patients. For detail on planned assessments for the Interim Analysis and the Final Analysis see Selumetinib PASS Protocol (version 2.0).

As previously described, demographic, treatment, and outcomes data will be collected by site investigators at specialty treatment centres under conditions of routine clinical care. Because of the non-interventional nature of this PASS, some variables will be more complete than others because, for example, the survey feasibility assessment suggests that clinical assessments for imaging of growth plates and assessment of height and weight to measure growth might not be routinely captured. In addition, as for all prospective studies, events

occurring outside the clinic may not be collected. Missing data will be categorised and analysed to describe the occurrence of safety events for the entire cohort and for just those without missing information.

It should also be noted that results for this Annual Progress Report and future Annual Progress Reports are based on 'snapshots' of the eCRF database as per the DCO. This means that data are not yet fully reviewed for cleanliness and not all queries on discrepant or inconsistent data have been resolved as of the DCO date. Nevertheless, detected discrepancies, inconsistencies, and corrections to eCRF data after the DCO date (21 July 2023) have been addressed in the text and footnoted to the applicable tables and listings.

11.3 Interpretation

For this first Annual Progress Report a snapshot of the study database was taken approximately one year after enrolment of the first patient (first patient enrolled: 23 May 2022; DCO: 21 July 2023). As per the SAP (version 1.0), the scope of the Annual Progress Reports for this study are limited to study progress, patient disposition, descriptive exposure, and safety data.

As of the DCO, 33 patients were enrolled in the study (Base Cohort), of which 16 were assigned to the Nested Prospective Cohort. Of note, one patient was erroneously not assigned to the Nested Prospective Cohort in the eCRF at the time of the DCO and was therefore not included in the analysis for the Nested Prospective Cohort for this first Annual Progress Report.

At the time of the DCO, 8 patients were reported as having discontinued from the study. Note that the disposition status for a patient assigned to the Nested Prospective Cohort was erroneously assigned as 'other' on the eCRF at the time of the DCO. Patient E2308003 did not discontinue from the study. There were no deaths reported in the study as of the DCO date.

Patient age ranged from 3 to 18 years (Base Cohort). Of note, at the time of the DCO the eCRF asked for age at time of enrolment (ie, date informed consent was signed) rather than age at time of selumetinib initiation. The eCRF was modified after DCO to collect age at time of selumetinib initiation. The distribution of sex in the older age group restricted to the Nested Prospective Cohort (ie, age 8 to < 18 years) showed that approximately two-thirds of the population were male.

As of the DCO date, data on exposure to selumetinib was recorded in the eCRF for 28 of the 33 patients enrolled (Base Cohort); queries to investigative sites regarding missing exposure data for 5 patients remained unresolved as of the DCO. The total daily dose at time of treatment start (ie, at baseline) was in line with the range for recommended daily dose as per product label. In the Nested Prospective Cohort, the mean duration of total exposure to selumetinib and mean actual cumulative exposure were similar indicating that the

interruptions had a limited effect on exposure to selumetinib. No patients in the Nested Prospective Cohort permanently discontinued treatment as of the DCO.

The majority of the AEs which were reported as possibly being related to selumetinib were gastrointestinal or skin disorders, which are known to be very common ADRs associated with selumetinib, as per the product label. No patients in the Nested Prospective Cohort experienced a SAE as of the DCO.

11.4 Generalisability

As of the DCO (21 July 2023), patients recruited in the study are from 4 European countries only: Austria, France, Germany, and Portugal. The number of patients by country is relatively small (less than 20 patients per country). In terms of patient demographics, the median age at selumetinib initiation was 13 (range: 3 to 18 years) for the Base Cohort and 12 (range: 8 to 15 years) for the Nested Prospective Cohort, indicating that a broad range of paediatric patients are being recruited into the study. Small patient numbers by country makes generalisability of results to NF1 PN patients in the above-mentioned regions difficult. Additionally, considering the relatively small sample size in the study at present, caution should be taken in attempting to draw any firm conclusions from this report. The Sponsor will continue to monitor the safety of patients in the study and will continue to submit Annual Progress and Interim Reports as per the planned milestones (Section 5).

12. OTHER INFORMATION

As of the DCO (21 July 2023), 11 sites out of a planned total of 36 sites have enrolled patients. A further 9 sites have been activated and are ready to enrol patients (total of 20 active sites). Patients have been enrolled in 4 European countries out of a planned 12 European countries. The total number of sites and countries enrolling patients is lower than planned due to delays in the commercial availability of selumetinib in Denmark, Italy, Spain, and the UK.

The relatively slow rate of patient accrual in the study is directly related to lengthy delays in reimbursement. Contrary to what had been assumed during the planning phase of the study (ie, that selumetinib would be available for prescription in all participating countries by Q1 2022), significant delays in reimbursement have been observed in several participating countries. Although measures have been taken to identify additional countries and investigative sites, it is anticipated that the patient recruitment period (and hence overall study duration) will need to be extended in order to meet the targeted number of patients and duration of follow-up needed for this study. To this end, a protocol amendment was submitted to the EMA PRAC in August 2023 (Selumetinib PASS Protocol [version 3.0]).

13. CONCLUSION

This is the first PASS Annual Progress Report for selumetinib with a DCO of 21 July 2023. As of the DCO, recruitment was ongoing (33 patients out of a planned total of 125 patients in the Base Cohort were enrolled). Due to the current sample size, a full evaluation of the data against the objectives of this study is not yet possible. However, the following conclusions may be tentatively drawn:

- Patient demographics indicate that a broad range of paediatric patients are being recruited into the study.
- More than half of the patients in the Nested Prospective Cohort reported at least one AE that was considered to be possibly related to selumetinib. The majority of these AEs were gastrointestinal or skin disorders, which are known to be very common ADRs associated with selumetinib, as per the product label.
- No patients in the Nested Prospective Cohort reported an AE of CTCAE Grade 3 or higher or a SAE.
- As small patient numbers by country make generalisability of results to NF1 PN patients in the regions that have currently recruited patients difficult the Sponsor will continue to monitor the safety of patients in the study and will continue to submit Annual Progress and Interim Reports as per the planned milestones.

14. REFERENCES

Gross et al 2020
Gross AM, Wolters PL, Dombi E, Baldwin A, Whitcomb, Fisher MJ, et al. Selumetinib in Children with Inoperable Plexiform Neurofibromas. N Engl J Med. 2020:382(15);1430-42.

Gross et al 2023
Gross AM, Dombi E, Wolters PL, Baldwin A, Dufek A, Herrera K, et al. Long-Term Safety and Efficacy of Selumetinib on Children with Neurofibromatosis Type 1 on a Phase 1/2Trial for Inoperable Plexiform Neurofibromas. Neuro Oncol. 2023. DOI: 10.1093/neuonc/noad086. Online ahead of print.

Appendix A List of Stand-alone Documents

Table 11 List of Stand Alone Documents

Number	Title	Date
1	SAP version 1.0	30 August 2022
2	Protocol version 2.0	05 November 2021
3	Protocol version 3.0	Submitted to the EMA PRAC August 2023

Abbreviations: EMA = European Medicines Agents; PRAC = Pharmacovigilance Risk Assessment Committee; SAP = Statistical analysis plan.

Appendix B Additional Information (Principal Investigator Contact Details)

Table 12 Principal Investigator Details

PI Name	Site Number	Site Address	PI Contact Information
PPD			

PPD			

PPD			

Appendix C Additional Information (Source Data: Tables, Figures, and Listings)

Appendix D Additional Information (Patient Narratives)

PPD

PPD

Statistical analysis plan	
Study code	D1346R00004
Version	1.0
Date	30 Aug 2022

Post-Authorisation Safety Study of Paediatric Patients Initiating Selumetinib: A Multiple-Country Prospective Cohort Study

Post-Authorisation Safety Study of Paediatric Patients Initiating Selumetinib: A Multiple-Country Prospective Cohort Study

Alexion Study Statistician

NA	Date

Post-Authorisation Safety Study of Paediatric Patients Initiating Selumetinib: A Multiple-Country Prospective Cohort Study)

Alexion Epidemiologist

PPD

Date

TABLE OF CONTENTS PAGE

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
CPK	Creatine Phosphokinase
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database Lock
DCO	Data Cut-Off
eCRF	electronic Case Report Form
EAP	Early Access Program
EMPOWER	Excellence in Medical Partnership for Outsourced Worldwide Evidence Research
GDPR	General Data Protection Regulation
KM	Kaplan Meier
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
NF1	Neurofibromatosis Type 1
PASS	Post-authorization safety study
PN	Plexiform Neurofibroma
PT	Preferred Term
Q2	Quarter 2
Q3	Quarter 3
RMP	Risk Management Plan
SAE	Serious Adverse Event
SOC	System Organ Class

AMENDMENT HISTORY

Date	Brief description of change
08 February 2022	Draft Version
30 Aug 2022	Final Version

1. OBJECTIVES

The primary objective of this study is:

- To characterise the safety of selumetinib, including up to 5 years of long-term safety, in paediatric patients with Neurofibromatosis Type 1 (NF1) - related symptomatic, inoperable plexiform neurofibroma (PN), 8 to < 18 years old who have not reached Tanner Stage V at the start of selumetinib treatment (Nested Prospective Cohort).

The secondary objective of this study is:

- To describe the paediatric and clinical profile of the paediatric population 3 to < 18 years old with NF1-related symptomatic inoperable PN who start selumetinib in routine clinical practice (Base Cohort).

2. STUDY DESIGN AND SAMPLE SIZE

This is a cohort study of paediatric patients (aged 3 to 18 years of age) with NF1 with symptomatic, inoperable PNs who begin selumetinib treatment at study sites across several European countries where selumetinib has been marketed for use.

The patient enrolment period will begin once the first patient is enrolled and end 2 years after that date (estimated end of enrolment = (Quarter 2 (Q2) 2024). Patients may continue in the study until the study end date which is 5 years after the first patient enrolment date (estimated end of study = Q2 2027). Each enrolled patient will be assigned an index date (Day 1). The index date is defined as the date of first prescription of selumetinib.

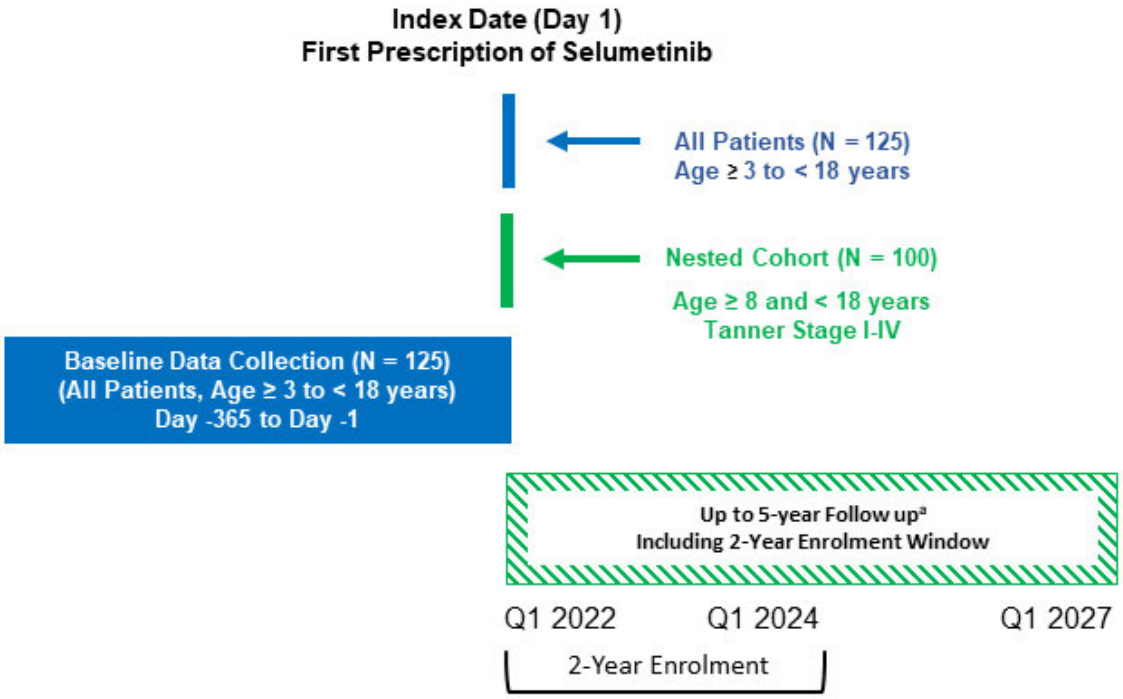
The target population for this study are patients with NF1 with symptomatic, inoperable PN who have been newly prescribed at least 1 dose of selumetinib and who are aged 3 to < 18 years at the start of selumetinib treatment, except for those patients receiving treatment with a mitogen-activated protein kinase inhibitor before the index date and who do not participate in any clinical study.

The study will enrol 2 cohorts:

1. The Base Cohort includes all enrolled patients aged 3 to <18 years.
2. The Nested Prospective Cohort will include the subset of Base Cohort patients aged 8 to <18 years who have not reached Tanner Stage V on the index date.

The study schematic is shown below in Figure 1.

Figure 1 Study Schema



[a] Patients in the Nested Prospective Cohort will be followed from index date to the censor date, defined as the earliest of the end of the 5-year study period, study withdrawal, loss to follow-up, or death.

Enrolment will occur at up to 36 sites in up to 12 European countries. The target enrolment for the Base Cohort is 125 patients. Of those, approximately 100 patients are expected to meet inclusion criteria for the Nested Prospective Cohort.

As shown below, Table 1 provides the 95% confidence intervals (CIs) associated with a range of observed cumulative incidence values for events associated with the safety outcomes of interest, across varying sample sizes. A range of cumulative incidence values is expected based on evidence from study D1532C00057 (SPRINT Phase 2) and, in cases where the event was not observed in SPRINT, from other studies of mitogen-activated protein kinase inhibitors given as monotherapy (eg, trametinib). With 100 patients expected in the Nested Prospective Cohort patients, there is a 90% probability of observing at least one event with an underlying real-world incidence of 2.28%.

Table 1 95% CI of the Cumulative Incidence of a Safety Outcome of Interest Given Sample Size

Observed Incidence	Number of Patients		
	95% CI for the cumulative incidence [a]		
	75	100	125
0%	(0.0%, 4.8%)	(0.0%, 3.6%)	(0.0%, 2.9%)
0.5%	(0.0%, 7.2%)	(0.0%, 5.4%)	(0.0%, 4.4%)
1%	(0.0%, 7.2%)	(0.0%, 5.4%)	(0.0%, 5.7%)
2.5%	(0.0%, 9.3%)	(0.2%, 8.5%)	(0.5%, 8.0%)
5%	(0.8%, 13.1%)	(1.6%, 11.3%)	(1.8%, 11.2%)
7.5%	(2.2%, 16.6%)	(2.9%, 15.2%)	(3.3%, 14.2%)
10%	(3.8%, 19.9%)	(4.9%, 17.6%)	(5.1%, 17.1%)
20%	(11.6%, 30.8%)	(12.7%, 29.2%)	(13.4%, 28.1%)
30%	(19.4%, 42.4%)	(21.2%, 40.0%)	(21.8%, 39.3%)
40%	(28.9%, 52.0%)	(30.3%, 50.3%)	(31.3%, 49.1%)
50%	(37.6%, 62.4%)	(39.8%, 60.2%)	(40.5%, 59.5%)

[a] Clopper-Pearson exact 95% CI. When the number of patients is not an integer, it is rounded down for the lower limit, and rounded up for the upper limit.

Abbreviations: CI = confidence interval.

3. ANALYSIS SETS

The following two analysis populations that will be used for reporting are:

3.1 The Base Cohort

The Base Cohort is the set of all enrolled patients aged ≥3 to < 18 years.

3.2 The Nested Prospective Cohort

The Nested Prospective Cohort is the subset of Base Cohort Patients aged ≥8 to < 18 years who have not reached Tanner Stage V on the index date.

Each safety outcome of interest (please refer to Table 2 of the primary objective will be analysed within the Nested Prospective Cohort and will be based on the data collected on the Safety Outcomes of Interest (SAFE_OUT) and Tanner Stage (TANNER) electronic case report forms (eCRFs) [left ventricular ejection function (LVEF) reduction, physeal dysplasia, myopathy, hepatotoxicity, ocular toxicity, and sexual maturation disorder (abnormal pubertal development)].

Patients in the Nested Prospective Cohort will be followed from the index date to the censor date, defined as the earliest of the end of the 5-year study period, study withdrawal, loss to follow-up, or death. The 5-year study period is defined as a maximum of 5 years from the time the first patient is enrolled (estimated time period = Q2 2022 to Q2 2027).

3.3 Important Protocol Deviations

Protocol deviations are defined as any change, divergence, or departure from the study design of procedures defined in the post-authorization safety study (PASS) protocol. Important protocol deviations are a subset of protocol deviations and may significantly impact the correctness, accuracy, and/or reliability of the study data. Important protocol deviations for this PASS are defined as those affecting patient eligibility to participate in the study.

The important protocol deviations (i.e., patients not meeting eligibility criteria) will be summarised as part of the patient disposition statistics (see Section 5.2.1).

4. EXPOSURE(S) AND OUTCOMES

4.1 Exposures

4.1.1 Definition of primary drug exposure

In the Nested Prospective Cohort, exposure to selumetinib will be collected from the index date to the date of the last dose of selumetinib using a standardised eCRF that captures e.g., date(s) (start and end date of selumetinib reporting period) selumetinib dose (dose per administration and total daily), treatment cycles, treatment modification(s) (including interruption, dose reduction, dose increase, and discontinuation), and associated main reasons (adverse event, response-related dose change, subject forgot to take dose, subject decision, subject not able to swallow tablet, other).

Selumetinib is administered orally twice daily (approximately every 12 hours) continuously for 28 -day cycles with no rest periods between cycles.

The beginning of exposure will be the date of initiation of selumetinib treatment (index date) and the end of exposure will be the date of the last dose of selumetinib being prescribed. Dose amount will be obtained at the date of first prescription of selumetinib for all patients and at each follow-up visit Exposure (i.e. duration of treatment) will be defined in months as follows:

Total (or intended) exposure of study treatment

Total (or intended) exposure = (min (last dose date where dose > 0 [mg], date of death, date of data cut-off (DCO)) – first dose date +1) / (365.25 / 12)), where DCO is the data cut-off date for each of the annual progress reports/interim analysis/final analysis

For patients still continuing treatment at DCO, the date of DCO will be used as the date of last dose.

Missed or forgotten doses

Missed and forgotten doses will be recorded on the EX module as a dose interruption with the reason recorded as “Subject forgot to take dose” or in the case of swallowability issues as “Subject not able to swallow tablet”. These missed or forgotten doses will not be included as dose interruptions in the summary tables but the information will appear in the listing for dosing.

4.1.2 Definition of comparison drug exposure

Not applicable

4.2 Outcomes

To characterise long-term safety, all patients in the Nested Prospective Cohort will be followed for up to a maximum of 5 years from the time the patient is enrolled under conditions of routine clinical care to collect data on the occurrence of the safety outcomes of interest listed in Table 2. These safety outcomes have been chosen to characterise the important identified risk (LVEF reduction), the important potential risks (physeal dysplasia, ocular toxicity, myopathy, and hepatotoxicity), and the missing information on long-term exposure described in the EU risk management plan (RMP); to describe any developmental toxicity during selumetinib use in children; and to further characterise the frequency and severity of safety outcomes of interest (Table 2) and adverse events (AEs) occurring during selumetinib treatment in real-world clinical practice.

Patients who may discontinue selumetinib treatment are to continue in the study for long-term safety follow-up assessment, unless consent is withdrawn.

All concomitant medications, including those taken due to AEs, are to be recorded on an eCRF.

The important potential risk of choking on the capsule will also be included in the analysis of the AEs and captured as an Adverse event of special interest (AESI) (please refer to section 4.2.1.2).

Table 2 Safety Outcomes of Interest and Corresponding Clinical Assessment [a]

EU-RMP Safety Concern	PASS Outcome	Collected Data and Outcome Definition
LVEF reduction	LVEF reduction	LVEF reduction will be detected as present or absent and when present if symptomatic or asymptomatic. All cardiac tests conducted will be collected
Physeal dysplasia	Physeal dysplasia	Physeal dysplasia will be detected as present or absent based on the physician reading of: • MRI: Knee (preferred) or wrist • X-ray: Knee (preferred) and/or wrist to assess growth plate • Height and weight records
Myopathy	Rise of serum creatine phosphokinase levels AND concurrent musculoskeletal symptoms	A clinically meaningful rise in serum creatine phosphokinase (eg, above the normal limit or increase by 1 or more CTCAE grade shift) combined with musculoskeletal symptoms will be detected as present or absent based on the physician's reading, as a marker of potential myopathy.
Hepatotoxicity	Rise in transaminase (ALT and AST) and concurrent rise in bilirubin	A clinically meaningful rise in the measured levels (eg, above the normal limit or increase by 1 or more CTCAE grade shift) will be detected as present or absent, and when present if symptomatic or asymptomatic, as a marker of potential hepatotoxicity
Ocular toxicity	Abnormalities of ophthalmological examination (e.g., vision changes, IOP, etc.)	An abnormal ocular examination will be detected as present or absent based on the physician's reading, as a marker of potential ocular toxicity ophthalmological exam. Recorded as present or absent.

EU-RMP Safety Concern	PASS Outcome	Collected Data and Outcome Definition
Sexual maturation disorder (abnormal pubertal development)	Abnormal pubertal development	Tanner staging criteria (Stages I-V). Abnormal pubertal development will require interpretation by the Investigator with respect to Tanner Stage in the context of the patient's age; recorded as normal or abnormal (if abnormal, further specified as delayed puberty or precocious puberty)

[a] All haematic and clinical test results will be collected as available.
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; EU = European Union; IOP = intraocular pressure; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PASS = post-authorisation safety study; RMP = Risk Management Plan.

4.2.1 Primary outcomes:

4.2.1.1 Safety Outcomes of Interest

Each safety outcome of interest will be summarised in the Nested Prospective Cohort. Incidence rate with 2-sided 95% confidence interval will also be presented for all safety outcomes. The Kaplan Meier (KM) curves will be presented and medians with Brookmeyer-Crowley CIs will be calculated. The cumulative incidence per safety outcome at 6, 12, 18, 24, 30, 36, 42, 48 and 60 monthswill be calculated using the KM technique and 95% CI calculating using the Brookmeyer-Crowley method.

Cumulative incidence or risk, of each safety outcome is defined as the cumulative proportion of patients with event over a specified time period and will be calculated as the Kaplan-Meier estimate for failure.

Incidence rates per 100 patient years with 95%-confidence intervals for safety outcome events will be calculated the following way:

Incidence rate λ is defined as:

$$Incidence\ rate\ \lambda\ [per\ 100\ patient\ years] = 100 * \frac{numbers\ of\ patients\ with\ event}{\frac{1}{365.25} * \sum_{patients} person\ time\ at\ risk\ (event)[days]}$$

where the denominator is the patient years under risk. The 2-sided 95% CI of λ will be calculated based on the Poisson distribution and its relation with the Chi-square distribution according to the following formula:

$$\left[\lambda_{lower}, \lambda_{upper}\right] = \left[\{0.5\ \chi^2(\alpha/2; 2x\}/n\ , \left\{0.5\ \chi^2(1-\frac{\alpha}{2}; 2x+2)\right\}/n\ \right],$$

where $\chi 2(\gamma, r)$ is the 100γth percentile of a chi-square distribution with r degrees of freedom, n is the patient years under risk for the event, x is the number of patients with event, and α=0.05 for 95% 2-sided CIs.

Time to event for each safety outcome of interest is defined below:

1. Time to LVEF reduction is defined as the time from index date to the first occurrence of LVEF reduction, whenever occurring. Patients not experiencing a reduction will be censored at their last LVEF assessment date.
2. Time to physeal dysplasia is defined as the time from index date to the first detection of physeal dysplasia, whenever detected. Patients not being detected with physeal dysplasia will be censored at their last assessment date.
3. Time to myopathy is defined as the time from index date to the first detection of myopathy, whenever detected. Patients not being detected with myopathy will be censored at their last assessment date.
4. Time to hepatotoxicity is defined as the time from index date to the first detection of hepatotoxicity, whenever detected. Patients not being detected with hepatotoxicity will be censored at their last assessment date.
5. Time to ocular toxicity is defined as the time from index date to the first detection of ocular toxicity, whenever detected. Patients not being detected with ocular toxicity will be censored at their last assessment date.
6. Time to sexual maturation disorder is defined as the time from index date to the first detection of abnormal sexual maturation disorder assessment, whenever detected. Patients being assessed as normal will be censored at their last collection date.

CCI [redacted]

4.2.1.2 Adverse Events

All AEs, (non-serious and Serious adverse events (SAEs), adverse drug reactions (ADRs) will be collected from the time of starting selumetinib (patient index date [Day 1]) throughout the treatment period and during the study 5-year follow-up maximum period in the Nested Prospective Cohort.

An AE during treatment is defined as an AE with onset at or after the first dose date and up to (and including) 30 days after the last dose date.

AE after treatment discontinuation is defined as an AE which onsets 30 days after the last dose date.

The Medical Dictionary for Regulatory Activities (MedDRA) (using the latest or current MedDRA version) will be used to code the AEs. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (CTCAE) as indicated in the PASS protocol).

If the maximum intensity (ie. CTCAE grading) is missing for an AE then it will be considered as severe only (i.e. CTCAE Grade ≥ 3) in the overall category in the summary tables. If the relationship to treatment is missing then the AE will be considered as related to treatment (i.e., reasonable possibility AE caused by selumetinib field in eCRF).

All collected AEs will be summarised in each of the annual progress reports, in the interim analysis and the final study report.

AEs of special interest

AESIs represent pre-specified risks that are considered to be of importance to a clinical development program.

The safety outcomes of interest, including instances of choking on the capsule, will be collected as an AE, and flagged as an AESI and presented in the analysis .

These AESIs are recorded in the [AE] eCRF (Is this an Event of Special Interest = Yes)

Special situations

Information on special situations (with or without AE, such as, overdose, medication error, product quality complaints/issues incl. counterfeit/tampering product, and lack of efficacy) will be collected and recorded throughout the course of the study

Deaths

All adverse events leading to death will be collected until the censor date.

4.2.2 Secondary outcome(s)

4.2.2.1 Description of the Paediatric Population

Baseline data collected from the Base Cohort will include patient characteristics (demographic and clinical) and site characteristics. Baseline data will be summarized for the Base and Nested Prospective Cohort and by site.

- **Demographics (inclusive of height, weight body surface area and Tanner staging level at baseline)**: Age, sex, height, weight, body surface area, Tanner staging level, and ethnicity (where allowed by general data protection regulation (GDPR)/privacy laws)
- **Clinical characteristics**: LVEF (reduction and symptoms) ocular assessment, sexual maturation disorder (assessment and reason), PN(s) (number, location, classification and morbidities), prior medication and relevant procedures, concomitant medications, comorbidities, date of initial NF1 and PN diagnosis, NF1 origin (familial or spontaneous), and genetic testing results

CCI [redacted]

4.3 Other variables and covariates

In addition to the demographic and clinical characteristics noted above that will be collected at baseline, the following data will be collected throughout follow up:

- Height (cm)
- Weight (kg)
- Body surface area (m^2)
- Tanner staging (level), specified as: Tanner stage - pubic hair, Female tanner stage – breast Male tanner stage - penis and testicle
- Concomitant and post-treatment medications, including any medications used to treat AEs

- Comorbidities
- NF1-related clinical manifestation and complications
- PN-related variables (including for any clinically important target PNs)
- PN-related symptoms/morbidities
- Number of PN-related morbidities
- Number of PN(s), PN location(s), PN size(s)

Location (country) will be also collected at locally participating sites.

5. ANALYSIS METHODS

5.1 General principles

The principal analyses outlined in this statistical analysis plan will be conducted by LabCorp., in accordance with the contract with AstraZeneca and following the Excellence in Medical Partnership for Outsourced Worldwide Evidence Research (EMPOWER) description of services.

The below mentioned general principles will be followed for analyses:

Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category. The number and percentage of missing values will be presented as a separate category.

Unless otherwise stated, percentages will be calculated out of corresponding cohort total

For continuous data the mean and median will be rounded to 1 additional decimal place compared to the original data. The standard deviation will be rounded to 2 additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data.

For categorical data, percentages will be rounded to 1 decimal place.

SAS® version 9.3 or higher will be used for all analyses.

It is acceptable to present large numerical values in more appropriate units. It is, however, important to keep the units consistent within the report and the precision consistent with that prior to conversion.

In general, baseline is defined as the last assessment made within 365 days prior to initiation of selumetinib treatment (i.e., index date). For repeated measurements during the baseline period, the value closest in time to the index date will be taken.

In all quantitative summaries from baseline, variables will be calculated as the post-treatment value minus the value at baseline. The percentage change from baseline will be calculated as (post-baseline value – baseline value) / baseline value x 100. Absolute and percentage change will be summarized.

In general, for each analysis population, summaries will be presented for the overall population and by country and site within country.

Safety outcomes of interest will be summarized for the patients of the Nested Prospective Cohort. These patients will be followed from the index date to the censor date defined as the earliest of the end of the 5-year study period, study withdrawal, loss to follow-up, or death.

Study population, patient characteristic (demography and clinical) data will be summarised for the Base Cohort and the Nested Prospective Cohort.

AEs as described in section 4.2.1.2, as well as safety and treatment exposure data will be summarised for the Nested Prospective Cohort.

Data from all cycles will be combined in the presentation of safety data.

5.1.1 Time Windows

Time windows will be defined for any presentations that summarise values by follow- up visit. The following conventions will apply:

- Assessments with missing data, assessments that were not performed, samples not collected and assessments marked "Not Done" will be considered as providing a missing response and are not permitted to be assigned to a time window.
- The worst value (e.g. out of reference range preferred to within range) will be used in each window. If multiple assessments fall within the same window with equal value, then the first non-missing will be used for the summary.
- The time windows will be exhaustive so that data recorded at any time point has the potential to be summarised. Inclusion within the time window will be based on the actual assessment/collection date
- All unscheduled visit data have the potential to be included in the summaries.
- Listings should display all values contributing to a time point for a patient.
- For summaries at a patient level, all values will be included, regardless of whether they appear in a corresponding visit based summary, when deriving a patient level statistic such as a maximum.

Table 3 Definition of Time Windows for Laboratory/Vital Signs Assessments

Visit	Target Day of Visit[a]	Analysis Time Window
Baseline	Day 1	Prior to Day 1
< Month 3	Day 46	Day 2 to Day 90
Month 6	Day 182	Day 91 to 273
Month 12	Day 365	Day 274 to 456
Month 18	Day 547	Day 457 to 638
Month 24	Day 730	Day 639 to 821
Month 30	Day 912	Day 822 to 1003
Month 36	Day 1095	Day 1004 to 1186
Month 42	Day 1278	Day 1187 to 1369
Month 48	Day 1460	Day 1370 to 1551
Month 54	Day 1643	Day 1552 to 1734

[a] Relative to index date

5.1.2 Handling of missing dates

Incomplete dates (partial or missing dates where a full date is permissible) will be presented in the data listings as recorded on the eCRF. However, for use in calculations (for instance in calculation of the duration of medication use and AE), dates will be estimated as follows:

5.1.2.1 Partial start dates

- If year is missing, do not impute.
- If the start date is completely missing, assume the date of first dose of study treatment unless the end date is present and suggests it could have started prior to the first dose of study treatment in which case impute the 01 January of the same year as the end date.
- If year only is recorded then it will be assumed to have started on the first day of the year, unless the year is the same as the start date of selumetinib, in which case the start date of selumetinib will be assumed.
- If year and month are present and day is missing, impute day as first day of the month, unless the month is the same as the start date of selumetinib, in which case the start date of selumetinib will be assumed.

For time from NF1 diagnosis to first study treatment and time from inoperable PN diagnosis to first study treatment start dates will be estimated as follows:

If the year is unknown, then:

- The date will not be imputed, and will be assigned a missing value

If the month is unknown, then:

- Assign the month as January

If the day is unknown, then:

- Assign the day as 1st of the month.

5.1.2.2 Partial end dates

- If year is missing, do not impute.
- If year only is recorded then it will be assumed to have ended on the last day of the year, unless the year is the same as the last dose date of selumetinib, in which case the last dose date of selumetinib will be assumed.
- If month and year is recorded, then it will be assumed to have ended on the last day of the month, unless the month is the same as the last dose date of selumetinib, in which case the last dose date of selumetinib will be assumed.
- If the end date is completely missing, the medication or adverse will be assumed ongoing.

5.1.3 Handling of Missing Safety Data

In general, missing chemistry laboratory data, vital signs, and other cardiac tests [including electrocardiogram (ECG) and Echocardiogram (ECHOC) data will not be imputed.

However, safety assessment values of the form of "< x" (i.e. below the lower limit of quantification) or > x (i.e. above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or "> x" in the listings. Adverse event imputations for missing severity or relationship are given in 4.2.1.2. AE date imputations are given in sections 5.1.2.1, 5.1.2.2.

Prior medications, concomitant and post treatment medications are defined based on imputed start and stop dates (as described in sections 5.1.2.1, 5.1.2.2) as follows:

- Prior medications are those taken prior to study treatment with a stop date prior to the first dose of study treatment.
- Concomitant medications are those with a stop date on or after the first dose date of study treatment (and could have started prior to or during treatment).
- Post-treatment medications are those with a start date after the last dose date of study treatment.

5.2 Analysis methods

No formal statistical hypotheses will be tested. All analyses will be descriptive and exploratory.

Data will be listed and summarised for the overall population and where appropriate, by country and site.

5.2.1 Patient disposition

Patient disposition will be listed and summarized by country, site and overall. The number and percentage of patients satisfying each of the following will be presented for all enrolled patients:

- Enrolled
- Previously treated under the Early Access Program (EAP) (Yes/No)
- Discontinued treatment and associated reasons
- Completed the study
- Ongoing in the study at data cut-off.
- Discontinued from the study and associated reasons
- Meeting vs not meeting eligibility criteria

The number of patients in each of the analysis sets (i.e., the Base and Nested Prospective Cohort) will be summarised for all enrolled patients.

The EAP patient population might be explored further in terms of disease severity, baseline disease characterises etc. in case it differs from non-EAP population.

5.2.2 Demographics and clinical characteristics

Clinical and demographic characteristics will be summarised and listed for both the Base Cohort and Nested Prospective Cohort by country and site. The demographic and clinical characteristics include the following:

- Age (years)
- Sex (Male, Female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race category (White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Other, Not reported)
- Country
- Baseline height (cm)
- Baseline weight (kg)
- Baseline Body surface area (m^2)
- Baseline medical and surgical history
- Disease Diagnosis [diagnosis of NF1 (Yes/ No) diagnosis of inoperable PNs (Yes/ No), Pubertal Status (Pre Pubertal/ Post Pubertal/Pubertal), NF1 diagnosis confirmed by a genetic test (Yes/ No) and NF1 origin (Familial/ Spontaneous), NF1-related clinical manifestation or complications]
- Time from NF1 diagnosis to first study treatment (months), defined as (diagnosis date of NF1 - first dose date of selumetinib +1) / (365.25 / 12).
- Time from inoperable PN diagnosis to first study treatment (months), defined as (diagnosis date of inoperable PN - first dose date of selumetinib +1) / (365.25 / 12)
- Disease extent (Number of Lesions, PN type (Target PN/ Non-Target PN / New), locations and associated symptoms and potential symptoms and overall morbidity type)
- PN evaluation [Target PN (Yes/ No), Date of scan/examination, PN diameter (mm), PN volume (ml), PN measurability method (MRI, X-Ray, Other) and Investigator overall status (Response/SD/ PD/ NE)]

- Baseline Clinical Characteristics [LVEF % at baseline, LVEF method (Echocardiography/ MUGA/ Myocardial perfusion imaging/ MRI/ Multi - detector computed tomography/ Other) LVEF reduction (Absent/ Present), LVEF reduction (Symptomatic/ Asymptomatic), Ocular assessment at baseline (Normal / Abnormal)
- Tanner staging level for males and females

5.2.3 Medical History

Medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [using the latest MedDRA version)]. The number and percentage of subjects with any medical or surgical history will be summarized and listed for the Base Cohort and Nested Prospective Cohort by system organ class (SOC) and preferred term (PT) overall.

5.2.4 Prior and concomitant medications

Medications received prior to, concomitantly, or post-treatment will be coded using the Anatomical Therapeutic Chemical (ATC) Classification codes. Concomitant medications will be summarised separately for the Base Cohort and Nested Prospective Cohort by ATC classification codes.

For the purpose of inclusion in prior and/or concomitant medication summaries, incomplete medication start and stop dates will be imputed as detailed in Section 5.1.1

Prior medications, concomitant and post treatment medications are defined based on imputed start and stop dates as follows:

- Prior medications are those taken prior to study treatment with a stop date prior to the first dose of study treatment.
- Concomitant medications, medical conditions and surgical procedures are those with a start or stop date on or after the date of the first dose of study treatment or those that started prior to the first dose of study treatment and are ongoing during the treatment period.
- Post-treatment medications are those with a start date after the last dose date of study treatment.

The following summaries will be produced:

- Summary of prior medications related to PNs
- Summary of prior medications not related to PNs
- Summary of concomitant medications, medical conditions and surgical procedures related to PNs
- Summary of concomitant medication, medical conditions and surgical procedures not related to PNs
- Summary of post-treatment medications, medical conditions and surgical procedures related to PNs
- Summary of post-treatment medications, medical conditions and surgical procedures not related to PNs

The number and percentages of subjects using each medication will be displayed together with the number and percentage of subjects using at least one medication or medical condition within each therapeutic class (ATC-Level 2), chemical subgroup (ATC-Level 4), and generic term.

Tables will be sorted by most frequent ATC followed by generic term.

All medication, medical condition and surgical procedures will be listed including verbatim descriptions and coded terms, and flags for prior and post-treatment.

Missing coding terms should be listed and summarised as "Not coded".

5.2.5 Safety

5.2.5.1 General considerations for safety assessments

In the setting of this non-interventional study there are no scheduled study visits. Based on the feasibility assessment, encounters between physicians and patients are anticipated to occur at a frequency of 6 to 12 months. All relevant clinical information (and respective dates of measurements/assessment) will be collected at each encounter throughout a patient's follow-up.

5.2.5.2 Safety Outcomes of Interest

An overview table will be provided for the Nested Prospective Cohort presenting the number and percentage of patients with:

- LVEF reduction (Present/ Absent)
- LVEF reduction at baseline (Present/ Absent)
- LVEF reduction (Present/ Absent) by LVEF reduction at baseline (Present/ Absent)
- Symptoms of present LVEF reduction (Symptomatic/ Asymptomatic)
- Symptoms of present LVEF reduction at baseline (Symptomatic/ Asymptomatic)
- Symptoms of present LVEF reduction (Present/ Absent) by symptoms of present LVEF reduction at baseline (Symptomatic/ Asymptomatic)
- Physeal dysplasia recorded in medical history (Recorded/ Not recorded)
- Physeal dysplasia detection (Present/ Absent)
- Physeal dysplasia detection (Present/ Absent) by physeal dysplasia recorded in medical history (Recorded/ Not recorded)
- Myopathy detection (Present/ Absent)
- Symptoms of present myopathy (Symptomatic/ Asymptomatic)
- Musculoskeletal examination result (Normal/ Abnormal, Not Clinically Significant/ Abnormal, Clinically Significant/ Not Done)

- Concurrent musculoskeletal symptoms (Yes/ No)
- Hepatotoxicity detection (Present/ Absent)
- Symptoms of present hepatotoxicity (Symptomatic/ Asymptomatic)
- Ocular toxicity detection (Present/ Absent)
- Ocular assessment at baseline (Normal/ Abnormal)
- Ocular toxicity detection (Present/ Absent) by Ocular assessment at baseline (Normal/ Abnormal)
- Sexual Maturation disorder assessment (Normal/Abnormal)
- Sexual Maturation disorder assessment at baseline(Normal/Abnormal)
- Sexual Maturation disorder assessment (Normal/Abnormal) by Sexual Maturation disorder assessment at baseline(Normal/Abnormal)
- Reason of abnormal sexual maturation disorder (Delayed Puberty/ Precocious Puberty)
- Reason of abnormal sexual maturation disorder at baseline (Delayed Puberty/ Precocious Puberty)
- Reason of abnormal sexual maturation disorder (Delayed Puberty/ Precocious Puberty) by Reason of abnormal sexual maturation disorder at baseline (Delayed Puberty/ Precocious Puberty)

The safety outcomes of interest as described above will be captured in the AE tables as well.

All safety outcomes of interest data will be listed.

Other cardiac tests including ECG and ECHOC will also be listed.

5.2.5.3 Adverse Events (AEs)

An overall summary table of the number of patients experiencing each category of AEs will be produced for the Nested Prospective Cohort. Analyses using the Nested Prospective Cohort will be restricted to AEs during treatment and AEs which occurred throughout the post- treatment period.

An overview table will summarize the number and percentage of patients with at least one of the following AEs, where patients with more than one AE in a particular category are counted only once in that category, as well as the absolute counts of number of AEs.

- Any AEs
- Any AEs with a reasonable possibility caused by treatment
- Any AEs with outcome of death
- Any AEs of CTCAE grade 3 or higher

- Any AEs of CTCAE grade 3 or higher with a reasonable possibility caused by treatment
- Any SAEs (including events with outcome of death)
- Any SAEs leading to permanent treatment discontinuation
- Any SAEs with a reasonable possibility caused by treatment
- Any AEs leading to permanent treatment discontinuation
- Any AEs leading to dose increase of study treatment
- Any AEs leading to dose reduction of study treatment
- Any AEs leading to dose interruption of study treatment
- Any AESIs
- Any AESIs of CTCAE grade 3 or higher
- Any AESIs with a reasonable possibility caused by treatment

The number and percentage of patients reporting each AE and the absolute count of AEs will be summarized by system organ class (SOC) and preferred term (PT). Tables will be sorted by international order for SOC and PTs will be sorted alphabetically. The following summaries will be produced using the Nested Prospective Cohort.

- All AEs;
- All AEs with a reasonable possibility caused by treatment;
- All AEs with CTCAE grade 3 or higher
- All AEs with CTCAE grade 3 or higher, with a reasonable possibility caused by treatment
- All AEs by maximum intensity;
- All AEs with a reasonable possibility caused by treatment by maximum CTC grade,
- All AEs leading to treatment discontinuation,
- All AEs with a reasonable possibility caused by treatment leading to treatment discontinuation,
- All SAEs,
- All SAEs with a reasonable possibility caused by treatment,
- All AEs with an outcome of death,
- All AEs with an outcome of death with a reasonable possibility caused by treatment
- All AESIs
- All AESIs with a reasonable possibility caused by treatment

All AE data will be listed appropriately for all patients including information on AE duration, intensity (ie. CTCAE grade), seriousness, action taken, outcome, causal relationship, timing of onset of AE in relation to the index date, study treatment at the time of event.

Special situations such as overdose, medication error and product complaint related data will be listed as well for all patients.

5.2.5.4 Deaths

Incidence of AE leading to death and primary cause of deaths reported during the study period will be presented. A data listing of all deaths will also be provided.

5.2.5.5 Laboratory Data

Laboratory chemistry data will be summarised and listed for the Nested Prospective Cohort.

Laboratory data outside the reference ranges will be indicated in the listings. If a subject has multiple results for a particular test at a particular assessment visit, the highest value will be used for the summary. System international (SI) units will be reported for all parameters.

More specifically, the following parameters will be summarised

- Chemistry: (Serum /Plasma) Creatine Kinase (CPK), (Serum /Plasma) Alanine Aminotransferase (ALT), (Serum /Plasma) Aspartate Aminotransferase (AST), (Serum /Plasma) Total bilirubin.

Descriptive summaries will be provided for both by-time windows measures and change from baseline measures.

In addition, the following summaries at each assessment visit will also be provided for each parameter:

- Shift tables of baseline versus maximum value for laboratory assessments recorded categorically.
- Listings of all laboratory values for each patient will be presented with abnormal and clinical significant values flagged.

Shift tables for laboratory values by worst common toxicity criteria (CTC) grade will be produced. For parameters with no CTCAE grading, shift tables from baseline to worst value on-treatment will be provided (i.e. on-treatment is defined as data collected up until the last dose of selumetinib).

5.2.5.6 Vital Signs

Vital signs, including height, weight and body surface area measured at baseline and follow-up assessment visits will be summarised and listed for the Nested Prospective Cohort.

Vital sign data absolute and change from baseline will be summarized at each time window with descriptive statistics. If a patient has multiple results for a particular measurement at a particular assessment visit the highest value will be used for the summary.

Vital signs will be listed including flags for clinical significance.

5.2.5.7 Exposure

Exposure (in months) to selumetinib i.e., total duration of study drug received will be summarised for the Nested Prospective Cohort separately and overall by country and site.

Total exposure and cumulative exposure (months) will be summarized by the following: mean, standard deviation, minimum, maximum, median and number of observations.

Descriptive summary statistics will also be obtained for year of initiation, and number of dose increases, reductions, discontinuations, or interruptions. The summaries will be provided for the Nested Prospective Cohort separately and overall by country and site.

Number of cycles will be presented using both descriptive statistics and categorically.

The cumulative dose (ie. the total dose received during the total exposure of selumetinib) will be summarised.

The dosage (mg/month) will be summarised and is calculated as:

The total cumulative dose received (mg)/ (Number of days receiving study drug) / (365.25 / 12)

The dose amount received at baseline will be summarized for the Base Cohort

In addition, the number and percentage of patients with at least one dose interruption, at least one dose increase and at least one dose reduction will be presented.

Exposure data will also be listed.

5.2.5.8 Pregnancy Report

Pregnancy related data will be listed only for the Nested Prospective Cohort.

6. BIAS

6.1 Methods to minimize bias

6.1.1.1 Information bias

The present study will be carried out using data recorded during routine clinical care. Some records are expected to be incomplete. In addition, the availability of the information in a patient's health record may depend on the study site and/or countries.

Given that the primary purpose of the study is to characterise the long-term safety profile of selumetinib in real-world practice, and that investigators participating in the study will treat the patient and provide data to a standard eCRF, this potential source of bias should be relatively minor with respect to these safety outcomes in the paediatric patient population. Nevertheless, it remains possible that participation in the study may lead to a more careful and comprehensive reporting of safety outcomes with a potential to overestimate their detection in routine clinical practice.

6.1.1.2 Selection bias

This study encompasses a self-selected population of paediatric patients with consenting parents / legal guardians and clinicians who have expressed their interest to participate. Participating investigators may be more likely to adopt new treatment options and may somehow differ from investigators who elect not to participate in the study. Similarly, the paediatric patients may have a profile not fully representative of the selumetinib treated population. However, several measures are introduced in the study design and analysis that can mitigate the potential for selection bias. First, the large number of study sites across numerous European countries can be anticipated to provide data representative of the treatment of NF1 patients with PN across Europe.

In addition, the enrolment of consecutive patients initiating selumetinib treatment at study sites, with inclusion and exclusion criteria that are well described in the protocol, will ensure that eligible patients at a given site have an equal chance of selection into the study.

6.2 Adjustment for multiple comparisons

Not Applicable.

7. ANNUAL PROGRESS REPORTS AND INTERIM ANALYSES

7.1 Annual Progress Reports

The annual progress reports (Quarter 3 (Q3) 2023, Q3 2024, Q3 2025, Q3 2026) will include relevant information to document the progress of the study such as patient disposition and safety data.

The below will be produced regarding the annual progress reports:

Patient disposition in terms of a listing and summary by country, site and overall will be presented. The number and percentage of patients satisfying each of the following will be presented for all enrolled patients:

- Enrolled
- Previously treated under the Early Access Program (EAP) (Yes/No)
- Discontinued treatment and associated reasons
- Ongoing in the study at the data cut off
- Completed the study
- Discontinued from the study and associated reasons

The number of patients in each of the analysis sets (i.e., the Base and Nested Prospective Cohorts) will be summarised for all enrolled patients.

Summaries and listings will be presented of demographic characteristics as described in section 5.2.2
An overview table of the number and percentage of patients with at least one AE as well as the absolute counts of number of AEs, will be presented for the following categories for the Nested Prospective Cohort:

- Any AEs
- Any AEs with a reasonable possibility caused by treatment
- Any AEs with outcome of death
- Any AEs of CTCAE grade 3 or higher
- Any AEs of CTCAE grade 3 or higher with a reasonable possibility caused by treatment
- Any SAEs (including events with outcome of death)
- Any SAEs leading to permanent treatment discontinuation
- Any AEs leading to permanent treatment discontinuation
- Any AEs leading to dose increase of study treatment
- Any AEs leading to dose reduction of study treatment
- Any AEs leading to dose interruption of study treatment
- Any AESIs
- Any AESIs of CTCAE grade 3 or higher

- Any AESIs with a reasonable possibility caused by treatment

An AE and SAE listing will also be presented.

Exposure data as described in section 5.2.5.7 will be presented.

7.2 Interim Analysis

Interim analysis will be conducted at the end of enrolment (Q3 2024) to present all baseline data for patients in the Base Cohort and the Nested Prospective Cohort separately and selected follow-up safety data for the patients in the Nested Prospective Cohort.

The below will be produced regarding the interim analysis:
All data mentioned above for the annual progress reports will also be produced for the interim analysis.

Additional outputs will include the below:

Summaries and a listing of clinical characteristics as described in section 5.2.2.
An overview table for the Nested Prospective Cohort, presenting the number and percentage of patients with the respective exact Clopper – Pearson 95 CIs for the safety outcomes of interest as described in section 5.2.5.2. A listing will also be provided.
Medical or surgical history summaries by SOC and PT overall along with a listing for the Base Cohort and Nested Prospective Cohort.

All medication, medical condition and surgical procedures summaries and listing as described in section 5.2.4

Summaries and listings of laboratory data as described in section 5.2.5.5

The following summaries using the Nested Prospective Cohort by SOC and PT:

- All AEs;
- All AEs with a reasonable possibility caused by treatment;
- All AEs with CTCAE grade 3 or higher
- All AEs with CTCAE grade 3 or higher, with a reasonable possibility caused by treatment
- All AEs by maximum intensity;
- All AEs with a reasonable possibility caused by treatment by maximum CTC grade,
- All AEs leading to treatment discontinuation,
- All AEs with a reasonable possibility caused by treatment leading to treatment discontinuation,
- All SAEs,
- All SAEs with a reasonable possibility caused by treatment,
- All AEs with an outcome of death,
- All AEs with an outcome of death with a reasonable possibility caused by treatment
- All AESIs
- All AESIs with a reasonable possibility caused by treatment

7.3 Final Analysis

All data mentioned above for the annual progress reports and interim analysis will also be produced for the final analysis inclusive of all data as described in sections 4.2.1 and 5.

8. CHANGES OF ANALYSIS FROM PROTOCOL

AEs will be collected and summarized only for patients in the Nested Prospective Cohort.

Site type (academic, community, or hospital) is not collected (during eCRF design it was agreed the item was non-critical). Summaries will be provided by country and site instead of country and type of clinic/site.

9. REFERENCES

Not Applicable.

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d1346r00004-sap-ed-1		
Document Title:	Statistical Analysis Plan Edition 1	
Document ID:	Doc ID-004963609	
Version Label:	1.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
02-Sep-2022 06:12 UTC	PPD (Alexion)	Author Approval

Notes: (1) Document details as stored in CCI an AstraZeneca document management system.

PASS Protocol

Active substance	Selumetinib
Product reference	D1346R00004
Version number	Protocol, Version 2.0
Date	05 November 2021

Post-Authorisation Safety Study of Paediatric Patients Initiating Selumetinib: A Multiple-Country Prospective Cohort Study

Marketing Authorisation Holder

Marketing authorisation holder	AstraZeneca AB, 151 85 Södertälje, Sweden
MAH contact person	PPD

KOSELUGO™ is a trademark of the AstraZeneca group of companies.

This document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Approved by:

PPD

Electronic signature is available at the end of the document

PASS INFORMATION

Title	Post-Authorisation Safety Study of Paediatric Patients Initiating Selumetinib: A Multiple-Country Prospective Cohort Study
Protocol version identifier	2.0
Date of last version of protocol	05 August 2021
EU PAS register number	Study not yet registered
Active substance	Selumetinib
Medicinal product	Selumetinib (KOSELUGO)
Product reference	EMEA/H/C/005244
Procedure number	EMEA/H/C/PSP/S/0095
Marketing authorisation holder(s)	AstraZeneca AB, 151 85 Södertälje, Sweden
Joint PASS	No
Research question and objectives	The primary objective of this study is: • To characterise the safety of selumetinib, including long-term safety, in paediatric patients with NF1-related symptomatic, inoperable PN, 8 to < 18 years old who have not reached Tanner Stage V at the start of selumetinib treatment. The secondary objective of this study is: • To describe the paediatric population 3 to < 18 years old with NF1-related symptomatic inoperable PN who start selumetinib in routine clinical practice.
Countries of study	Up to 12 European countries
Authors	PPD

1 TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

2 LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADR	Adverse Drug Reaction
AE	Adverse event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AZ	AstraZeneca
BMI	Body Mass Index
CI	Confidence Interval
CPK	Creatine Phosphokinase
CRF	Case Report Form
CRO	Contract Research Organisation
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practice
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IR	Incidence Rate
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology

Abbreviation or special term	Explanation
LFT	Liver Function Test
LVEF	Left ventricular ejection fraction
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MEK 1/2	Mitogen-Activated Protein Kinases 1 And 2
MRI	Magnetic Resonance Imaging
NF1	Neurofibromatosis Type 1
OCT	Optical Coherence Tomography
PASS	Post-authorisation Safety Study
PN	Plexiform Neurofibroma
PSUR	Periodic Safety Update Reports
Q1	Quarter 1
Q2	Quarter 2
Q3	Quarter 3
QC	Quality Control
RMP	Risk Management Plan
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
UK	United Kingdom

3 RESPONSIBLE PARTIES

AstraZeneca	
PPD AstraZeneca City House, 126-130 Hills Road Cambridge, United Kingdom	
PPD	

MSD or Merck, Sharpe & Dohme	
PPD	

4 ABSTRACT

4.1 Title

Post-Authorisation Safety Study of Paediatric Patients Initiating Selumetinib: A Multiple-Country Prospective Cohort Study

4.2 Rationale and Background

Neurofibromatosis type 1 (NF1) is a rare, autosomal dominant genetic disorder that is caused by germline mutations in the NF1 tumour suppressor gene, which encodes the tumour suppressor protein neurofibromin 1. Plexiform neurofibromas (PN) are histologically benign nerve sheath tumours, which typically grow along large nerves and plexi.

On 5 March 2020, a centralised Marketing Authorisation Application was submitted to the European Medicines Agency (EMA), with approval received on 17 June 2021.

As part of the approval process, a Risk Management Plan (RMP) was developed and submitted to the EMA to summarise the safety concerns emerging from the clinical development program. The RMP included additional pharmacovigilance plans for a non-interventional Post-authorisation Safety Study (PASS) to further characterise the safety of selumetinib in paediatric patients with NF1-related PN in routine clinical practice.

The planned non-interventional PASS will address gaps in knowledge identified by the RMP, including the important identified risk and some of the potential risks and missing information on long-term developmental toxicity in children, by characterising the safety profile associated with selumetinib use among paediatric patients (ages > 8 to < 18 years old) with a diagnosis of NF1 with symptomatic, inoperable PN.

This study is a specific obligation in the context of a conditional marketing authorisation for selumetinib (ie, Category 2 PASS). Study results will contribute to updating the safety profile of selumetinib in a relatively large population of patients with different personal characteristics across multiple health care systems and patterns of real-world clinical practice in the European Union (EU) and in the UK.

The study will enrol 2 cohorts:

1 The Base Cohort includes all enrolled patients aged 3 to < 18 years.

2 The Nested Prospective Cohort will include the subset of Base Cohort patients aged 8 to < 18 years who have not reached Tanner Stage V on the index date.

4.3 Research Question and Objectives

The primary objective of this study is:

- To characterise the safety of selumetinib, including up to 5 years of long-term safety, in paediatric patients with NF1-related symptomatic, inoperable PN, 8 to < 18 years old who have not reached Tanner Stage V at the start of selumetinib treatment (Nested Prospective Cohort).

The secondary objective of this study is:

- To describe the demographic and clinical profile of the paediatric population 3 to < 18 years old with NF1-related symptomatic inoperable PN who start selumetinib in routine clinical practice (Base Cohort).

4.4 Study Design

This is a cohort study of paediatric patients (aged 3 to 18 years of age) with NF1 with symptomatic, inoperable PNs who begin selumetinib treatment at study sites across several European countries where selumetinib has been marketed for use.

Selumetinib treatment will remain a decision of the treating clinicians and is not mandated by this study protocol. All patients prescribed selumetinib at the study sites in the usual manner and according to the terms of the marketing authorisation will be invited to participate in the study. Patients who meet the eligibility criteria, including parental/legal guardian consent to participation, will be enrolled.

Patients will be enrolled over a period of 2 years and assigned an index date (Day 1) defined as the date of first prescription of selumetinib. Baseline data will be collected at enrolment through retrospective chart abstraction from Day -365 to Day -1.

The Nested Prospective Cohort of patients (aged 8 to <18 years who have not reached Tanner Stage V on the index date) will be followed prospectively to further characterise the safety of selumetinib. Data from this cohort will be collected on the occurrence of the safety outcomes of interest identified in Section 4.6 (Table 1).

Enrolment will occur at up to 36 sites in up to 12 European countries, after commercial launch of selumetinib in each participating country. To meet study timelines and minimize any delay in delivering the study results, countries where selumetinib is first available will be selected for the study.

4.5 Population

The target population for this study are patients with NF1 with symptomatic, inoperable PN who have been prescribed at least 1 dose of selumetinib and who are aged 3 to < 18 years at the start of selumetinib treatment, except for those patients receiving treatment with a mitogen-activated protein kinase inhibitor before the index date.

The study will enrol 2 cohorts:

1 The Base Cohort includes all enrolled patients aged 3 to < 18 years.

2 The Nested Prospective Cohort will include the subset of Base Cohort patients aged 8 to < 18 years who have not reached Tanner Stage V on the index date.

4.6 Variables

The following baseline data will be collected via medical chart abstraction for all patients in the Base Cohort, where baseline will include the most recent assessments made within 365 days before the index date. For repeated measurements during the baseline period, the value closest in time to the index date will be taken:

- Demographics: Age, sex, height, weight, Tanner staging level, and ethnicity (where allowed by General Data Protection Regulation/privacy laws)
- Clinical characteristics: PN(s) (number, location, classification and morbidities), prior medication and relevant procedures, concomitant medications, comorbidities, date of initial NF1 and PN diagnosis, NF1 origin (familial or spontaneous), and genetic testing results

To monitor long-term safety, all patients in the Nested Prospective Cohort will be followed for up to 5 years under conditions of routine clinical care to collect data on the occurrence of the safety outcomes of interest listed in Table 1. These safety outcomes have been chosen to characterise the important identified risk (Left ventricular ejection fraction [LVEF] reduction), the important potential risks (physeal dysplasia, ocular toxicity, myopathy, and hepatotoxicity), and the missing information on long-term exposure described in the RMP; to describe any developmental toxicity during selumetinib use in children; and to further characterise the frequency and severity of safety outcomes (Table 1) and adverse events (AEs) occurring during selumetinib treatment in real-world clinical practice.

Patient who may discontinue selumetinib treatment are to continue in the study for long-term safety follow-up assessment, unless consent is withdrawn.

All concomitant medications, including those taken due to AEs, are to be recorded on an electronic case report form (eCRF).

Table 1 Safety Outcomes of Interest and Corresponding Clinical Assessment[a]

EU-RMP Safety Concern	PASS Outcome	Collected Data and Outcome Definition
LVEF reduction	LVEF reduction	LVEF reduction will be detected as present or absent and when present if symptomatic or asymptomatic. All cardiac tests conducted will be collected
Physeal dysplasia	Physeal dysplasia	Physeal dysplasia will be detected as present or absent based on the physician reading of: • MRI: Knee (preferred) or wrist • X-ray: Knee (preferred) and/or wrist to assess growth plate • Height and weight records
Myopathy	Rise of serum creatine phosphokinase levels AND concurrent musculoskeletal symptoms	A clinically meaningful rise in serum creatine phosphokinase (eg, above the normal limit or increase by 1 or more CTCAE grade shift) combined with musculoskeletal symptoms will be detected as present or absent based on the physician's reading, as a marker of potential myopathy
Hepatotoxicity	Rise in transaminase (ALT and AST) and concurrent rise in bilirubin	A clinically meaningful rise in the measured levels (eg, above the normal limit or increase by 1 or more CTCAE grade shift) will be detected as present or absent, and when present if symptomatic or asymptomatic, as a marker of potential hepatotoxicity
Ocular toxicity	Abnormalities of ophthalmological examination (eg, vision changes, IOP, etc)	An abnormal ocular examination will be detected as present or absent based on the physician's reading, as a marker of potential ocular toxicity
Sexual maturation disorder (abnormal pubertal development)	Abnormal pubertal development	Tanner staging criteria (Stages I-V). Abnormal pubertal development will require interpretation by the Investigator with respect to Tanner Stage in the context of the patient's age; recorded as normal or abnormal (if abnormal, further specified as

EU-RMP Safety Concern	PASS Outcome	Collected Data and Outcome Definition
		delayed puberty or precocious puberty)

[a] All haematic and clinical test results will be collected as available.
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; EU = European Union; IOP = intraocular pressure; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PASS = post-authorisation safety study; RMP = Risk Management Plan.

The feasibility analysis suggested that the majority of safety outcomes will be captured in the course of routine clinical care, but some study outcomes might not be routinely captured for all patients.

Exposure to selumetinib will be collected from the index date to the date of the last dose of selumetinib using a standardised eCRF that captures, eg, date(s), selumetinib dose (daily and cumulative), treatment cycles, treatment modification(s) (including interruption, dose reduction, and discontinuation), and associated reasons.

4.7 Data Sources

Baseline data will be abstracted from medical charts (either electronic or paper) by trained site staff and entered into a standard eCRF.

All follow-up data will be entered directly into eCRFs provided to participating study physicians, with a specific focus on safety outcomes of interest.

4.8 Study Size

The target enrolment for the Base Cohort is 125 patients. Of these, approximately 100 patients are expected to meet eligibility criteria for the Nested Prospective Cohort.

4.9 Statistical Analysis

Tabular summaries will be provided for the baseline characteristics of the Base Cohort. Demographic and clinical characteristics data obtained at baseline will be summarised using descriptive statistics: mean, standard deviation, median, minimum and maximum for continuous variables and number and percentages for categorical variables.

Safety outcomes of interest will be summarised at each follow-up visit. For each outcome cumulative incidence and incidence rate with 2-sided 95% exact confidence interval will be provided.

Descriptive summary statistics will be obtained for duration of exposure to selumetinib, cumulative exposure to selumetinib, and number of dose reductions, discontinuations, or interruptions.

The frequency of missing values for each variable will be examined and evaluated to determine whether data are missing at random in the data source.

Details of the statistical analysis are described in the Statistical Analysis Plan, including detailed information on any interim analyses and on the final statistical analysis.

4.10 Milestones

See protocol Section 6 (Table 3) for the study milestones.

5 AMENDMENTS AND UPDATES

Table 2 Protocol Amendments and Updates

Number	Date	Section of study protocol	Amendment or update	Reason
Protocol Version 2.0	*05 Nov 2021*	*Synopsis, Section 4.4 & 9.2*	Updated the list of participating countries	To permit countries where selumetinib is first available to participate in the study.
		Section 4.4 & 9.1	Confirmed selumetinib will be prescribed according to the terms of the marketing authorisation	Response to comments from EMA
		Section 6	Revised the timing of study milestones	Updated to reflect current status
		Section 11.4.3	Clarified the reporting of important risks per the EU RMP and the application of follow-up questionnaires	Response to comments from EMA

6 MILESTONES

Table 3 Study Milestones

Milestone	Planned date
Start of data collection	Q2 2022
End of data collection	Q2 2027
Annual progress reports	Q3 2023 Q3 2024 Q3 2025 Q3 2026
Interim analysis	Q3 2024
Final report of study results	31 March 2028

Abbreviations: Q2 = Quarter 2; Q3 = Quarter 3.
Study milestones are planned on the assumption that selumetinib will be available for prescribing in all study countries by Q1 2022. Those might be subject to variations based on enrolment rate and other external factors.

The statistical analyses for each milestone (Table 3) will be provided in the SAP.

7 BACKGROUND AND RATIONALE

7.1 Background

Neurofibromatosis type 1 is a rare, autosomal dominant genetic disorder that is caused by germline mutations in the NF1 tumour suppressor gene, which encodes the tumour suppressor protein neurofibromin 1. Plexiform neurofibromas are histologically benign nerve sheath tumours, which typically grow along large nerves and plexi.

In the pivotal Phase 2 study (Study D1532C00057) that led to marketing authorisation in the United States, selumetinib was well tolerated in paediatric patients with NF1 and inoperable PN. The median total treatment duration was 2.2 years at twice-daily doses of 25 mg/m^2. The most commonly reported (≥70% of patients) AEs were vomiting (41 [82.0%] patients), blood CPK increased (38 [76.0%] patients) and diarrhoea (35 [70.0%] patients). All of these AEs are well characterised ADRs for selumetinib. Generally, AEs were mild or moderate in severity and most resolved whilst on treatment. Others were successfully managed by either dose modification or with additional intervention (symptomatic/supportive treatment). Most SAEs were managed with intervention (symptomatic/supportive treatment) and/or dose modification. The majority of patients recovered without selumetinib discontinuation. Patients were to be followed annually (±2 months) for either 7 years following initiation of treatment or 5 years after study drug discontinuation, whichever was longer; the last patient was enrolled on 22 August 2016. Selumetinib monotherapy was well tolerated and had a manageable safety profile in these paediatric patients.

7.2 Rationale

On 5 March 2020, a centralised MAA was submitted to the EMA, with approval received on 17 June 2021.

As part of the approval process, an RMP was developed and submitted to the EMA to summarise the safety concerns emerging from the clinical development program. The RMP included plans for a non-interventional PASS to further characterise the safety of selumetinib in paediatric patients with NF1-related PN receiving treatment in routine clinical practice.

The RMP version 1.0 (succession 4) approved by EMA on 22 April 2021 had 1 important identified risk with selumetinib treatment:

- LVEF reduction

The RMP also identified 5 important potential risks with selumetinib treatment:

- Physeal dysplasia
- Ocular toxicity

- Myopathy
- Hepatotoxicity
- Choking on the capsule

Long-term exposure (including long-term safety data on developmental toxicity in children) was identified in the RMP as an area of missing information.

This study will address gaps in knowledge identified by the RMP, including the important identified risk and some of the potential risks and missing information on long-term developmental toxicity in children, by characterising the safety profile associated with selumetinib use among paediatric patients (ages ≥ 8 to < 18 years old) with a diagnosis of NF1 with symptomatic, inoperable PN. Conduct of this study is a specific obligation in the context of a conditional marketing authorisation for selumetinib (ie, Category 2 PASS). Study results will contribute to updating the safety profile of selumetinib in a relatively large population of patients with different personal characteristics across multiple health care systems and patterns of real-world clinical practice in the EU and in the UK.

8 RESEARCH QUESTION AND OBJECTIVES

The primary objective of this study is:

- To characterise the safety of selumetinib, including up to 5 years of long-term safety, in paediatric patients with NF1-related symptomatic, inoperable PN, 8 to < 18 years old who have not reached Tanner Stage V at the start of selumetinib treatment (Nested Prospective Cohort).

The secondary objective of this study is:

- To describe the demographic and clinical profile of the paediatric population 3 to < 18 years old with NF1-related symptomatic inoperable PN who start selumetinib in routine clinical practice (Base Cohort).

For details on the outcomes related to the primary objective, see Section 9.3.

9 RESEARCH METHODS

9.1 Study Design

This is a cohort study of paediatric patients (aged 3 to 18 years of age) with NF1 with symptomatic, inoperable PNs who begin selumetinib treatment at study sites across several European countries where selumetinib has been marketed for use.

Selumetinib treatment will remain a decision of the treating clinicians and is not mandated by this study protocol. All patients prescribed selumetinib at the study sites in the usual manner and according to the terms of the marketing authorisation will be invited to participate in the study. Patients who meet the eligibility criteria, including parental/legal guardian consent to participation, will be enrolled.

The patient enrolment period will begin once the first patient is enrolled and end 2 years after that date (estimated end of enrolment = Q2 2024). Patients may continue in the study until the study end date which is 5 years after the first patient enrolment date (estimated end of study = Q2 2027). Each enrolled patient will be assigned an index date (Day 1) defined as the date of first prescription of selumetinib. Baseline data will be collected at enrolment through retrospective chart abstraction from Day -365 to Day -1.

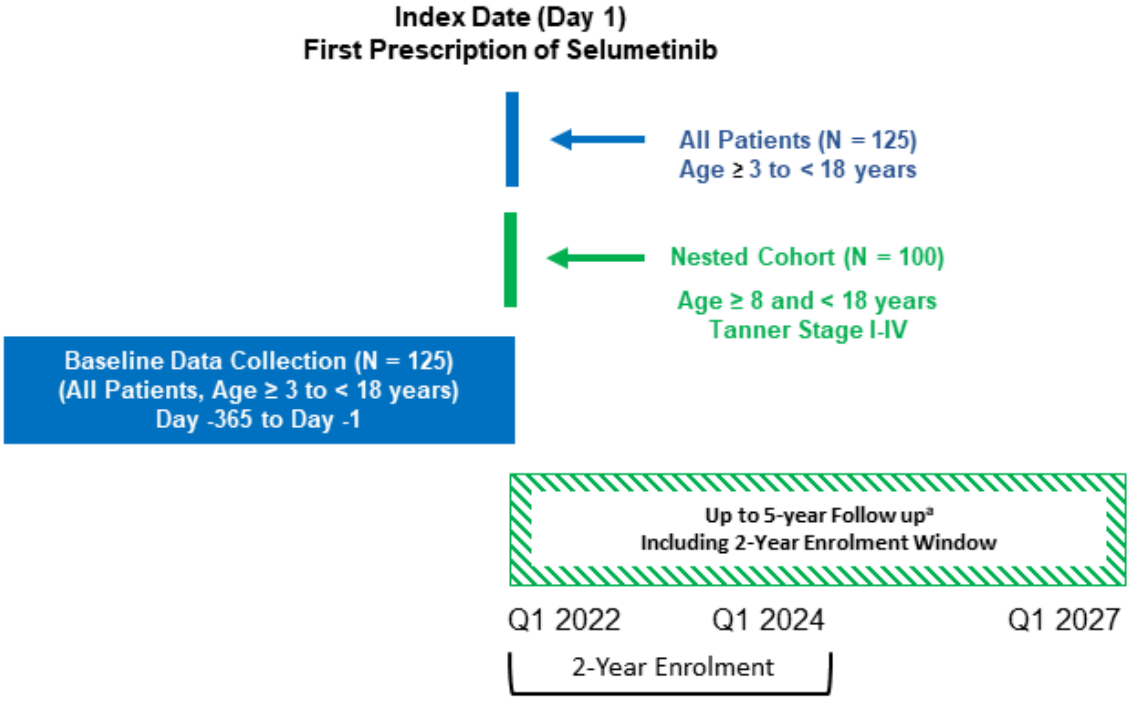
An eligible subset of patients (aged 8 to < 18 years who have not reached Tanner Stage V on the index date) will be enrolled in the Nested Prospective Cohort. Data will be collected following the first dose of selumetinib (Day 1) for the duration of the study and will focus on assessing the safety outcomes of interest identified in Section 9.3.2 (see Table 4).

Patients in the Nested Prospective Cohort will be followed from the index date to the censor date, defined as the earliest of the end of the 5-year study period, study withdrawal, loss to follow-up, or death. The 5-year study period is defined as a maximum of 5 years from the time the first patient is enrolled (estimated time period = Q2 2022 to Q2 2027).

Whether to treat the patient with selumetinib will be based on the decision of the prescribing physician under conditions of routine clinical care. Participating study sites will treat patients according to normal clinical practice and no intervention will be assigned.

The study schematic is shown below in Figure 1.

Figure 1 Study Schema



[a] Patients in the Nested Prospective Cohort will be followed from index date to the censor date, defined as the earliest of the end of the 5-year study period, study withdrawal, loss to follow-up, or death.

9.2 Setting

This study will be conducted in up to 36 specialist clinics for the treatment of paediatric patients with NF1 across up to 12 European countries.

The study observation period is anticipated to begin in Q2 of 2022, with some variation by country. Patients will be enrolled after commercial launch of selumetinib in each participating country, when patients/physicians have access to medicine as part of standard clinical practice.

The target population for this study are patients with NF1 in the EU with symptomatic, inoperable PN who have been prescribed at least 1 dose of selumetinib and who are aged 3 to < 18 years at the start of selumetinib treatment, except for those patients receiving treatment with a mitogen-activated protein kinase inhibitor before the index date.

The study will enrol 2 cohorts:

1 The Base Cohort includes all enrolled patients aged 3 to <18 years.

2 The Nested Prospective Cohort will include the subset of Base Cohort patients aged 8 to <18 years who have not reached Tanner Stage V on the index date.

Patient screening will be conducted throughout the enrolment period and baseline data for all patients will be abstracted from medical records. Those meeting the criteria for enrolment in the Nested Prospective Cohort will be followed up during their routine encounters with the treating clinician (expected to occur every 6 to 12 months) for up to 5 years.

A site may have multiple eligible patients and there will be a limit on the number of patients per site to ensure appropriate representation of patients, given that treatments administered may vary across sites and countries.

This study protocol will be adopted at each study site. An SAP will be prepared by the study CRO for AZ approval before performing the analysis.

9.2.1 Eligibility Criteria

All patients meeting study inclusion and not meeting exclusion criteria will be eligible for the study.

9.2.1.1 Inclusion Criteria

Patients are eligible to be included in the study only if all the following criteria apply:

1 Have been diagnosed with NF1 with symptomatic, inoperable PN
2 Have been newly prescribed at least one dose of selumetinib
3 Are aged 3 years and above, and are < 18 years of age on the index date
4 Parent or legal guardian, as required by country-specific regulation, have provided informed consent (see Section 10.1) (unless a country-specific waiver is obtained)

Additional Criteria for Nested Prospective Cohort

5 Are at least 8 years old and
6 Are prior to attainment of Tanner Stage V on the index date

9.2.1.2 Exclusion Criteria

Patients are excluded from the study if the following criteria applies:

1 Have received treatment with a mitogen-activated protein kinase inhibitor before the index date
2 Are participating in a randomised controlled trial

9.3 Variables

Study variables will be collected as detailed below:

9.3.1 Baseline Data

The following baseline data will be collected via medical chart abstraction for all patients in the Base Cohort, where baseline will include the most recent assessments made within 365 days before the index date. For repeated measurements during the baseline period, the value closest in time to the index date will be taken:

- **Demographics**: Age, sex, height, weight, Tanner staging level, and ethnicity (where allowed by GDRP/privacy laws)
- **Clinical characteristics**: PN(s) (number, location, classification and morbidities), prior medication and relevant procedures, concomitant medications, comorbidities, date of initial NF1 and PN diagnosis, NF1 origin (familial or spontaneous), and any genetic testing results

9.3.2 Outcomes – Nested Prospective Cohort

To monitor long-term safety, all patients in the Nested Prospective Cohort will be followed for up to 5 years under conditions of routine clinical care to collect data on the occurrence of the safety outcomes of interest listed in Table 4. These safety outcomes have been chosen to characterise the important identified risk (LVEF reduction), the important potential risks (physeal dysplasia, ocular toxicity, myopathy, and hepatotoxicity), and the missing information on long-term exposure described in the RMP; to describe any developmental toxicity during selumetinib use in children; and to further characterise the frequency and severity of safety outcomes of interest (Table 4) and AEs occurring during selumetinib treatment in real-world clinical practice.

Patients who may discontinue selumetinib treatment are to continue in the study for long-term safety follow-up assessment, unless consent is withdrawn.

All concomitant medications, including those taken due to AEs, are to be recorded on an eCRF.

Table 4 Safety Outcomes of Interest and Corresponding Clinical Assessment[a]

EU-RMP Safety Concern	PASS Outcome	Collected Data and Outcome Definition
LVEF reduction	LVEF reduction	LVEF reduction will be detected as present or absent and when present if symptomatic or asymptomatic. All cardiac tests conducted will be collected
Physeal dysplasia	Physeal dysplasia	Physeal dysplasia will be detected as present or absent based on the physician reading of: • MRI: Knee (preferred) or wrist • X-ray: Knee (preferred) and/or wrist to assess growth plate • Height and weight records
Myopathy	Rise of serum creatine phosphokinase levels AND concurrent musculoskeletal symptoms	A clinically meaningful rise in serum creatine phosphokinase (eg, above the normal limit or increase by 1 or more CTCAE grade shift) combined with musculoskeletal symptoms will be detected as present or absent based on the physician's reading, as a marker of potential myopathy
Hepatotoxicity	Rise in transaminase (ALT and AST) and concurrent rise in bilirubin	A clinically meaningful rise in the measured levels (eg, above the normal limit or increase by 1 or more CTCAE grade shift) will be detected as present or absent, and when present if symptomatic or asymptomatic, as a marker of potential hepatotoxicity
Ocular toxicity	Abnormalities of ophthalmological examination (eg, vision changes, IOP, etc)	An abnormal ocular examination will be detected as present or absent based on the physician's reading, as a marker of potential ocular toxicity
Sexual maturation disorder (abnormal pubertal development)	Abnormal pubertal development	Tanner staging criteria (Stages I-V). Abnormal pubertal development will require interpretation by the Investigator with respect to Tanner Stage in the context of the patient's age; recorded as normal or abnormal (if abnormal, further specified as

EU-RMP Safety Concern	PASS Outcome	Collected Data and Outcome Definition
		delayed puberty or precocious puberty)

[a] All haematic and clinical test results will be collected as available.
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; EU = European Union; IOP = intraocular pressure; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PASS = post-authorisation safety study; RMP = Risk Management Plan.

The feasibility analysis suggested that the majority of safety outcomes will be captured in the course of routine clinical care, but some study outcomes might not be routinely captured for all patients.

In the setting of a non-interventional study there are no scheduled study visits. Based on the feasibility assessment, encounters between physicians and patients are anticipated to occur at a frequency of 6 to 12 months. All relevant clinical information (and respective dates of measurements/assessment) will be collected at each encounter throughout a patient's follow-up.

9.3.3 Exposure

Exposure to selumetinib will be collected from the index date to the date of the last dose of selumetinib using a standardised electronic eCRF that captures, eg, date(s), selumetinib dose (daily and cumulative), treatment cycles, treatment modification(s) (including interruption, dose reduction, and discontinuation), and associated reasons.

9.3.4 Other Variables and Covariates

In addition to the demographic and clinical characteristics noted above that will be collected at baseline, the following data will be collected throughout follow-up:

- Height (cm)
- Weight (kg)
- Body surface area
- Tanner staging (level from I to V)
- Concomitant medications, including any medications used to treat AEs
- Comorbidities
- NF1-related clinical manifestation and complications
- PN-related variables (including for any clinically important target PNs)
- PN-related symptoms/morbidities

- Number of PN-related morbidities
- Number of PN(s), PN location(s), PN size(s), size change (if available)

9.3.4.1 Site Characteristics

The following data will be collected at local participating sites:

- Location (country)
- Type (academic, community, or hospital)

9.4 Data Sources

Baseline data will be abstracted from medical charts (either electronic or paper) by trained site staff and entered into a standard eCRF. All follow-up data will be entered directly into CRFs provided to participating study physicians at each study visit, with a specific focus on safety outcomes of interest.

Data collection and validation procedures will be provided in the study manuals.

9.5 Study Size

The target enrolment for the Base Cohort is 125 patients. Of those, approximately 100 patients are expected to meet eligibility criteria for the Nested Prospective Cohort. For details of sample size calculation, see Section 9.7.8.

9.6 Data Management

Routine procedures performed at each site will be recorded in electronic files, maintaining security and data confidentiality, following analysis plans, and performing QC checks of all eCRF's. Each site will maintain any patient-identifying information securely on site according to internal SOPs or guidance documents.

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff.

Appropriate data storage and archiving procedures will be followed (ie, storage on secure servers), with periodic backup of files. Standard procedures will be in place at each research centre to restore files in the event of a hardware or software failure.

9.7 Statistical Analysis

9.7.1 Statistical Methods – General Consideration

All statistical analyses will be performed by the study CRO, after AZ review and approval of an SAP. Analyses supporting the milestones (Table 3) will be provided in the SAP.

The analysis populations that will be used in reporting are:

1 The set of All Enrolled Patients (the Base Cohort)
2 The set of Nested Prospective Patients (the Nested Prospective Cohort)

Tabular summaries will be provided for the baseline characteristics of the Base and Nested Prospective Cohorts. Demographic and clinical characteristics data obtained at baseline will be summarised using descriptive statistics. Unless otherwise specified, baseline is defined as the last assessment made within the 365 days prior to initiation of selumetinib treatment (ie, index date). Categorical data will be summarised by the number and percentage of subjects in each category. Continuous variables will be summarised by descriptive statistics including number of patients, mean, standard deviation, median, minimum, and maximum.

For each analysis population, tabular summaries will be provided for the overall population and by country and type of clinic/site. Additional details of the statistical analyses will be provided in the SAP, including detailed information on any interim analyses and final statistical analysis. The SAP will be finalised prior to the beginning of analyses. The definitions of derived variables will be described. For any time to event analyses, data will be censored for patients when lost to follow-up or study end (ie, still alive as of their last visit/contact prior to data cut-off).

9.7.2 Research Objectives

9.7.2.1 Primary Objective: Safety Outcomes of Interest

In the Nested Prospective Cohort, for each safety outcome of interest, the cumulative incidence and IR (as best appropriate) and corresponding 2-sided 95% CI estimates will be provided using relevant data collected at each follow-up visit throughout follow-up. These statistics will be provided for the overall population as well as by country and type of clinic/site within country.

Any additional analysis of these outcomes will be described in the SAP.

9.7.2.2 Secondary Objective: Describe the Paediatric Population

Baseline data collected from the Base Cohort will include patient characteristics (demographic and clinical) and site characteristics. Baseline data will be summarised as appropriate, for the overall population and by type of clinic/site, as described in the corresponding section of this protocol. Any additional analysis of these outcomes will be described in the SAP.

9.7.3 Exposure

The beginning of exposure will be the date of initiation of selumetinib treatment (index date) and the end of exposure will be estimated as the date of the last dose of selumetinib being prescribed. Dose amount will be obtained at baseline for all patients and at each follow-up

visit for the Nested Prospective Cohort. Descriptive summary statistics will be obtained for dose amount of selumetinib received at baseline, duration of exposure to selumetinib, cumulative exposure to selumetinib, year of initiation, and number of dose reductions, discontinuations, or interruptions. The summaries will be provided for the overall population and by country and type of clinic/site. Any additional analysis of exposure data will be described in the SAP.

9.7.4 Demographic and Clinical Characteristics

Demographic and clinical characteristics data obtained at baseline will be summarised using descriptive statistics: mean, standard deviation, median, minimum, and maximum for continuous variables and number and percentages for categorical variables.

9.7.5 Subgroups Analyses

Sub-group analyses may be conducted and will be described in the SAP as required. Additional sensitivity analyses may be performed to evaluate potential for bias, and will be described in the SAP as required.

9.7.6 Methods to Minimise Bias

9.7.6.1 Information Bias

The present study will be carried out using data recorded during routine clinical care. Some records are expected to be incomplete. In addition, the availability of the information in a patient's health record may depend on the study site and/or countries.

Given that the primary purpose of the study is to characterise the long-term safety profile of selumetinib in real-world practice, and that investigators participating in the study will treat the patient and provide data to a standard eCRF, this potential source of bias should be relatively minor with respect to these safety outcomes in the paediatric patient population. Nevertheless, it remains possible that participation in the study may lead to a more careful and comprehensive reporting of safety outcomes with a potential to overestimate their detection in routine clinical practice.

9.7.6.2 Selection Bias

This study encompasses a self-selected population of paediatric patients with consenting parents/legal guardians and clinicians who have expressed their interest to participate. Participating investigators may be more likely to adopt new treatment options and may somehow differ from investigators who elect not to participate in the study. Similarly, the paediatric patients may have a profile not fully representative of the selumetinib treated population. However, several measures are introduced in the study design and analysis that can mitigate the potential for selection bias. First, the large number of study sites across numerous European countries can be anticipated to provide data representative of the treatment of NF1 patients with PN across Europe.

In addition, the enrolment of consecutive patients initiating selumetinib treatment at study sites, with inclusion and exclusion criteria that are well described in the protocol, will ensure that eligible patients at a given site have an equal chance of selection into the study. Information regarding physician and hospital characteristics will be collected and analytical approaches will be applied in the analyses if marked differences are observed in the study population as provided in the SAP.

9.7.7 Missing Data

Missing data is likely to be present in retrospective medical chart review studies. An assessment of the extent and mechanism of missingness in measurements relevant to key study variables and critical data elements is, therefore, an important component of site feasibility assessment. Efforts will be made to ensure that sites with reasonable amount of key data elements (eg baseline characteristics; treatment history; ability to collect outcome measures) are provided the opportunity to participate in the study.

The number of missing values for key data elements will be reported, and the likely impact of missing data on the analysis and the pattern of the missing information will be assessed. If systematic patterns are observed, adjustments may be made to account for missing data, Details and conventions of missing data handling are specified in the SAP.

9.7.8 Sample Size

A site-based feasibility assessment was conducted between October to November 2020 to assess the potential number of patients that could be recruited into the study. Questionnaires were sent to 131 NF1-experienced clinicians in the EU representing 17 European countries. The 36 sites from the 12 European countries that expressed interest in participating in the non-interventional PASS indicated they could enrol 180 patients into the Base Cohort and 144 patients into the Nested Prospective Cohort. Assuming approximately 80% of sites will ultimately participate and 70% of eligible patient numbers will enrol yields approximately 125 patients for the Base Cohort and approximately 100 patients for the Nested Prospective Cohort.

As shown below, Table 5 provides the 95% CIs associated with a range of observed cumulative incidence values for events associated with the safety outcomes of interest, across varying sample sizes. A range of cumulative incidence values is expected based on evidence from study D1532C00057 (SPRINT Phase 2) and, in cases where the event was not observed in SPRINT, from other studies of mitogen-activated protein kinase inhibitors given as monotherapy (eg, trametinib). With 100 patients expected in the Nested Prospective Cohort patients, there is a 90% probability of observing at least one event with an underlying real-world incidence of 2.28%.

Table 5 95% CI of the Cumulative Incidence of a Safety Outcome of Interest Given Sample Size

Observed Incidence	Number of Patients		
	95% CI for the cumulative incidence [a]		
	75	100	125
0%	(0.0%, 4.8%)	(0.0%, 3.6%)	(0.0%, 2.9%)
0.5%	(0.0%, 7.2%)	(0.0%, 5.4%)	(0.0%, 4.4%)
1%	(0.0%, 7.2%)	(0.0%, 5.4%)	(0.0%, 5.7%)
2.5%	(0.0%, 9.3%)	(0.2%, 8.5%)	(0.5%, 8.0%)
5%	(0.8%, 13.1%)	(1.6%, 11.3%)	(1.8%, 11.2%)
7.5%	(2.2%, 16.6%)	(2.9%, 15.2%)	(3.3%, 14.2%)
10%	(3.8%, 19.9%)	(4.9%, 17.6%)	(5.1%, 17.1%)
20%	(11.6%, 30.8%)	(12.7%, 29.2%)	(13.4%, 28.1%)
30%	(19.4%, 42.4%)	(21.2%, 40.0%)	(21.8%, 39.3%)
40%	(28.9%, 52.0%)	(30.3%, 50.3%)	(31.3%, 49.1%)
50%	(37.6%, 62.4%)	(39.8%, 60.2%)	(40.5%, 59.5%)

[a] Clopper-Pearson exact 95% CI. When the number of patients is not an integer, it is rounded down for the lower limit, and rounded up for the upper limit.
Abbreviations: CI = confidence interval.

9.8 Quality Control

The study will be conducted in accordance with the relevant SOPs of the Sponsor or designee as appropriate and/or agreed.

Standard operating procedures or internal process guidance at each study site will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, and methods to maintain and archive project documents.

All relevant patient data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF. A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, timely, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GPP, and all applicable regulatory requirements.

All key study documents, such as the analysis plan, abstraction forms, and study reports, will undergo QC review, senior scientific review, and editorial review. Furthermore, to ensure consistency of results both within and across tables, the table shells that accompany the core

SAP will contain simple descriptive checks that will be performed to verify the consistency and accuracy of the study results.

A quality assurance audit of this study may be conducted by the Sponsor or the Sponsor's designees. The Investigator must permit study related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

Appropriate data storage and archiving procedures will be followed (ie, storage on secure servers), with periodic backup of files to tape. Standard procedures will be in place at each research centre to restore files in the event of a hardware or software failure.

9.9 Limitations of the Research Methods

There are potential challenges with enrolment in a prospective data collection study with consideration of each participating site's capacity and need for patient/legal guardian consent. However, a previously conducted feasibility assessment has identified treating centres in most European countries and found that recruitment of the target number of patients required will be possible in the specified time period.

As well, the prospective data collection study will include a self-selected sample, creating selection bias with patients having demographic and clinical characteristics that may differ from the broader population of NF1 patients. We plan to assess the impact of self-selection and the generalisability of the patient population by describing key patient characteristics and discussing these in the context of published literature to provide comparison to the wider disease population.

In general, and as previously described, demographic, treatment, and outcomes data will be collected by site investigators at specialty treatment centres under conditions of routine clinical care. Because of the non-interventional nature of this PASS, some variables will be more complete than others because, for example, the survey feasibility assessment suggests that clinical assessments for imaging of growth plates, Tanner staging, and assessment of height and weight to measure growth might not be routinely captured. In addition, as for all prospective studies, events occurring outside the clinic may not be collected. Missing data will be categorised and analysed to describe the occurrence of safety events for the entire cohort and for just those without missing information.

9.10 Other Aspects

The Study Coordinating Centre will advise and support study sites during the conduct of this multinational PASS. The International Coordinating Investigator will be located at this centre and will oversee its activities. Detailed responsibilities of the International Coordinating Investigator, including his or her relationship to other actors responsible for the management and conduct of the study, will be described later.

An Adjudication Committee consists of clinicians with expertise in NF1. The Adjudication Committee reviews materials provided to it by study sites and any third-party vendors. The Adjudication Committee will form its own charter, laying out criteria for case adjudication and specifying materials to be abstracted from medical records of potential cases.

10 PROTECTION OF HUMAN SUBJECTS

The study will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, ICH GVPs, GPP, and the applicable legislation on non-interventional studies.

The final protocol of the Observational Study, including the final version of the paediatric patient assent and parent/ legal guardian (ICF), must be approved or given a favourable opinion in writing by the Ethics Committees/IRB/IEC.

The Ethics Committees/IRB/IEC must also approve any amendment to the protocol and all advertising used to recruit subjects for the study, according to local regulations

This is a non-interventional study using routine clinical records and does not pose any direct risks for patients. All data collected in the study will be de-identified, and the risk of inadvertent breach of confidentiality with regard to personal identifiers or health information will be minimised.

European Union-specific Data Protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

10.1 Patient Informed Consent

The Investigator at each site will ensure full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study is given to the patient, or the patient's parents or legal guardian if he/she is a child. Where deemed appropriate by the clinician and the child's parents or legal guardian, and where approved by local IRB and country regulations, the child will also be included in all discussions about the trial and asked to provide assent to participate in the study. The Investigator or an associate investigator of the trial will obtain parental/legal guardian consent and child assent (where appropriate). The parent or legal guardian will sign the designated line on the informed consent attesting to the fact that the child has given assent.

Patients or their parents/legal guardians must also be notified that they are free to discontinue from the study at any time. The patients should be given the opportunity to ask questions and allowed time to consider the information provided.

The signed and dated patient informed consent must be obtained before any specific procedure for the study is performed, including:

- Interviews with the Investigator
- Completing any questionnaires
- eCRF completion

A patient who becomes a legal adult during the course of a study (eg, turns 18 years) must provide a signed ICF prior to any additional study procedures being conducted.

The Investigator must store the original, signed ICF(s) and any assent. A copy of the signed ICF must be given to the patient or the patient's parents or legal guardian if he/she is a child.

10.2 Confidentiality of Study/Patient Data

The study assent and ICFs will incorporate wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, patients or their guardians will authorise the collection, use and disclosure of their personal data by the Investigator and by those persons who need that information for the purposes of the Observational Study.

The study ICF will explain that Observational Study data will be stored in a computer database, maintaining confidentiality in accordance with the local law for Data Protection.

The study ICF will also explain that for quality check purposes, a monitor of AZ or a monitor of company representing AZ will require direct access to the signed patient ICF. In case source data verification will be planned as quality check, the study ICF will explain that for data verification purposes, monitor of AZ or a monitor of company representing AZ may require direct access to source documents that are part of the hospital or practice records relevant to the Observational Study.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Base Cohort – Secondary Data Collection

For all patients in the Base Cohort, AEs occurring from Day -365 to Day -1 will be collected via medical chart review and summarised in any interim report(s) and in the final study report. For non-interventional study designs that are based on secondary use of data, submission of individual AEs/ADR case reports is not required.

Nested Prospective Cohort – Primary Data Collection

For patients in the Nested Prospective Cohort, AEs must be managed and reported as described in the sections below.

11.1 Definition of AEs

An AE is any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs.

11.2 Definition of SAEs

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is life-threatening (life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe)
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above. Medical and scientific judgement should be exercised in deciding whether other situations should be considered an SAE.
- Any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and may be subject to expedited reporting requirements in some countries. Any organism, virus, or infectious particle (for example Prion Protein Transmitting Transmissible Spongiform Encephalopathy); pathogenic or non-pathogenic; is considered an infectious agent.

11.3 Definition of Adverse Drug Reactions

An ADR is an AE suspected to be causally related to the medicinal product.

An ADR is a response to a medicinal product which is noxious and unintended. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure.

11.4 Collection of AEs

All AEs, including those with a fatal outcome, will be recorded in the eCRF.

For each AE the following variables will be collected:

- AE term (verbatim and preferred term)
- The date when the AE started and stopped
- CTCAE grade
- Whether the AE is serious or not
- Investigator causality assessment against the medicinal product (yes or no)
- Action taken in regard to the medicinal product
- Outcome of AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity represented by CTCAE grade, whereas seriousness is defined by the criteria in Section 11.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets one of the criteria shown in Section 11.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE if it satisfies one of the criteria shown in Section 11.2.

11.4.1 Causality Collection

The Investigator will assess the causal relationship between the studied medicinal product(s) and each AE, and answer 'yes' or 'no' to the question "Do you consider that there is a reasonable possibility that the event may have been caused by selumetinib?"

11.4.2 Time Period for Collection of AEs

Adverse Events will be collected from the time of starting the medicinal product under study (patient index date [Day 1]) throughout the treatment period and during the study 5-year follow-up period.

11.4.3 Reporting of AEs

Information on all AEs and special situations (with or without AE) should be collected and recorded during the course of the study.

Special situations which must also be collected are:

- Exposure to product during pregnancy
- Exposure to product whilst breastfeeding
- Overdose

- Medication error
- Off label use/product use issue
- Drug Abuse
- Drug Misuse
- Occupational exposure
- Product Quality Complaints/issues incl. Counterfeit/Falsified product
- Lack of efficacy and disease progression

Reports for all important risks listed in the EU RMP, including choking on the capsule, will be collected as AEs and follow-up questionnaires will be used in accordance to routine PV practices to collect additional structured information on reported suspected events.

The Investigators or other site personnel will inform the appropriate AZ representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of:

- All AEs with a fatal outcome
- All SAEs (related and unrelated)
- All non-serious ADRs
- Special situation reports (with or without an AE)

The designated AZ representative works with the Investigator to ensure that all the necessary information is provided to the AZ Patient Safety data entry site within 2 calendar days of initial receipt for fatal and life-threatening events and within 4 calendar days of initial receipt for all other AEs and special situation reports.

For all collected AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AZ representatives of any follow-up information within the same timeframe as the original report.

All collected AEs will be summarised (descriptive summary statistics) in any interim safety analysis and the final study report.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study protocol, study progress reports, and final study report will be included in regulatory communications in line with the RMP, PSUR, and other regulatory reporting requirements. Study reports will be prepared using a template following the GVP Module VIII Section B.6.3.

In its Guidelines for GPPs, the ISPE contends that "there is an ethical obligation to disseminate findings of potential scientific or public health importance" (ISPE 2015); for example, results pertaining to the safety of a marketed medication. "…the marketing authorisation holder should communicate to the Agency and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within two weeks after first acceptance for publication."

Study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors (ICMJE 2014). When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology checklist will be followed (Von Elm et al 2007).

Communication via appropriate scientific venues, eg, ISPE, will be considered.

The research team, including the MAH, the Primary Investigator, and the site investigators will develop a publication plan which will outline the planned publications, potentially including a drug utilisation study and the overall study results.

The MAH and the Investigators have agreed upon a publication policy allowing the Principal Investigator to independently prepare publications based on the study results, irrespective of data ownership. The MAH will be entitled to view the results and interpretations included in the manuscript and provide comments before submission of the manuscript for publication. The MAH and the research team are aware that the MAH should communicate to the Agency (and the competent authorities of the Member States in which the product is authorised) the final manuscript of the article within 2 weeks after first acceptance for publication (EMA2017b). If the Primary Investigator fails to pursue publication of the study results within one year of the conclusion of the study, the site investigators may pursue publication, either individually or in collaboration with the other included countries.

13 REFERENCES

EMA2017b
EMA. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies (EMA/813938/2011 Rev 3). European Medicines Agency; 09 October 2017b. Available at: https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf. Accessed 15 April 2019.

ICMJE 2014
International Committee of Medical Journal Editors (ICMJE). Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. 2014. Available at: http://www.icmje.org/icmje-recommendations.pdf

ISPE 2015
International Society for Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf 2008;17:200-8. Available at: https://www.pharmacoepi.org/pub/1c2a23af-2354-d714-516a-7175549e3a88

KOSELUGO (selumetinib)
KOSELUGO (selumetinib) capsules, for oral use, initial US Approval: 2020. Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850. USPI revised April 2020, Reference ID 4590044.

Von Elm et al 2007
von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-1457. doi:10.1016/S0140-6736(07)61602-X

Annex 1. List of Standalone Documents

None.

Annex 2. ENCePP Checklist for Study Protocols

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the Investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Post-Authorisation Safety Study of Paediatric Patients Initiating Selumetinib: A Multiple-Country Prospective Cohort Study

EU PAS Register® number:
Study reference number (if applicable): D1346R00004

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	N/A
1.1.6 Final report of study results	☒	☐	☐	6

Comments:

The study will be registered with the EU PAS Register before the study begins.

Section 2: Research Question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.2
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (ie, population or sub-group to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	N/A
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	N/A

Comments:

Section 3: Study Design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (eg, cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary, or combined data collection?	☒	☐	☐	11
3.3 Does the protocol specify measures of occurrence? (eg, rate, risk, prevalence)	☒	☐	☐	9.7.2.1
3.4 Does the protocol specify measure(s) of association? (eg, risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	N/A

Section 3: Study Design	**Yes**	**No**	**N/A**	**Section Number**
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and Study Populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.1
4.2.2 Age and sex	☒	☐	☐	9.2.1
4.2.3 Country of origin	☒	☐	☐	9.2.1
4.2.4 Disease/indication	☒	☐	☐	9.2.1
4.2.5 Duration of follow-up	☒	☐	☐	9.2
4.3 Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1

Comments:

Section 5: Exposure Definition and Measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (eg, operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.7.3
5.2 Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☐	☒	☐	N/A
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.7.3
5.4 Is intensity of exposure addressed? (eg, dose, duration)	☒	☐	☐	9.7.3

Section 5: Exposure Definition and Measurement	**Yes**	**No**	**N/A**	**Section Number**
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	N/A
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	N/A

Comments:

In this non-interventional study, exposure will be measured by dose amount rather than by pharmacokinetic and pharmacodynamic measurements.

Section 6: Outcome Definition and Measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.1 9.3.2
6.3 Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	N/A
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (eg, HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	N/A

Comments:

Outcome measurements will be abstracted from medical charts or recorded by treating physicians in the course of routine clinical practice.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (eg, confounding by indication)	☐	☐	☒	N/A
7.2 Does the protocol address selection bias? (eg, healthy user/adherer bias)	☒	☐	☐	9.7.6.2
7.3 Does the protocol address information bias? (eg, misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.7.6.1

Comments:

Section 8: Effect Measure Modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (eg, collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.5

Comments:

Section 9: Data Sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (eg, clinical records, laboratory markers, or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.3
9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
9.2.3 Covariates and other characteristics? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	N/A
9.3.2 Outcomes? (eg, International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	N/A
9.3.3 Covariates and other characteristics?	☐	☒	☐	N/A
9.4 Is a linkage method between data sources described? (eg, based on a unique identifier or other)	☐	☐	☒	N/A

Comments:

Section 10: Analysis Plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.1
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.7.8
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.4 Are stratified analyses included?	☐	☐	☒	N/A
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	N/A
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	N/A
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.7
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.5

Comments:

Section 11: Data Management and Quality Control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.10

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.3 Residual/unmeasured confounding? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.
12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.7.8

Comments:

Section 13: Ethical/Data Protection Issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.8, 10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.2

Comments:

Outcome of the ethical review procedure is not yet available. This will be addressed in due course.

Section 14: Amendments and Deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for Communication of Study Results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____

Annex 3. Additional Information

None.

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d1346r00004-csp-v2		
Document Title:	D1346R00004 Clinical Study Protocol version 2	
Document ID:	Doc ID-004508017	
Version Label:	2.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
05-Nov-2021 12:34 UTC	PPD	Qualified Person Approval

Notes: (1) Document details as stored in CCI, an AstraZeneca document management system.

PASS Protocol

Active substance	Selumetinib
Product reference	D1346R00004
Version number	Protocol, Version 3.0
Date	16 August 2023

TITLE

Post-Authorisation Safety Study of Paediatric Patients Initiating Selumetinib: A Multiple-Country Prospective Cohort Study

Marketing Authorisation Holder

Marketing authorisation holder	AstraZeneca AB, 151 85 Södertälje, Sweden
MAH contact person	PPD

KOSELUGO™ is a trademark of the AstraZeneca group of companies.

This document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

APPROVAL PAGE

Approved by:

PPD

Electronic signature is available at the end of the document

PASS INFORMATION

Title	Post-Authorisation Safety Study of Paediatric Patients Initiating Selumetinib: A Multiple-Country Prospective Cohort Study
Protocol version identifier	3.0
Date of last version of protocol	05 November 2021
EU PAS register number	EUPAS45972
Active substance	Selumetinib
Medicinal product	Selumetinib (KOSELUGO)
Product reference	EMEA/H/C/005244
Procedure number	EMEA/H/C/PSP/S/0095
Marketing authorisation holder(s)	AstraZeneca AB, 151 85 Södertälje, Sweden
Joint PASS	No
Research question and objectives	The primary objective of this study is: • To characterise the safety of selumetinib, including long-term safety, in paediatric patients with NF1-related symptomatic, inoperable PN, 8 to < 18 years old who have not reached Tanner Stage V at the start of selumetinib treatment. The secondary objective of this study is: • To describe the paediatric population 3 to < 18 years old with NF1-related symptomatic inoperable PN who start selumetinib in routine clinical practice.
Countries of study	Up to 12 European countries and Israel
Authors	PPD

1 TABLE OF CONTENTS

LIST OF TABLES

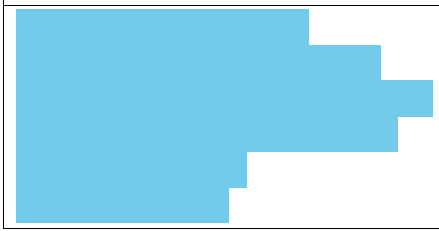
LIST OF FIGURES

2 LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADR	Adverse Drug Reaction
AE	Adverse event
AESI	Adverse event of special interest
AZ	AstraZeneca
CI	Confidence Interval
CPK	Creatine Phosphokinase
CRF	Case Report Form
CRO	Contract Research Organisation
CTCAE	Common Terminology Criteria for Adverse Events
DES	Data entry site
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practice
ICF	Informed Consent Form

Abbreviation or special term	Explanation
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IR	Incidence Rate
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
LVEF	Left ventricular ejection fraction
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MEK	Mitogen-Activated Protein Kinase
MRI	Magnetic Resonance Imaging
NF1	Neurofibromatosis Type 1
PASS	Post-authorisation Safety Study
PN	Plexiform Neurofibroma
PSUR	Periodic Safety Update Reports
Q1	Quarter 1
Q2	Quarter 2
Q3	Quarter 3
QC	Quality Control
RMP	Risk Management Plan
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure

3 RESPONSIBLE PARTIES

AstraZeneca
PPD


4 ABSTRACT

4.1 Title

Post-Authorisation Safety Study of Paediatric Patients Initiating Selumetinib: A Multiple-Country Prospective Cohort Study

4.2 Rationale and Background

Neurofibromatosis type 1 (NF1) is a rare, autosomal dominant genetic disorder that is caused by germline mutations in the NF1 tumour suppressor gene, which encodes the tumour suppressor protein neurofibromin 1. Plexiform neurofibromas (PN) are histologically benign nerve sheath tumours, which typically grow along large nerves and plexi.

On 5 March 2020, a centralised Marketing Authorisation Application was submitted to the European Medicines Agency (EMA), with approval received on 17 June 2021.

As part of the approval process, a Risk Management Plan (RMP) was developed and submitted to the EMA to summarise the safety concerns emerging from the clinical development program. The RMP included additional pharmacovigilance plans for a non-interventional Post-authorisation Safety Study (PASS) to further characterise the safety of selumetinib in paediatric patients with NF1-related PN in routine clinical practice.

The planned non-interventional PASS will address gaps in knowledge identified by the RMP, including the important identified risk and some of the potential risks and missing information on long-term developmental toxicity in children, by characterising the safety profile associated with selumetinib use among paediatric patients (aged 8 to < 18 years old) with a diagnosis of NF1 with symptomatic, inoperable PN.

This study is a specific obligation in the context of a conditional marketing authorisation for selumetinib (ie, Category 2 PASS). Study results will contribute to updating the safety profile of selumetinib in a relatively large population of patients with different personal characteristics across multiple health care systems and patterns of real-world clinical practice in European countries and Israel.

The study will enrol 2 cohorts:

1 The Base Cohort includes all enrolled patients aged 3 to < 18 years.

2 The Nested Prospective Cohort will include the subset of Base Cohort patients aged 8 to < 18 years who have not reached Tanner Stage V on the index date.

4.3 Research Question and Objectives

The primary objective of this study is:

- To characterise the safety of selumetinib, including up to 6 years of long-term safety, in paediatric patients with NF1-related symptomatic, inoperable PN, 8 to < 18 years old who have not reached Tanner Stage V at the start of selumetinib treatment (Nested Prospective Cohort).

The secondary objective of this study is:

- To describe the demographic and clinical profile of the paediatric population 3 to < 18 years old with NF1-related symptomatic inoperable PN who start selumetinib in routine clinical practice (Base Cohort).

4.4 Study Design

This is a cohort study of paediatric patients (aged 3 to < 18 years of age) with NF1 with symptomatic, inoperable PNs who begin selumetinib treatment at study sites across several European countries where selumetinib has been marketed for use.

Selumetinib treatment will remain a decision of the treating clinicians and is not mandated by this study protocol. All patients prescribed selumetinib at the study sites in the usual manner and according to the terms of the marketing authorisation will be invited to participate in the study. Patients who meet the eligibility criteria, including parental/legal guardian consent to participation, will be enrolled.

One hundred and twenty-five patients (approximately 100 patients of which will be in the Nested Prospective Cohort) will be enrolled over a period of up to 3 years and assigned an index date (Day 1) defined as the date of first prescription of selumetinib. Baseline data will be collected at enrolment through retrospective chart abstraction from Day -365 to Day -1 (baseline period).

The Nested Prospective Cohort of patients (aged 8 to < 18 years who have not reached Tanner Stage V on the index date) will be followed prospectively to further characterise the safety of selumetinib. Data from this cohort will be collected on the occurrence of the safety outcomes of interest identified in Section 4.6 (Table 1).

Enrolment will occur at approximately 52 sites in up to 12 European countries and Israel, after selumetinib is commercially available in the country and patients are able to receive the medicine as part of local clinical practice. To meet study timelines and minimise any delay in delivering the study results, countries where selumetinib is first available will be selected for the study.

4.5 Population

The target population for this study are patients with NF1 with symptomatic, inoperable PN who have been prescribed at least 1 dose of selumetinib and who are aged 3 to < 18 years at the start of selumetinib treatment, except for those patients receiving treatment with a mitogen-activated protein kinase inhibitor before the index date.

The study will enrol 2 cohorts:

1 The Base Cohort includes all enrolled patients aged 3 to < 18 years.
2 The Nested Prospective Cohort will include the subset of Base Cohort patients aged 8 to < 18 years who have not reached Tanner Stage V on the index date.

4.6 Variables

The following baseline data will be collected via medical chart abstraction for all patients in the Base Cohort, where baseline will include the most recent assessments made within 365 days before the index date. For repeated measurements during the baseline period, the value closest in time to the index date will be taken:

- **Demographics:** Age, sex, race, and ethnicity (where allowed by General Data Protection Regulation/privacy laws)
- **Clinical characteristics:** Anthropometrics (height, weight, body mass index, and body surface area), PN(s) (number, location, type [target versus non-target PN], potential and associated symptoms, and overall morbidity type), prior medication and relevant procedures, concomitant medications, comorbidities, date of initial NF1 and PN diagnosis, NF1 origin (familial or spontaneous), Tanner Stage, and genetic testing results
- **Baseline history of safety outcomes of interest:** Refer to Table 1

To monitor long-term safety, all patients in the Nested Prospective Cohort will be followed for up to 6 years under conditions of routine clinical care to collect data on the occurrence of the safety outcomes of interest listed in Table 1. These safety outcomes have been chosen to characterise the important identified risk (Left ventricular ejection fraction [LVEF] reduction), the important potential risks (physeal dysplasia, ocular toxicity, myopathy, and hepatotoxicity), and the missing information on long-term exposure described in the RMP; to describe any developmental toxicity during selumetinib use in children; and to further characterise the frequency and severity of safety outcomes (Table 1) and adverse events (AEs) occurring during selumetinib treatment in real-world clinical practice.

Patients who may discontinue selumetinib treatment are to continue in the study for long-term safety follow-up assessment, unless consent is withdrawn.

All concomitant medications, including those taken due to AEs, are to be recorded on an electronic case report form (eCRF).

Table 1 Safety Outcomes of Interest and Corresponding Clinical Assessment[a]

EU-RMP Safety Concern	PASS Outcome	Collected Data and Outcome Definition
LVEF reduction	LVEF reduction	LVEF reduction will be detected as present or absent and when present if symptomatic or asymptomatic. All cardiac tests conducted will be collected
Physeal dysplasia	Physeal dysplasia	Physeal dysplasia will be detected as present or absent based on the physician reading of: • MRI: Knee (preferred) or wrist • X-ray: Knee (preferred) and/or wrist to assess growth plate • Height and weight records
Myopathy	Rise of serum creatine phosphokinase levels AND concurrent musculoskeletal symptoms	A clinically meaningful rise in serum creatine phosphokinase (eg, above the normal limit or increase by 1 or more CTCAE grade shift) combined with musculoskeletal symptoms will be detected as present or absent based on the physician's reading, as a marker of potential myopathy
Hepatotoxicity	Rise in transaminase (ALT and AST) and concurrent rise in bilirubin	A clinically meaningful rise in the measured levels (eg, above the normal limit or increase by 1 or more CTCAE grade shift) will be detected as present or absent, and when present if symptomatic or asymptomatic, as a marker of potential hepatotoxicity
Ocular toxicity	Abnormalities of ophthalmological examination (eg, vision changes, IOP, etc)	An abnormal ocular examination will be detected as present or absent based on the physician's reading, as a marker of potential ocular toxicity

EU-RMP Safety Concern	PASS Outcome	Collected Data and Outcome Definition
Sexual maturation disorder (abnormal pubertal development)	Abnormal pubertal development	Tanner stage criteria (Stages I-V). Abnormal pubertal development will require interpretation by the Investigator with respect to Tanner Stage in the context of the patient's age; recorded as normal or abnormal (if abnormal, further specified as delayed puberty or precocious puberty)

[a] All haematic and clinical test results will be collected as available.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; EU = European Union; IOP = intraocular pressure; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PASS = post-authorisation safety study; RMP = Risk Management Plan.

The feasibility analysis suggested that the majority of safety outcomes will be captured in the course of routine clinical care, but some study outcomes might not be routinely captured for all patients.

For patients in the Base Cohort only, start date and starting dose of selumetinib will be collected in the eCRF. For patients in the Nested Prospective Cohort, exposure to selumetinib will be collected in the eCRF from the index date to the date of the last dose of selumetinib, eg, date(s), selumetinib dose (per administration and total daily), treatment modification(s) (including interruption, dose reduction, and discontinuation), and associated reasons.

4.7 Data Sources

Baseline data and data collected between the index date and the enrolment date for the Nested Prospective Cohort will be abstracted from medical charts (either electronic or paper retrospectively) by trained site staff and entered into a standard eCRF (ie, secondary use of data).

For the Nested Prospective Cohort, all follow-up data after enrolment will be entered directly into eCRFs at each visit (ie, primary data collection).

4.8 Study Size

The target enrolment for the Base Cohort is 125 patients. Of these, approximately 100 patients are expected to meet eligibility criteria for the Nested Prospective Cohort.

4.9 Statistical Analysis

Tabular summaries will be provided for the baseline characteristics of the Base Cohort. Demographic and clinical characteristics data obtained at baseline will be summarised using descriptive statistics: mean, standard deviation, first quartile, median, third quartile, minimum and maximum for continuous variables and number and percentages for categorical variables.

Safety outcomes of interest will be summarised for the Nested Prospective Cohort. For each outcome cumulative incidence and incidence rate with 2-sided 95% exact confidence interval will be provided.

Descriptive summary statistics will be obtained for duration of total exposure to selumetinib, actual cumulative exposure to selumetinib, and number of dose reductions, discontinuations, or interruptions.

The frequency of missing values for each variable will be examined and evaluated to determine whether data are missing at random in the data source.

Details of the statistical analysis are described in the Statistical Analysis Plan, including detailed information on any interim analyses and on the final statistical analysis.

4.10 Milestones

See protocol Section 6 (Table 3) for the study milestones.

5 AMENDMENTS AND UPDATES

Table 2 Protocol Amendments and Updates

Number	Date	Section of study protocol	Amendment or update	Reason
Protocol Version 3.0	*16 August 2023*	Title page	Updated MAH contact person and approver.	Administrative change.
		PASS Information & Annex 2	EU PAS register number added.	EU PAS registration number now available.
		PASS Information	Updated authors.	Administrative change.
		PASS Information, Section 4.4, & 9.2	Updated number of sites and countries that enrolment will occur at.	To reflect the current status of the study.

Number	Date	Section of study protocol	Amendment or update	Reason
		Section 3	Updated AstraZeneca responsible parties and removed the MSD responsible party.	Administrative change.
		Section 4.2 & 7.2	Text updated from 'in the EU and in the UK' to 'in **European countries and Israel**'.	To reflect the current status of the study.
		Section 4.2 & 7.2	Format of age range in text updated to (aged X to X years).	Consistency.
		Section 4.3, 4.4, 4.6, 8, 9.1, 9.2, 9.3.2, & 11.7.2	Update to end of enrolment period from 2 years after first patient enrolled to 3 years after first patient enrolled and update to study follow-up period from 5 years after first patient enrolled to 6 years after first patient enrolled.	Extension of enrolment and follow-up periods based on delays in reimbursement of Koselugo in certain participating countries having an impact on recruitment rate assumptions.
		Section 4.4 & 9.1	• Updated age range to 3 to < 18 years. • Text updated to include the number of patients enrolled and the number of patients in the Nested Prospective Cohort. • 'Baseline period' detail added in parenthesis at the relevant time point.	• Correction of typographical error. • Clarification. • For clarification and to align with Figure 1 (Study Schema).
		Section 4.4 & 9.2	Text updated to remove use of 'commercial launch' and 'in each participating country' and to replace '**standard** clinical practice' with '**local** clinical practice'.	Clarification. Commercial launch defines a specific activity whereas patients can access the commercial drug prior to commercial launch in some countries.
		Section 4.6 & 9.3.1	• Height, weight, and Tanner Stage moved from demographics to clinical characteristics. • Race added to demographics. • Anthropometrics category (which includes height, weight, body mass index, and body surface area) and potential and associated	• 'Anthropometrics' rather than 'demographics' is a more fitting and specific term for measurements of the human body. • Alignment to ongoing revision of SAP (post version 1.0).

Number	Date	Section of study protocol	Amendment or update	Reason
			symptoms added to clinical characteristics. • PN classification updated to type to cover target and non-target PNs. • Morbidities updated to overall morbidity type. • Baseline history of safety outcomes of interest added to the list of baseline data.	
		Section 4.6 9.3.1, 9.3.2, and 9.3.4	'Tanner staging level' terminology updated to '**Tanner Stage**'.	Correction and consistency.
		Section 4.6 & 9.3.3	• Clarified that for patients in the Base Cohort only, start date and starting dose of selumetinib will be collected in the eCRF but for the Nested Prospective Cohort exposure to selumetinib will be collected from the index date to the last dose of selumetinib. • Text relating to 'treatment cycles' removed.	• Clarification. • Treatment cycles for selumetinib are not routinely recorded in the real-world setting.
		Section 4.7 & 9.4	• Text updated to highlight that there is a specific focus on safety outcomes of interest for the Nested Prospective Cohort. • Text stating 'provided to participating study physicians' removed.	• Clarification. • Unnecessary and self-evident.
		Section 4.7, 9.3.1, 9.3.2, & 9.4	Text updated to clarify timings of data collection and to specify the type of data being collected (ie, primary data collection or secondary use of data).	To capture what is considered to be secondary use of data versus primary data collection.
		Section 4.9, 9.7.1, & 9.7.4	Interquartile range added to list of descriptive statistics for continuous variables.	Alignment to ongoing revision of SAP (post version 1.0).

Number	Date	Section of study protocol	Amendment or update	Reason
		Section 4.9	Safety outcomes text updated to specify that it will be summarised for the Nested Prospective Cohort.	Alignment to ongoing revision of SAP (post version 1.0).
		Section 4.9 & 9.7.3	Distinction between total and actual cumulative exposure provided. Definitions of both terms added (Section 9.7.3 only).	Alignment to ongoing revision of SAP (post version 1.0).
		Section 6	• Study milestones for end of data collection, annual progress reports, interim analysis, and final report of study results updated. • Updated the date it is assumed that selumetinib will be available for prescribing in all study countries from 'Q1 2022' to '**Q1 2024**'. • Footnote added to clarify that the Q3 2025 Annual Progress Report will encompass both the annual progress and interim results.	• To reflect the updates to enrolment and follow-up periods. • To reflect the current status of the study. • Clarification.
		Section 7.1	Updated text, including the addition of new references, to include long term safety and efficacy data which was published in April 2023.	To reflect the current study background.
		Section 9.1	• 'Follow-up period' detail added in parenthesis at relevant time points. • 'Study period' terminology replaced with 'follow-up period'.	For clarification and to align with Figure 1 (Study Schema).

Number	Date	Section of study protocol	Amendment or update	Reason
		Section 9.2	• Study observation period text updated to include the actual start date (23 May 2022).	• Study observation period started and no longer anticipated.
			• Text updated to include detail that countries where selumetinib is first available will be selected for study in order to meet timelines.	• To align with the equivalent abstract section (Section 4.4)
		Section 9.2, 9.3.2, & 9.4	• Text updated to replace 'encounter' with 'standard of care visit' (Sections 9.2 and 9.3.2 only). • Explanatory sentence added to clarify that the term 'visit' refers to the aforementioned 'standard of care visit' (Section 9.2 only). • Text updated to replace 'study visit' with 'visit' (Sections 9.3.2 and 9.4 only).	There are no study visits mandated per protocol; given the nature of the non-interventional study, patients are seen as per standard of care (approximately every 6 to 12 months).
		Section 9.2.1.1	Updated inclusion criterion 2 to allow patients who have initiated treatment with selumetinib up to 6 months (ie, 182 days) prior to enrolment into the study (ie, signature of the ICF).	As per Administrative Letter 1 (10 May 2022), to define time window for 'newly prescribed'.
		Section 9.2.1.2	Text updated from '…participating **in a randomised controlled trial**' to '…participating in **an interventional study at index date**'.	To clarify that patients in any type of interventional study are excluded, not only those interventional studies having a randomised design and to clarify that the eligibility criterion are applied at the index date.
		Section 9.3.1	Footnotes added to provide definitions for potential and associated PN symptoms and overall morbidity type.	Clarification.

Number	Date	Section of study protocol	Amendment or update	Reason
		Section 9.3.4	• 'Or derived' added to variable and covariate list descriptor for both baseline and follow-up.	• To clarify that not all variables and covariates listed were 'collected'.
			• Body mass index added to list of variables and covariates.	• Body mass index variable will be derived from the weight and height data and will be presented in the study results.
			• Units (m^2) added to body surface area.	• Alignment with SAP (version 1.0).
		Section 9.3.4.1	Type of site (academic, community, or hospital) data removed from list of data to be collected at local participating sites.	Assessed as a non-critical variable, hence it is not collected in the eCRF.
		Section 9.7.1	Text updated to remove reference to type of clinic/site and put where appropriate by country.	Alignment to ongoing revision of SAP (post version 1.0) and change in Section 9.3.4.1.
		Section 9.7.2.1	Sentence relating to analyses by country/type of clinic/site within country for primary objective removed and detail relating to the 'overall population' included in the preceding sentence.	• Study population is to be spread across a relatively large number of countries (up to 12 European countries and Israel) and sites (> 50) resulting in very small N numbers for many countries and sites resulting in unstable incidence rates by country/site/type of site. • Alignment to ongoing revision of SAP (post version 1.0).
		Section 9.7.2.2	Analysis by type of clinic/site for secondary objective removed.	Alignment to ongoing revision of SAP (post version 1.0) and change in Section 9.3.4.1.

Number	Date	Section of study protocol	Amendment or update	Reason
		Section 9.7.3	• Text updated to clarify that the 'end of exposure' only applies to patients in the Nested Prospective Cohort.	• Clarification.
			• Last dose of selumetinib updated to last known exposure to selumetinib.	• Clarification.
			• Duration of exposure from index date to enrolment date added.	• Additional characteristic.
			• Summaries by country and type of clinic removed.	• To align with change in Section 9.3.4.1.
		Section 9.7.8	Text updated to specify that it was the '**initial**' 36 sites that expressed interest in participating.	Clarification.
		Section 9.9	• Text updated to highlight that the self-selected sample only **potentially** creates selection bias.	• Clarification.
			• Reference to 'Tanner score' removed.	• As per Administrative Change Letter 5 (16 August 2023), to reflect that assessment of Tanner Stage is mandatory for the enrolment of patients into the Nested Prospective Cohort.
			• Text relating to missing data for safety events updated from 'entire cohort' to '**Nested Prospective Cohort**'.	• Clarification.
		Section 9.10	Deletion of paragraph relating to the Adjudication Committee.	There is no Adjudication Committee or process for case adjudication established for this study.
		Section 11	Structure and ordering of Section 11 rearranged.	To improve the readability of the section and to provide clarification on safety data collection and reporting since patient eligibility was expanded to

Number	Date	Section of study protocol	Amendment or update	Reason
				allow inclusion of those who initiated selumetinib treatment up to 6 months prior to study.
		Section 11.4	New section 'Definition of Adverse Events of Special Interest' added.	For site guidance, clarity, and consistency with program-wide safety management.
		Section 11.5	• 'Base Cohort' heading updated to remove 'Secondary Data Collection'. • Clarified that no AEs will be collected during the baseline period and text added to clarify the difference in data collection for patients enrolled in the study and patients enrolled in the Base Cohort only.	• Study patients will not have been treated with selumetinib prior to index date. • Adverse event data during this period is not needed for any study objective. • As per Administrative Change Letter 2 (11 March 2022). • To better clarify the requirements and processes for the management of AEs/ADRs.
		Section 11.6	• Title updated to include 'Secondary Use of Data' as well as 'Primary Data Collection'. • Text updated to clarify the difference between AE reporting for primary data collection and secondary use of data.	• Corrections/clarifications to reflect possible data collection modalities for this cohort and their corresponding differences in management and reporting of AEs/ADRs. • As per Administrative Letter 2 (21 September 2022).
		Section 11.7	Title and text updated to include detail of special situations and to clarify how they should be collected and recorded in the eCRF including follow-up questionnaires.	To better clarify the requirements and processes for the management of AEs/ADRs.
		Section 11.7.2	Text updated to specify that this section pertains to the Nested Prospective Cohort and to clarify that AEs were to be collected in the eCRF until the end of the maximum follow-up period.	As per Administrative Letter 2 (21 September 2022), to better clarify the requirements and processes for the management of AEs/ADRs.

Number	Date	Section of study protocol	Amendment or update	Reason
		Section 11.8	• Text updated and figure added to graphically represent the collection and reporting of AEs for this study. • Detail on action to be taken for AEs not systematically collected or reported added.	To better clarify the requirements and processes for the management of AEs/ADRs.
		Section 12	GVP Module VIII Section corrected from 'B.**6**.3' to 'B.**4**.3'.	Reference to incorrect section in GVP Module VIII/correction of typographical error.
		Annex 2	• Date the study was registered with the EU PAS Register added. • Section number for 4.2.3 (Country of origin) corrected from Section 9.2.1 to 9.2. • Entry for 9.3.2 (Outcomes) changed from 'no' to 'yes' and section number added. • Section 13.2 section number populated with 'N/A'.	• Study registered and date consequently available. • Correction. • Correction. • Cell previously blank.
Protocol Version 2.0	05 Nov 2021	Synopsis, Section 4.4 & 9.2	Updated the list of participating countries	To permit countries where selumetinib is first available to participate in the study.
		Section 4.4 & 9.1	Confirmed selumetinib will be prescribed according to the terms of the marketing authorisation	Response to comments from EMA
		Section 6	Revised the timing of study milestones	Updated to reflect current status
		Section 11.4.3	Clarified the reporting of important risks per the EU RMP and the application of follow-up questionnaires	Response to comments from EMA

Abbreviations: ADR = Adverse Drug Reaction; AE = Adverse Event; eCRF = Electronic Case Report Form; EMA = European Medicines Agency; EU = European Union; EU PAS = European Union Electronic Register of Past-authorisation Studies; GVP = Good Pharmacovigilance Practice; ICF = Informed Consent Form; MAH = Marketing Authorisation Holder; MSD = Merck Sharp & Dohme; N/A = Not Applicable; PASS = Post-authorisation Safety Study; PN = Plexiform Neurofibroma; Q1 = Quarter 1; Q3 = Quarter 3; RMP = Risk Management Plan; SAP = Statistical Analysis Plan; UK = United Kingdom.

6 MILESTONES

Table 3 Study Milestones

Milestone	Planned date
Start of data collection	Q2 2022
End of data collection	Q2 2028
Annual progress reports	Q3 2023 Q3 2024 Q3 2025 [a] Q3 2026 Q3 2027
Interim analysis	Q3 2025 [a]
Final report of study results	31 March 2029

[a] The Q3 2025 Annual Progress Report will encompass both the annual progress and interim results.

Abbreviations: Q1 = Quarter 1; Q2 = Quarter 2; Q3 = Quarter 3.

Study milestones are planned on the assumption that selumetinib will be available for prescribing in all study countries by Q1 2024. Those might be subject to variations based on enrolment rate and other external factors.

The statistical analyses for each milestone (Table 3) will be provided in the SAP.

7 BACKGROUND AND RATIONALE

7.1 Background

Neurofibromatosis type 1 is a rare, autosomal dominant genetic disorder that is caused by germline mutations in the NF1 tumour suppressor gene, which encodes the tumour suppressor protein neurofibromin 1. Plexiform neurofibromas are histologically benign nerve sheath tumours, which typically grow along large nerves and plexi.

In the pivotal Phase 2 study (NCT01362803; SPRINT) that led to marketing authorisation in the United States, selumetinib was well tolerated in paediatric patients with NF1 and inoperable PN. The median total number of treatment cycles was 36, approximately 3 years at twice-daily doses of 25 mg/m^2 at the data cut-off of 2019. Approximately 2 years of additional safety and efficacy data published in 2023 showed that the most patients (n = 49 from 50) had ≥ one AE at least possibly related to treatment (97% Grade ≤ 2). The most common AEs were gastrointestinal symptoms, asymptomatic CPK increase, paronychia, and acneiform rash. Sixteen patients had ≥ one dose reduction; 5 of these had 2 dose reductions for toxicity. Three Grade 4 AEs possibly related to study drug were reported (CPK increase, hyperuricemia, and skin ulceration). Five patients were removed from treatment for an AE considered possibly related to selumetinib (Grade 4 skin ulceration, Grade 3 weight gain, Grade 3 paronychia, Grade 3 acute kidney injury, and Grade 3 diarrhoea).

No new or concerning safety signals were identified during the additional years of observation. As a class, MEK inhibitors are known to have rare but potentially serious ocular and cardiac side effects. Long-term safety follow-up analysis of both Phase 1 and Phase 2 Stratum 1 studies have shown that out of a total of 74 paediatric patients only one participant developed shallow asymptomatic bilateral central serous retinopathy (Grade 1). Several patients developed known AEs such as asymptomatic decreased LVEF in both Phase 1 and Phase 2 Stratum 1 studies (15 patients [14 patients with Grade 2 events and one patient with a Grade 3 event]). These findings highlight that though generally tolerated, treatment with selumetinib is not without potential toxicities, and that long term monitoring for adverse events, such as cardiac and ophthalmologic toxicities, is indicated. In summary, selumetinib monotherapy was well tolerated and had a manageable safety profile in these paediatric patients however long-term safety monitoring is ongoing (Gross et al 2023; Gross et al 2020).

7.2 Rationale

On 5 March 2020, a centralised MAA was submitted to the EMA, with approval received on 17 June 2021.

As part of the approval process, an RMP was developed and submitted to the EMA to summarise the safety concerns emerging from the clinical development program. The RMP

included plans for a non-interventional PASS to further characterise the safety of selumetinib in paediatric patients with NF1-related PN receiving treatment in routine clinical practice.

The RMP version 1.0 (succession 4) approved by EMA on 22 April 2021 had 1 important identified risk with selumetinib treatment:

- LVEF reduction

The RMP also identified 5 important potential risks with selumetinib treatment:

- Physeal dysplasia
- Ocular toxicity
- Myopathy
- Hepatotoxicity
- Choking on the capsule

Long-term exposure (including long-term safety data on developmental toxicity in children) was identified in the RMP as an area of missing information.

This study will address gaps in knowledge identified by the RMP, including the important identified risk and some of the potential risks and missing information on long-term developmental toxicity in children, by characterising the safety profile associated with selumetinib use among paediatric patients (aged ≥ 8 to < 18 years old) with a diagnosis of NF1 with symptomatic, inoperable PN. Conduct of this study is a specific obligation in the context of a conditional marketing authorisation for selumetinib (ie, Category 2 PASS). Study results will contribute to updating the safety profile of selumetinib in a relatively large population of patients with different personal characteristics across multiple health care systems and patterns of real-world clinical practice in European countries and Israel.

8 RESEARCH QUESTION AND OBJECTIVES

The primary objective of this study is:

- To characterise the safety of selumetinib, including up to 6 years of long-term safety, in paediatric patients with NF1-related symptomatic, inoperable PN, 8 to < 18 years old who have not reached Tanner Stage V at the start of selumetinib treatment (Nested Prospective Cohort).

The secondary objective of this study is:

- To describe the demographic and clinical profile of the paediatric population 3 to < 18 years old with NF1-related symptomatic inoperable PN who start selumetinib in routine clinical practice (Base Cohort).

For details on the outcomes related to the primary objective, see Section 9.3.

9 RESEARCH METHODS

9.1 Study Design

This is a cohort study of paediatric patients (aged 3 to < 18 years of age) with NF1 with symptomatic, inoperable PNs who begin selumetinib treatment at study sites across several European countries where selumetinib has been marketed for use.

Selumetinib treatment will remain a decision of the treating clinicians and is not mandated by this study protocol. All patients prescribed selumetinib at the study sites in the usual manner and according to the terms of the marketing authorisation will be invited to participate in the study. Patients who meet the eligibility criteria, including parental/legal guardian consent to participation, will be enrolled.

One hundred and twenty-five patients (approximately 100 patients of which will be in the Nested Prospective Cohort) will be enrolled. The patient enrolment period will begin once the first patient is enrolled and end at latest 3 years after that date (estimated end of enrolment = Q2 2025). Patients may continue in the study until the study end date which is up to 6 years after the first patient enrolment date (estimated end of study = Q2 2028). Each enrolled patient will be assigned an index date (Day 1) defined as the date of first prescription of selumetinib. Baseline data will be collected at enrolment through retrospective chart abstraction from Day -365 to Day -1 (baseline period).

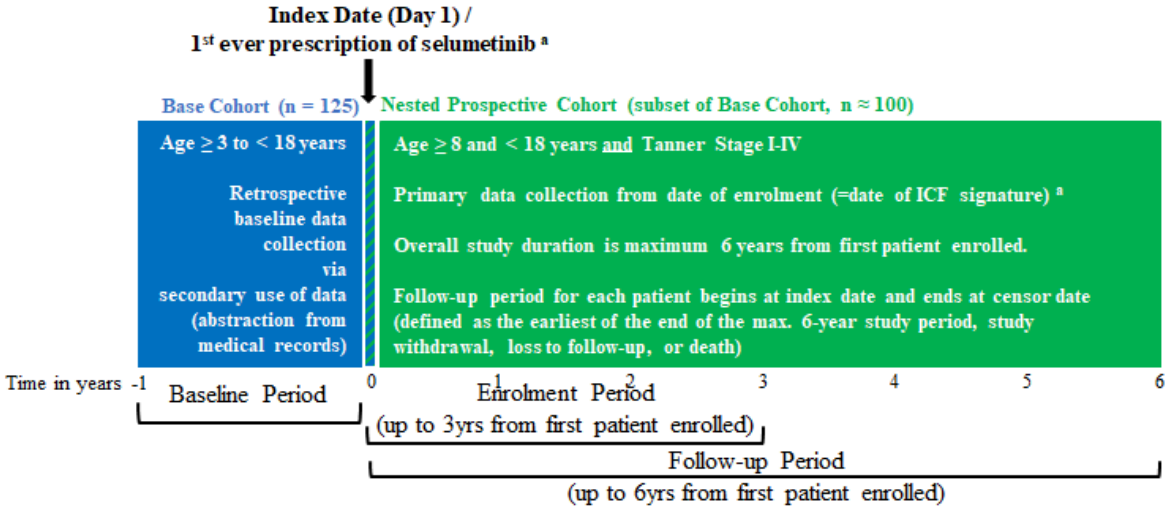
An eligible subset of patients (aged 8 to < 18 years who have not reached Tanner Stage V on the index date) will be enrolled in the Nested Prospective Cohort. Data will be collected following the first dose of selumetinib (Day 1) for the duration of the study and will focus on assessing the safety outcomes of interest identified in Section 9.3.2 (see Table 4).

Patients in the Nested Prospective Cohort will be followed from the index date to the censor date, defined as the earliest of the end of the 6-year follow-up period, study withdrawal, loss to follow-up, or death (follow-up period). The 6-year follow-up period is defined as a maximum of 6 years from the time the first patient is enrolled (estimated time period = Q2 2022 to Q2 2028).

Whether to treat the patient with selumetinib will be based on the decision of the prescribing physician under conditions of routine clinical care. Participating study sites will treat patients according to normal clinical practice and no intervention will be assigned.

The study schematic is shown below in Figure 1.

Figure 1 Study Schema



[a] Index date can be up to 6 months prior to enrolment (date of ICF signature) provided that, for patients enrolled in the Nested Prospective Cohort, key data are available in the medical record (eg, baseline characteristics; any safety outcome measures and AEs); in such cases, data collected from the index date until the date of enrolment is considered **secondary use of data** (ie, data are abstracted from patients' medical records).

Abbreviations: AE = Adverse Events; ICF = Informed Consent Form.

9.2 Setting

This study will be conducted in up to 52 specialist clinics for the treatment of paediatric patients with NF1 across up to 12 European countries and Israel.

The study observation period was anticipated to begin in Q2 of 2022, with some variation by country (actual start date was 23 May 2022). Patients will be enrolled after selumetinib access is commercially available and patients are able to receive the medicine as part of local clinical practice. To meet study timelines and minimise any delay in delivering the study results, countries where selumetinib is first available will be selected for the study.

The target population for this study are patients with NF1 in the EU with symptomatic, inoperable PN who have been prescribed at least 1 dose of selumetinib and who are aged 3 to < 18 years at the start of selumetinib treatment, except for those patients receiving treatment with a mitogen-activated protein kinase inhibitor before the index date.

The study will enrol 2 cohorts:

1 The Base Cohort includes all enrolled patients aged 3 to <18 years.

2 The Nested Prospective Cohort will include the subset of Base Cohort patients aged 8 to <18 years who have not reached Tanner Stage V on the index date.

Patient screening will be conducted throughout the enrolment period and baseline data for all patients will be abstracted from medical records. Those meeting the criteria for enrolment in the Nested Prospective Cohort will be followed up during their routine standard of care visits with the treating clinician (expected to occur every 6 to 12 months) for up to 6 years. The term 'visit' has been used to denote these 'standard of care visits'.

A site may have multiple eligible patients and there will be a limit on the number of patients per site to ensure appropriate representation of patients, given that treatments administered may vary across sites and countries.

This study protocol will be adopted at each study site. An SAP will be prepared by the study CRO for AZ approval before performing the analysis.

9.2.1 Eligibility Criteria

All patients meeting study inclusion and not meeting exclusion criteria will be eligible for the study.

9.2.1.1 Inclusion Criteria

Patients are eligible to be included in the study only if all the following criteria apply:

1 Have been diagnosed with NF1 with symptomatic, inoperable PN

2 Have initiated treatment with selumetinib up to 6 months (ie, 182 days) prior to enrolment into the study (ie, signature of the ICF) [1]

3 Are aged 3 years and above, and are < 18 years of age on the index date

4 Parent or legal guardian, as required by country-specific regulation, have provided informed consent (see Section 10.1) (unless a country-specific waiver is obtained)

Additional Criteria for Nested Prospective Cohort

5 Are at least 8 years old and

6 Are prior to attainment of Tanner Stage V on the index date

9.2.1.2 Exclusion Criteria

Patients are excluded from the study if the following criteria apply:

[1] Provided that, for patients enrolled in the Nested Cohort, key retrospective data are available (eg, baseline characteristics; any safety outcome measures, and AEs).

1 Have received treatment with a mitogen-activated protein kinase inhibitor before the index date

2 Are participating in an interventional study at index date

9.3 Variables

Study variables will be collected as detailed below:

9.3.1 Baseline Data

The following baseline data will be collected via medical chart abstraction (ie, secondary use of data) for all patients in the Base Cohort, where baseline will include the most recent assessments made within 365 days before the index date. For repeated measurements during the baseline period, the value closest in time to the index date will be taken:

- **Demographics**: Age, sex, race, and ethnicity (where allowed by GDRP/privacy laws)
- **Clinical characteristics**: Anthropometrics (height, weight, body mass index, and body surface area), PN(s) (number, location, type [target versus non-target PN], potential and associated symptoms [2], and overall morbidity type [3]), prior medication and relevant procedures, concomitant medications, comorbidities, date of initial NF1 and PN diagnosis, NF1 origin (familial or spontaneous), Tanner Stage, and genetic testing results
- **Baseline history of safety outcomes of interest:** Refer to Table 4

9.3.2 Outcomes – Nested Prospective Cohort

To monitor long-term safety, all patients in the Nested Prospective Cohort will be followed for up to 6 years under conditions of routine clinical care to collect data on the occurrence of the safety outcomes of interest listed in Table 4. These safety outcomes have been chosen to characterise the important identified risk (LVEF reduction), the important potential risks (physeal dysplasia, ocular toxicity, myopathy, and hepatotoxicity), and the missing information on long-term exposure described in the RMP; to describe any developmental toxicity during selumetinib use in children; and to further characterise the frequency and severity of safety outcomes of interest (Table 4) and AEs occurring during selumetinib treatment in real-world clinical practice. Data are abstracted from patients' medical

[2] Potential PN symptoms are defined as possible symptoms based on location/site of the PN, as assessed by the Investigator, but not necessarily reported by the patient. Associated PN symptoms are defined as symptoms of the PN reported by the patients or as determined by the Investigator during clinical assessment.

[3] Overall morbidity type is defined as the main morbidity assignment based on location/site of the PN, as assessed by the Investigator.

charts/records from index date until date of enrolment (ie, secondary use of data). Data collected from enrolment onwards is primary data collection.

Patients who may discontinue selumetinib treatment are to continue in the study for long-term safety follow-up assessment, unless consent is withdrawn.

All concomitant medications, including those taken due to AEs, are to be recorded on an eCRF.

Table 4 Safety Outcomes of Interest and Corresponding Clinical Assessment[a]

EU-RMP Safety Concern	PASS Outcome	Collected Data and Outcome Definition
LVEF reduction	LVEF reduction	LVEF reduction will be detected as present or absent and when present if symptomatic or asymptomatic. All cardiac tests conducted will be collected
Physeal dysplasia	Physeal dysplasia	Physeal dysplasia will be detected as present or absent based on the physician reading of: • MRI: Knee (preferred) or wrist • X-ray: Knee (preferred) and/or wrist to assess growth plate • Height and weight records
Myopathy	Rise of serum creatine phosphokinase levels AND concurrent musculoskeletal symptoms	A clinically meaningful rise in serum creatine phosphokinase (eg, above the normal limit or increase by 1 or more CTCAE grade shift) combined with musculoskeletal symptoms will be detected as present or absent based on the physician's reading, as a marker of potential myopathy
Hepatotoxicity	Rise in transaminase (ALT and AST) and concurrent rise in bilirubin	A clinically meaningful rise in the measured levels (eg, above the normal limit or increase by 1 or more CTCAE grade shift) will be detected as present or absent, and when present if symptomatic or asymptomatic, as a marker of potential hepatotoxicity

EU-RMP Safety Concern	PASS Outcome	Collected Data and Outcome Definition
Ocular toxicity	Abnormalities of ophthalmological examination (eg, vision changes, IOP, etc)	An abnormal ocular examination will be detected as present or absent based on the physician's reading, as a marker of potential ocular toxicity
Sexual maturation disorder (abnormal pubertal development)	Abnormal pubertal development	Tanner stage criteria (Stages I-V). Abnormal pubertal development will require interpretation by the Investigator with respect to Tanner Stage in the context of the patient's age; recorded as normal or abnormal (if abnormal, further specified as delayed puberty or precocious puberty)

[a] All haematic and clinical test results will be collected as available.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; EU = European Union; IOP = intraocular pressure; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PASS = post-authorisation safety study; RMP = Risk Management Plan.

The feasibility analysis suggested that the majority of safety outcomes will be captured in the course of routine clinical care, but some study outcomes might not be routinely captured for all patients.

In the setting of a non-interventional study there are no scheduled visits. Based on the feasibility assessment, standard of care visits between physicians and patients are anticipated to occur at a frequency of 6 to 12 months. All relevant clinical information (and respective dates of measurements/assessment) will be collected at each standard of care visit throughout a patient's follow-up.

9.3.3 Exposure

For patients in the Base Cohort only, start date and starting dose of selumetinib will be collected in the eCRF. For patients in the Nested Prospective Cohort, exposure to selumetinib will be collected in the eCRF from the index date to the date of the last dose of selumetinib, eg, date(s), selumetinib dose (per administration and total daily), treatment modification(s) (including interruption, dose reduction, and discontinuation), and associated reasons.

9.3.4 Other Variables and Covariates

In addition to the demographic and clinical characteristics noted above that will be collected or derived at baseline, the following data will be collected or derived throughout follow-up:

- Height (cm)
- Weight (kg)
- Body mass index (kg/m^2)
- Body surface area (m^2)
- Tanner stage (from I to V)
- Concomitant medications, including any medications used to treat AEs
- Comorbidities
- NF1-related clinical manifestation and complications
- PN-related variables (including for any clinically important target PNs)
- PN-related symptoms/morbidities
- Number of PN-related morbidities
- Number of PN(s), PN location(s), PN size(s), size change (if available)

9.3.4.1 Site Characteristics

The following data will be collected at local participating sites:

- Location (country)

9.4 Data Sources

Baseline data and data collected between index date and enrolment date for the Nested Prospective Cohort will be abstracted from medical charts (either electronic or paper) by trained site staff and entered into a standard eCRF (ie, secondary use of data).

For the Nested Prospective Cohort, all follow-up data after enrolment will be entered directly into eCRFs at each visit (ie, primary data collection).

For the Nested Prospective Cohort there is a specific focus on safety outcomes of interest during follow-up after index date, regardless of the data collection modality (ie, secondary use versus primary data collection).

Data collection and validation procedures will be provided in the study manuals.

9.5 Study Size

The target enrolment for the Base Cohort is 125 patients. Of those, approximately 100 patients are expected to meet eligibility criteria for the Nested Prospective Cohort. For details of sample size calculation, see Section 9.7.8.

9.6 Data Management

Routine procedures performed at each site will be recorded in electronic files, maintaining security and data confidentiality, following analysis plans, and performing QC checks of all eCRF's. Each site will maintain any patient-identifying information securely on site according to internal SOPs or guidance documents.

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff.

Appropriate data storage and archiving procedures will be followed (ie, storage on secure servers), with periodic backup of files. Standard procedures will be in place at each research centre to restore files in the event of a hardware or software failure.

9.7 Statistical Analysis

9.7.1 Statistical Methods – General Consideration

All statistical analyses will be performed by the study CRO, after AZ review and approval of an SAP. Analyses supporting the milestones (Table 3) will be provided in the SAP.

The analysis populations that will be used in reporting are:

1 The set of All Enrolled Patients (the Base Cohort)
2 The set of Nested Prospective Patients (the Nested Prospective Cohort)

Tabular summaries will be provided for the baseline characteristics of the Base and Nested Prospective Cohorts. Demographic and clinical characteristics data obtained at baseline will be summarised using descriptive statistics. Unless otherwise specified, baseline is defined as the last assessment made within the 365 days prior to initiation of selumetinib treatment (ie, index date). Categorical data will be summarised by the number and percentage of subjects in each category. Continuous variables will be summarised by descriptive statistics including number of patients, mean, standard deviation, first quartile, median, third quartile, minimum, and maximum.

For each analysis population, tabular summaries will be provided for the overall population and where appropriate by country. Additional details of the statistical analyses will be provided in the SAP, including detailed information on any interim analyses and final statistical analysis. The SAP will be finalised prior to the beginning of analyses. The definitions of derived variables will be described. For any time to event analyses, data will be censored for patients when lost to follow-up or study end (ie, still alive as of their last visit/contact prior to data cut-off).

9.7.2 Research Objectives

9.7.2.1 Primary Objective: Safety Outcomes of Interest

In the Nested Prospective Cohort, for each safety outcome of interest, the cumulative incidence and IR (as best appropriate) and corresponding 2-sided 95% CI estimates will be provided for the overall population using relevant data collected at each follow-up visit throughout follow-up.

Any additional analysis of these outcomes will be described in the SAP.

9.7.2.2 Secondary Objective: Describe the Paediatric Population

Baseline data collected from the Base Cohort will include patient characteristics (demographic and clinical) and site characteristics. Baseline data will be summarised as appropriate, for the overall population, as described in the corresponding section of this protocol. Any additional analysis of these outcomes will be described in the SAP.

9.7.3 Exposure

The beginning of exposure will be the date of initiation of selumetinib treatment (index date) and the end of exposure, applicable only to patients in the Nested Prospective Cohort, will be estimated as the date of last known exposure to selumetinib. Dose amount will be obtained at baseline for all patients and during the course of follow-up for patients in the Nested Prospective Cohort. Descriptive summary statistics will be obtained for dose amount of selumetinib received at baseline, duration of exposure from index date to enrolment date, duration of total exposure to selumetinib (defined as [min (last dose date where dose > 0 [mg], date of death, date of data cut-off) – first dose date + 1]), actual cumulative exposure to selumetinib (defined as total exposure excluding dose interruptions), year of initiation, and number of dose reductions, discontinuations, or interruptions. The summaries will be provided for the overall population. Any additional analysis of exposure data will be described in the SAP.

9.7.4 Demographic and Clinical Characteristics

Demographic and clinical characteristics data obtained at baseline will be summarised using descriptive statistics: mean, standard deviation, first quartile, median, third quartile, minimum, and maximum for continuous variables and number and percentages for categorical variables.

9.7.5 Subgroups Analyses

Sub-group analyses may be conducted and will be described in the SAP as required. Additional sensitivity analyses may be performed to evaluate potential for bias, and will be described in the SAP as required.

9.7.6 Methods to Minimise Bias

9.7.6.1 Information Bias

The present study will be carried out using data recorded during routine clinical care. Some records are expected to be incomplete. In addition, the availability of the information in a patient's health record may depend on the study site and/or countries.

Given that the primary purpose of the study is to characterise the long-term safety profile of selumetinib in real-world practice, and that investigators participating in the study will treat the patient and provide data to a standard eCRF, this potential source of bias should be relatively minor with respect to these safety outcomes in the paediatric patient population. Nevertheless, it remains possible that participation in the study may lead to a more careful and comprehensive reporting of safety outcomes with a potential to overestimate their detection in routine clinical practice.

9.7.6.2 Selection Bias

This study encompasses a self-selected population of paediatric patients with consenting parents/legal guardians and clinicians who have expressed their interest to participate. Participating investigators may be more likely to adopt new treatment options and may somehow differ from investigators who elect not to participate in the study. Similarly, the paediatric patients may have a profile not fully representative of the selumetinib treated population. However, several measures are introduced in the study design and analysis that can mitigate the potential for selection bias. First, the large number of study sites across numerous European countries can be anticipated to provide data representative of the treatment of NF1 patients with PN across Europe.

In addition, the enrolment of consecutive patients initiating selumetinib treatment at study sites, with inclusion and exclusion criteria that are well described in the protocol, will ensure that eligible patients at a given site have an equal chance of selection into the study. Information regarding physician and hospital characteristics will be collected and analytical approaches will be applied in the analyses if marked differences are observed in the study population as provided in the SAP.

9.7.7 Missing Data

Missing data is likely to be present in retrospective medical chart review studies. An assessment of the extent and mechanism of missingness in measurements relevant to key study variables and critical data elements is, therefore, an important component of site feasibility assessment. Efforts will be made to ensure that sites with reasonable amount of key data elements (eg, baseline characteristics; treatment history; ability to collect outcome measures) are provided the opportunity to participate in the study.

The number of missing values for key data elements will be reported, and the likely impact of missing data on the analysis and the pattern of the missing information will be assessed. If systematic patterns are observed, adjustments may be made to account for missing data, Details and conventions of missing data handling are specified in the SAP.

9.7.8 Sample Size

A site-based feasibility assessment was conducted between October to November 2020 to assess the potential number of patients that could be recruited into the study. Questionnaires were sent to 131 NF1-experienced clinicians in the EU representing 17 European countries. The initial 36 sites from the 12 European countries that expressed interest in participating in the non-interventional PASS indicated they could enrol 180 patients into the Base Cohort and 144 patients into the Nested Prospective Cohort. Assuming approximately 80% of sites will ultimately participate and 70% of eligible patient numbers will enrol yields approximately 125 patients for the Base Cohort and approximately 100 patients for the Nested Prospective Cohort.

As shown below, Table 5 provides the 95% CIs associated with a range of observed cumulative incidence values for events associated with the safety outcomes of interest, across varying sample sizes. A range of cumulative incidence values is expected based on evidence from study D1532C00057 (SPRINT Phase 2) and, in cases where the event was not observed in SPRINT, from other studies of mitogen-activated protein kinase inhibitors given as monotherapy (eg, trametinib). With 100 patients expected in the Nested Prospective Cohort patients, there is a 90% probability of observing at least one event with an underlying real-world incidence of 2.28%.

Table 5 95% CI of the Cumulative Incidence of a Safety Outcome of Interest Given Sample Size

Observed Incidence	Number of Patients		
	95% CI for the cumulative incidence [a]		
	75	100	125
0%	(0.0%, 4.8%)	(0.0%, 3.6%)	(0.0%, 2.9%)
0.5%	(0.0%, 7.2%)	(0.0%, 5.4%)	(0.0%, 4.4%)
1%	(0.0%, 7.2%)	(0.0%, 5.4%)	(0.0%, 5.7%)
2.5%	(0.0%, 9.3%)	(0.2%, 8.5%)	(0.5%, 8.0%)
5%	(0.8%, 13.1%)	(1.6%, 11.3%)	(1.8%, 11.2%)
7.5%	(2.2%, 16.6%)	(2.9%, 15.2%)	(3.3%, 14.2%)
10%	(3.8%, 19.9%)	(4.9%, 17.6%)	(5.1%, 17.1%)
20%	(11.6%, 30.8%)	(12.7%, 29.2%)	(13.4%, 28.1%)
30%	(19.4%, 42.4%)	(21.2%, 40.0%)	(21.8%, 39.3%)
40%	(28.9%, 52.0%)	(30.3%, 50.3%)	(31.3%, 49.1%)
50%	(37.6%, 62.4%)	(39.8%, 60.2%)	(40.5%, 59.5%)

[a] Clopper-Pearson exact 95% CI. When the number of patients is not an integer, it is rounded down for the lower limit, and rounded up for the upper limit.
Abbreviations: CI = confidence interval.

9.8 Quality Control

The study will be conducted in accordance with the relevant SOPs of the Sponsor or designee as appropriate and/or agreed.

Standard operating procedures or internal process guidance at each study site will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, and methods to maintain and archive project documents.

All relevant patient data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF. A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, timely, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GPP, and all applicable regulatory requirements.

All key study documents, such as the analysis plan, abstraction forms, and study reports, will undergo QC review, senior scientific review, and editorial review. Furthermore, to ensure

consistency of results both within and across tables, the table shells that accompany the core SAP will contain simple descriptive checks that will be performed to verify the consistency and accuracy of the study results.

A quality assurance audit of this study may be conducted by the Sponsor or the Sponsor's designees. The Investigator must permit study related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

Appropriate data storage and archiving procedures will be followed (ie, storage on secure servers), with periodic backup of files to tape. Standard procedures will be in place at each research centre to restore files in the event of a hardware or software failure.

9.9 Limitations of the Research Methods

There are potential challenges with enrolment in a prospective data collection study with consideration of each participating site's capacity and need for patient/legal guardian consent. However, a previously conducted feasibility assessment has identified treating centres in most European countries and found that recruitment of the target number of patients required will be possible in the specified time period.

As well, the prospective data collection study will include a self-selected sample, potentially creating selection bias with patients having demographic and clinical characteristics that may differ from the broader population of NF1 patients. We plan to assess the impact of self-selection and the generalisability of the patient population by describing key patient characteristics and discussing these in the context of published literature to provide comparison to the wider disease population.

In general, and as previously described, demographic, treatment, and outcomes data will be collected by site investigators at specialty treatment centres under conditions of routine clinical care. Because of the non-interventional nature of this PASS, some variables will be more complete than others because, for example, the survey feasibility assessment suggests that clinical assessments for imaging of growth plates and assessment of height and weight to measure growth might not be routinely captured. In addition, as for all prospective studies, events occurring outside the clinic may not be collected. Missing data will be categorised and analysed to describe the occurrence of safety events for the Nested Prospective Cohort and for just those without missing information.

9.10 Other Aspects

The Study Coordinating Centre will advise and support study sites during the conduct of this multinational PASS. The International Coordinating Investigator will be located at this centre and will oversee its activities. Detailed responsibilities of the International Coordinating

Investigator, including his or her relationship to other actors responsible for the management and conduct of the study, will be described later.

10 PROTECTION OF HUMAN SUBJECTS

The study will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, ICH GVPs, GPP, and the applicable legislation on non-interventional studies.

The final protocol of the Observational Study, including the final version of the paediatric patient assent and parent/ legal guardian (ICF), must be approved or given a favourable opinion in writing by the Ethics Committees/IRB/IEC.

The Ethics Committees/IRB/IEC must also approve any amendment to the protocol and all advertising used to recruit subjects for the study, according to local regulations.

This is a non-interventional study using routine clinical records and does not pose any direct risks for patients. All data collected in the study will be de-identified, and the risk of inadvertent breach of confidentiality with regard to personal identifiers or health information will be minimised.

European Union-specific Data Protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

10.1 Patient Informed Consent

The Investigator at each site will ensure full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study is given to the patient, or the patient's parents or legal guardian if he/she is a child. Where deemed appropriate by the clinician and the child's parents or legal guardian, and where approved by local IRB and country regulations, the child will also be included in all discussions about the trial and asked to provide assent to participate in the study. The Investigator or an associate investigator of the trial will obtain parental/legal guardian consent and child assent (where appropriate). The parent or legal guardian will sign the designated line on the informed consent attesting to the fact that the child has given assent.

Patients or their parents/legal guardians must also be notified that they are free to discontinue from the study at any time. The patients should be given the opportunity to ask questions and allowed time to consider the information provided.

The signed and dated patient informed consent must be obtained before any specific procedure for the study is performed, including:

- Interviews with the Investigator
- Completing any questionnaires
- eCRF completion

A patient who becomes a legal adult during the course of a study (eg, turns 18 years) must provide a signed ICF prior to any additional study procedures being conducted.

The Investigator must store the original, signed ICF(s) and any assent. A copy of the signed ICF must be given to the patient or the patient's parents or legal guardian if he/she is a child.

10.2 Confidentiality of Study/Patient Data

The study assent and ICFs will incorporate wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, patients or their guardians will authorise the collection, use and disclosure of their personal data by the Investigator and by those persons who need that information for the purposes of the Observational Study.

The study ICF will explain that Observational Study data will be stored in a computer database, maintaining confidentiality in accordance with the local law for Data Protection.

The study ICF will also explain that for quality check purposes, a monitor of AZ or a monitor of company representing AZ will require direct access to the signed patient ICF. In case source data verification will be planned as quality check, the study ICF will explain that for data verification purposes, monitor of AZ or a monitor of company representing AZ may require direct access to source documents that are part of the hospital or practice records relevant to the Observational Study.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 Definition of AEs

An AE is any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs.

11.2 Definition of SAEs

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is life-threatening (life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe)
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above. Medical and scientific judgement should be exercised in deciding whether other situations should be considered an SAE.
- Any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and may be subject to expedited reporting requirements in some countries. Any organism, virus, or infectious particle (for example Prion Protein Transmitting Transmissible Spongiform Encephalopathy); pathogenic or non-pathogenic; is considered an infectious agent.

11.3 Definition of Adverse Drug Reactions

An ADR is an AE suspected to be causally related to the medicinal product.

An ADR is a response to a medicinal product which is noxious and unintended. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure.

11.4 Definition of Adverse Events of Special Interest

An AESI is an AE of scientific and medical interest specific to the further understanding of selumetinib's safety profile and requires close monitoring and rapid communication by the Investigators to AstraZeneca. Adverse events of special interest for this study are described in Table 6. An AESI can be serious or non-serious and must be collected and reported as described in Section 11.7 and Section 11.8.

Table 6 AESIs For Adult/Paediatric Population

AESI medical concept	MedDRA preferred terms defining the AESI medical concept
Ocular toxicity	Chorioretinopathy (central serous retinopathy), retinal detachment, retinal tear, vision blurred, visual impairment, vitreous floaters, photopsia, eye disorder, photophobia, retinal vein occlusion, detachment of retinal pigment epithelium (retinal pigment epithelial detachment).
Hepatotoxicity	Drug-induced liver injury, ALT increased, AST increased.
Muscular toxicity	Blood creatine phosphokinase increased, musculoskeletal pain, muscular weakness, myalgia, rhabdomyolysis, myoglobin blood increased, myoglobin urine present, acute kidney injury, myopathy.

Table 6 AESIs For Adult/Paediatric Population

AESI medical concept	MedDRA preferred terms defining the AESI medical concept
Cardiac toxicity	Ejection fraction decreased, oedema peripheral, peripheral swelling, oedema, left ventricular dysfunction, ventricular dysfunction.
For the paediatric population only	
Physeal dysplasia	Metaphyseal dysplasia, multiple epiphyseal dysplasia, arthralgia, joint stiffness, joint hyperextension, gait disturbance, short stature.
Choking on the capsule	Choking, retching.

Abbreviations: AESI = adverse event of special interest; ALT = alanine aminotransferase; AST = aspartate aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities.

11.5 Base Cohort

For all patients enrolled in the study, no AEs will be collected in the eCRF or reported to the AstraZeneca DES during the baseline period as patients will not be receiving treatment with selumetinib at that time (ie, from Day -365 to Day -1).

If any AE occurs from the index date onwards in patients assigned to the Base Cohort only, such events should be reported to the local AstraZeneca office according to local requirements and the reporting of any follow-up of these events will follow the same procedure via the local AstraZeneca office.

11.6 Nested Prospective Cohort – Secondary Use of Data and Primary Data Collection

Secondary Use of Data: From index date (ie, start of selumetinib treatment/Day 1) until date of enrolment in the study (ie, signature of ICF), all AEs and special situations will be collected in the eCRF, but not reported to the AstraZeneca DES. For non-interventional study designs based on secondary use of data, reporting to the AstraZeneca DES and submission of individual AEs/ADR case reports are not required. Such events should be reported to the local AstraZeneca office according to local requirements and the reporting of any follow-up of these events will follow the same procedure via the local AstraZeneca office.

Primary Data Collection: From enrolment date onwards, all AEs and special situations must be managed as described in the following sections.

11.7 Collection of AEs and Special Situations

With exception of the baseline period (Day -365 to Day -1), all AEs, including those with a fatal outcome, and special situations (with or without AE), will be collected in the eCRF.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity represented by CTCAE grade, whereas seriousness is defined by the criteria in Section 11.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets one of the criteria shown in Section 11.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE if it satisfies one of the criteria shown in Section 11.2.

For each AE the following variables will be collected:

- AE term (verbatim and preferred term)
- The date when the AE started and stopped
- CTCAE grade
- Whether the AE is serious or not
- Investigator causality assessment against the medicinal product (yes or no)
- Action taken in regard to the medicinal product
- Outcome of AE

Special situations which must also be collected are (where applicable, the corresponding eCRF should be used; otherwise, the corresponding paper form should be used):

- Exposure to product during pregnancy
- Exposure to product whilst breastfeeding
- Overdose
- Medication error
- Off label use/product use issue
- Drug Abuse
- Drug Misuse
- Occupational exposure
- Product Quality Complaints/issues incl. Counterfeit/Falsified product
- Lack of efficacy and disease progression

All important identified and potential risks listed in the EU RMP, including choking on the capsule, will be collected in the eCRF as AEs, and follow-up questionnaires (ie, Targeted Safety Questionnaires), where applicable, will be used in accordance with routine PV practices to collect additional structured information on reported suspected events.

All collected AEs will be recorded and summarised (descriptive summary statistics) in any interim safety analysis and the final study report.

11.7.1 Causality Collection

The Investigator will assess the causal relationship between the studied medicinal product(s) and each AE, and answer 'yes' or 'no' to the question "Do you consider that there is a reasonable possibility that the event may have been caused by selumetinib?"

11.7.2 Time Period for Collection of AEs

For patients in the Nested Prospective Cohort, AEs will be collected in the eCRF from the time of starting the medicinal product under study (patient index date [Day 1]) until the end of the maximum 6-year follow-up period.

11.8 Reporting of AEs

For patients in the Nested Prospective Cohort all non-serious related AEs/ADRs, SAEs, and special situations (with or without AE) occurring from the date of enrolment in the study (ie, signature of ICF) until the end of the follow-up period will be reported to the AstraZeneca DES.

The Investigators or other site personnel will inform the appropriate AZ representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of:

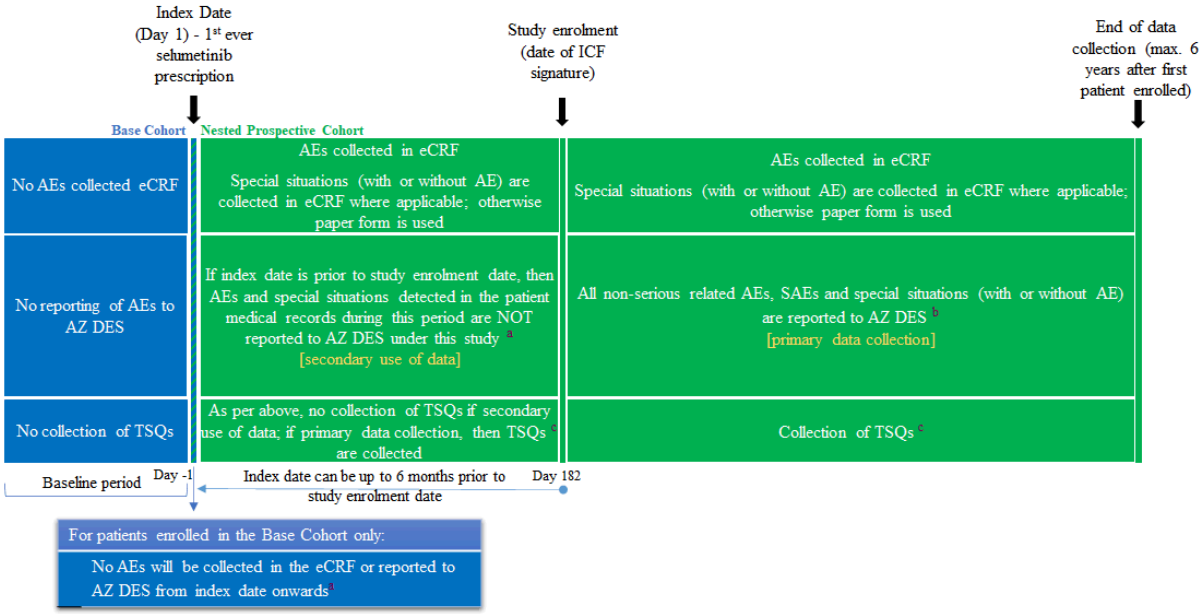
- All AEs with a fatal outcome
- All SAEs (related and unrelated)
- All non-serious ADRs
- Special situation reports (with or without an AE)

The designated AZ representative works with the Investigator to ensure that all the necessary information is provided to the AZ Patient Safety DES within 2 calendar days of initial receipt for fatal and life-threatening events and within 4 calendar days of initial receipt for all other AEs and special situation reports.

For all collected AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AZ representatives of any follow-up information within the same timeframe as the original report.

For AEs not systematically collected or reported as detailed in Section 11 of this protocol, study investigators and consumers are hereby informed of the possibility to report AEs/ADRs (for which they suspect a causal role of a medicine) to the MAH of the suspected medicinal product (studied or not) or to the concerned competent authority via the national spontaneous reporting system (Figure 2).

Figure 2 Overview of Collection and Reporting for AEs and Special Situations



[a] Such AEs should be reported by the Investigator/site as per local requirements.

[b] Triggered by entry of AE on eCRF.

[c] Collected for all important risks as per Risk Management Plan.

Abbreviations: AE = Adverse Event; AZ DES = AstraZeneca (Patient Safety) Data Entry Site; eCRF = Electronic Case Report Form; TSQ = Targeted Safety Questionnaire.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study protocol, study progress reports, and final study report will be included in regulatory communications in line with the RMP, PSUR, and other regulatory reporting requirements. Study reports will be prepared using a template following the GVP Module VIII Section B.4.3.

In its Guidelines for GPPs, the ISPE contends that "there is an ethical obligation to disseminate findings of potential scientific or public health importance" (ISPE 2015); for example, results pertaining to the safety of a marketed medication. "…the marketing authorisation holder should communicate to the Agency and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within two weeks after first acceptance for publication."

Study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors (ICMJE 2014). When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology checklist will be followed (Von Elm et al 2007).

Communication via appropriate scientific venues, eg, ISPE, will be considered.

The research team, including the MAH, the Primary Investigator, and the site investigators will develop a publication plan which will outline the planned publications, potentially including a drug utilisation study and the overall study results.

The MAH and the Investigators have agreed upon a publication policy allowing the Principal Investigator to independently prepare publications based on the study results, irrespective of data ownership. The MAH will be entitled to view the results and interpretations included in the manuscript and provide comments before submission of the manuscript for publication. The MAH and the research team are aware that the MAH should communicate to the Agency (and the competent authorities of the Member States in which the product is authorised) the final manuscript of the article within 2 weeks after first acceptance for publication (EMA2017b). If the Primary Investigator fails to pursue publication of the study results within one year of the conclusion of the study, the site investigators may pursue publication, either individually or in collaboration with the other included countries.

13 REFERENCES

EMA2017b
EMA. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies (EMA/813938/2011 Rev 3). European Medicines Agency; 09 October 2017b. Available at: https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf. Accessed 15 April 2019.

Gross et al 2023
Gross AM, Dombi E, Wolters PL, Baldwin A, Dufek A, Herrera K, et al. Long-Term Safety and Efficacy of Selumetinib on Children with Neurofibromatosis Type 1 on a Phase 1/2Trial for Inoperable Plexiform Neurofibromas. Neuro Oncol. 2023. DOI: 10.1093/neuonc/noad086. Online ahead of print.

Gross et al 2020
Gross AM, Wolters PL, Dombi E, Baldwin A, Whitcomb, Fisher MJ, et al. Selumetinib in Children with Inoperable Plexiform Neurofibromas. N Engl J Med. 2020:382(15);1430-42.

ICMJE 2014
International Committee of Medical Journal Editors (ICMJE). Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. 2014. Available at: http://www.icmje.org/icmje-recommendations.pdf

ISPE 2015
International Society for Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf 2008;17:200-8. Available at: https://www.pharmacoepi.org/pub/1c2a23af-2354-d714-516a-7175549e3a88

KOSELUGO (selumetinib)
KOSELUGO (selumetinib) capsules, for oral use, initial US Approval: 2020. Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850. USPI revised April 2020, Reference ID 4590044.

Von Elm et al 2007
von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-1457. doi:10.1016/S0140-6736(07)61602-X

Annex 1. List of Standalone Documents

None.

Annex 2. ENCePP Checklist for Study Protocols

Annex 3. Additional Information

None.

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d1346r00004-csp-v3		
Document Title:	D1346R00004 Clinical Study Protocol Version 3	
Document ID:	Doc ID-004508017	
Version Label:	3.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
18-Aug-2023 15:08 UTC	PPD	Qualified Person Approval

Notes: (1) Document details as stored in CCI an AstraZeneca document management system.

Table of Contents

Table 10.1.1 Patient Disposition
(Base Cohort)

Country: Austria

	Number (%) of patients	
	Overall	
Patients enrolled[a]	2	
Patients previously treated under the EAP	0	
Patients who received treatment	0	
Patients who discontinued treatment	0	
Adverse event	0	
Patient decision	0	
Patient forgot to take dose	0	
Patient not able to swallow tablet	0	
Response-related dose change	0	
Other	0	
Patients ongoing in the study at the data cut-off	2	(100.0)
Patients discontinued from study	0	
Withdrawal by parent/guardian	0	
Completed	0	
Death	0	
Lost to follow-up	0	
Withdrawal by patient	0	
Other	0	
Patients included in Nested Prospective Cohort	0	
Patients who met all eligibility criteria	2	(100.0)
Patients who did not meet all eligibility criteria	0	

EAP Early Access Program.
[a] Informed consent/assent received
The disposition status for Subject E2308003 was erroneously entered as 'Other' on the eCRF as per data cut-off; the Subject has not been discontinued from the study.
One Subject in France (E2310001) was erroneously not assigned to the Nested Prospective Cohort in the eCRF at the time of data cut-off.

Table 10.1.1 Patient Disposition
(Base Cohort)

Country: France

	Number (%) of patients
	Overall
Patients enrolled[a]	16
Patients previously treated under the EAP	0
Patients who received treatment	14 (87.5)
Patients who discontinued treatment	1 (6.3)
Adverse event	0
Patient decision	0
Patient forgot to take dose	0
Patient not able to swallow tablet	0
Response-related dose change	0
Other	0
Missing	1 (6.3)
Patients ongoing in the study at the data cut-off	15 (93.8)
Patients discontinued from study	1 (6.3)
Withdrawal by parent/guardian	0
Completed	0
Death	0
Lost to follow-up	0
Withdrawal by patient	0
Other	1 (6.3)
Patients included in Nested Prospective Cohort	11 (68.8)
Patients who met all eligibility criteria	15 (93.8)
Patients who did not meet all eligibility criteria	1 (6.3)
EXCL01	1 (6.3)

EAP Early Access Program.
[a] Informed consent/assent received
The disposition status for Subject E2308003 was erroneously entered as 'Other' on the eCRF as per data cut-off; the Subject has not been discontinued from the study.
One Subject in France (E2310001) was erroneously not assigned to the Nested Prospective Cohort in the eCRF at the time of data cut-off.

Table 10.1.1 Patient Disposition
(Base Cohort)

Country: Germany

	Number (%) of patients
	Overall
Patients enrolled[a]	6
Patients previously treated under the EAP	0
Patients who received treatment	5 (83.3)
Patients who discontinued treatment	2 (33.3)
Adverse event	0
Patient decision	1 (16.7)
Patient forgot to take dose	0
Patient not able to swallow tablet	0
Response-related dose change	0
Other	0
Missing	1 (16.7)
Patients ongoing in the study at the data cut-off	4 (66.7)
Patients discontinued from study	2 (33.3)
Withdrawal by parent/guardian	0
Completed	1 (16.7)
Death	0
Lost to follow-up	0
Withdrawal by patient	0
Other	1 (16.7)
Patients included in Nested Prospective Cohort	1 (16.7)
Patients who met all eligibility criteria	6 (100.0)
Patients who did not meet all eligibility criteria	0

EAP Early Access Program.
[a] Informed consent/assent received
The disposition status for Subject E2308003 was erroneously entered as 'Other' on the eCRF as per data cut-off; the Subject has not been discontinued from the study.
One Subject in France (E2310001) was erroneously not assigned to the Nested Prospective Cohort in the eCRF at the time of data cut-off.

Table 10.1.1 Patient Disposition
(Base Cohort)

Country: Portugal

	Number (%) of patients
	Overall
Patients enrolled[a]	9
Patients previously treated under the EAP	0
Patients who received treatment	9 (100.0)
Patients who discontinued treatment	1 (11.1)
Adverse event	0
Patient decision	0
Patient forgot to take dose	0
Patient not able to swallow tablet	0
Response-related dose change	0
Other	0
Missing	1 (11.1)
Patients ongoing in the study at the data cut-off	4 (44.4)
Patients discontinued from study	5 (55.6)
Withdrawal by parent/guardian	0
Completed	5 (55.6)
Death	0
Lost to follow-up	0
Withdrawal by patient	0
Other	0
Patients included in Nested Prospective Cohort	4 (44.4)
Patients who met all eligibility criteria	9 (100.0)
Patients who did not meet all eligibility criteria	0

EAP Early Access Program.
[a] Informed consent/assent received
The disposition status for Subject E2308003 was erroneously entered as 'Other' on the eCRF as per data cut-off; the Subject has not been discontinued from the study.
One Subject in France (E2310001) was erroneously not assigned to the Nested Prospective Cohort in the eCRF at the time of data cut-off.

Table 10.1.1 Patient Disposition
(Base Cohort)

Country: Overall

	Number (%) of patients
	Overall
Patients enrolled[a]	33
Patients previously treated under the EAP	0
Patients who received treatment	28 (84.8)
Patients who discontinued treatment	4 (12.1)
Adverse event	0
Patient decision	1 (3.0)
Patient forgot to take dose	0
Patient not able to swallow tablet	0
Response-related dose change	0
Other	0
Missing	3 (9.1)
Patients ongoing in the study at the data cut-off	25 (75.8)
Patients discontinued from study	8 (24.2)
Withdrawal by parent/guardian	0
Completed	6 (18.2)
Death	0
Lost to follow-up	0
Withdrawal by patient	0
Other	2 (6.1)
Patients included in Nested Prospective Cohort	16 (48.5)
Patients who met all eligibility criteria	32 (97.0)
Patients who did not meet all eligibility criteria	1 (3.0)
EXCL01	1 (3.0)

EAP Early Access Program.
[a] Informed consent/assent received
The disposition status for Subject E2308003 was erroneously entered as 'Other' on the eCRF as per data cut-off; the Subject has not been discontinued from the study.
One Subject in France (E2310001) was erroneously not assigned to the Nested Prospective Cohort in the eCRF at the time of data cut-off.

Table 10.1.2.1 Patient enrolment by country and site
(Base Cohort)

Country	Site	Number (%) of patients Overall (N=33)
France	Total	16 (48.5)
	PPD	7 (21.2)
		4 (12.1)
		2 (6.1)
		1 (3.0)
		1 (3.0)
		1 (3.0)
Portugal	Total	9 (27.3)
	PPD	9 (27.3)
Germany	Total	6 (18.2)
	PPD	4 (12.1)
	PPD	1 (3.0)
	PPD	1 (3.0)
Austria	Total	2 (6.1)
	PPD	2 (6.1)

N Number of patients in cohort group.

Program Name: t_adsl_enrl_site_base.sas • Output Name: T_10_01_02_01.rtf • Execution Date: 28JUL2023:6:49 AM

Table 10.1.2.2 Patient enrolment by country and site
(Nested Prospective Cohort)

Country	Site	Number (%) of patients Overall (N=16)
France	Total	11 (68.8)
	PPD	6 (37.5)
		3 (18.8)
		1 (6.3)
		1 (6.3)
Portugal	Total	4 (25.0)
	PPD	4 (25.0)
Germany	Total	1 (6.3)
	PPD	1 (6.3)

N Number of patients in cohort group.
One Subject in France (E2310001) was erroneously not assigned to the Nested Prospective Cohort in the eCRF at the time of data cut-off.

Table 10.2.1.1 Demographic characteristics
(Base Cohort)

Demographic characteristic		Overall (N=33)	
Age* (years)	n	33	
	Mean	12.3	
	SD	4.08	
	Min	3	
	Q1	10.0	
	Median	13.0	
	Q3	16.0	
	Max	18	
Age group* (years) n (%)	n	33	(100.0)
	<12	13	(39.4)
	>=12	20	(60.6)
Sex n (%)	n	33	(100.0)
	Male	21	(63.6)
	Female	12	(36.4)
Race n (%)	n	33	(100.0)
	White	6	(18.2)
	Black or African American	2	(6.1)
	Asian	0	
	Native Hawaiian or Other Pacific Islander	0	
	American Indian or Alaskan Native	0	
	Other	1	(3.0)
	Not Reported	23	(69.7)
	Multiple	0	
	Missing	1	(3.0)

Max Maximum. Min Minimum. N Number of patients in cohort group. n Number of patients included in analysis. Q1 25th percentile. Q3 75th percentile. SD Standard deviation. *Age at date of informed consent as collected in the eCRF.

Table 10.2.1.1 Demographic characteristics
(Base Cohort)

Demographic characteristic		Overall (N=33)	
Ethnic group n (%)	n	33	(100.0)
	Hispanic or Latino	11	(33.3)
	Not Hispanic or Latino	9	(27.3)
	Missing	13	(39.4)
Country n (%)	n	33	(100.0)
	Austria	2	(6.1)
	France	16	(48.5)
	Germany	6	(18.2)
	Portugal	9	(27.3)

Max Maximum. Min Minimum. N Number of patients in cohort group. n Number of patients included in analysis. Q1 25th percentile. Q3 75th percentile. SD Standard deviation. *Age at date of informed consent as collected in the eCRF.

Table 10.2.1.2 Demographic characteristics
(Nested Prospective Cohort)

Demographic characteristic		Overall (N=16)	
Age* (years)	n	16	
	Mean	11.9	
	SD	2.13	
	Min	8	
	Q1	10.0	
	Median	12.0	
	Q3	13.5	
	Max	15	
Age group* (years) n (%)	n	16	(100.0)
	<12	7	(43.8)
	>=12	9	(56.3)
Sex n (%)	n	16	(100.0)
	Male	11	(68.8)
	Female	5	(31.3)
Race n (%)	n	16	(100.0)
	White	1	(6.3)
	Black or African American	1	(6.3)
	Asian	0	
	Native Hawaiian or Other Pacific Islander	0	
	American Indian or Alaskan Native	0	
	Other	0	
	Not Reported	13	(81.3)
	Multiple	0	
	Missing	1	(6.3)

Max Maximum. Min Minimum. N Number of patients in cohort group. n Number of patients included in analysis. Q1 25th percentile. Q3 75th percentile. SD Standard deviation. *Age at date of informed consent as collected in the eCRF.

Table 10.2.1.2 Demographic characteristics
(Nested Prospective Cohort)

Demographic characteristic		Overall (N=16)	
Ethnic group n (%)	n	16	(100.0)
	Hispanic or Latino	6	(37.5)
	Not Hispanic or Latino	2	(12.5)
	Missing	8	(50.0)
Country n (%)	n	16	(100.0)
	France	11	(68.8)
	Germany	1	(6.3)
	Portugal	4	(25.0)

Max Maximum. Min Minimum. N Number of patients in cohort group. n Number of patients included in analysis. Q1 25th percentile. Q3 75th percentile. SD Standard deviation. *Age at date of informed consent as collected in the eCRF.

Table 10.4.2 Duration of exposure to Selumetinib
(Nested Prospective Cohort)

Characteristic	Statistic	Overall (N=16)
Duration of total exposure (months)	n	16
	Mean	10.14
	SD	9.55
	Min	0.3
	Q1	5.85
	Median	9.32
	Q3	12.41
	Max	42.0
Duration of actual cumulative exposure (months)	n	16
	Mean	9.87
	SD	9.52
	Min	0.3
	Q1	5.85
	Median	8.84
	Q3	11.91
	Max	42.0
Total cumulative dose (mg)	n	16
	Mean	17526.9
	SD	15673.59
	Min	450
	Q1	8180.0
	Median	14770.0
	Q3	25830.0
	Max	63950

Max Maximum. Min Minimum. N Number of patients in cohort group. n Number of patients included in analysis. Q1 25th percentile. Q3 75th percentile. SD Standard deviation. Total (or intended) exposure = [min (last dose date where dose > 0 [mg], date of death, date of data cut-off) − first dose date +1] / (365.25 / 12).
Actual cumulative exposure = Total (or intended) exposure, excluding dose interruptions.
Dosage (mg/month) = total cumulative dose received (mg)/ (Number of days receiving study drug) / (365.25 / 12)
Total cumulative dose is the total dose received during the total exposure of selumetinib.
Date of first exposure to selumetinib for Subject E2307001 was corrected to 20JAN2023 in the eCRF after DCO; subject-specific values and summary characteristics for selumetinib exposure are affected.

Table 10.4.2 Duration of exposure to Selumetinib
(Nested Prospective Cohort)

Characteristic	Statistic	Overall (N=16)
Dosage (mg/month)	n	16
	Mean	1712.56
	SD	397.18
	Min	1065.5
	Q1	1510.95
	Median	1601.76
	Q3	2130.33
	Max	2452.0
Year of initiation of Selumetinib	n	16 (100.0)
	2020	1 (6.3)
	2022	12 (75.0)
	2023	3 (18.8)

Max Maximum. Min Minimum. N Number of patients in cohort group. n Number of patients included in analysis. Q1 25th percentile. Q3 75th percentile. SD Standard deviation. Total (or intended) exposure = [min (last dose date where dose > 0 [mg], date of death, date of data cut-off) – first dose date +1] / (365.25 / 12).
Actual cumulative exposure = Total (or intended) exposure, excluding dose interruptions.
Dosage (mg/month) = total cumulative dose received (mg)/ (Number of days receiving study drug) / (365.25 / 12)
Total cumulative dose is the total dose received during the total exposure of selumetinib.
Date of first exposure to selumetinib for Subject E2307001 was corrected to 20JAN2023 in the eCRF after DCO; subject-specific values and summary characteristics for selumetinib exposure are affected.

Table 10.4.3.1 Total daily Selumetinib dose at baseline
(Base Cohort)

Characteristic	Statistic	Overall (N = 33)
Total daily Selumetinib dose at baseline (mg)	n	28
	Mean	62.0
	SD	17.97
	Min	30
	Q1	50.0
	Median	65.0
	Q3	70.0
	Max	100
	Missing	5

Max Maximum. Min Minimum. N Number of patients in cohort group. n Number of patients included in analysis. Q1 25th percentile. Q3 75th percentile. SD Standard deviation.

Table 10.4.3.2 Total daily Selumetinib dose at baseline
(Nested Prospective Cohort)

Characteristic	Statistic	Overall (N = 16)
Total daily Selumetinib dose at baseline (mg)	n	16
	Mean	56.6
	SD	14.46
	Min	35
	Q1	50.0
	Median	50.0
	Q3	70.0
	Max	90

Max Maximum. Min Minimum. N Number of patients in cohort group. n Number of patients included in analysis. Q1 25th percentile. Q3 75th percentile. SD Standard deviation.

Table 10.4.4 Selumetinib discontinuation, interruption, dose increase and dose reduction during follow-up
(Nested Prospective Cohort)

	Number (%) of patients
	Overall (N = 16)
Number of patients with at least one treatment interruption	6(37.5)
Number of patients with 2 or more treatment interruptions	3(18.8)
Number of treatment interruptions[a]	10(62.5)
Reasons for treatment interruption	
Adverse Event	2(20.0)[b]
Response-Related Dose Change	0
Patient forgot to take dose	0
Patient Decision	2(20.0)[b]
Patient not able to swallow tablet	0
Other	6(60.0)[b]
Number of patients with at least one dose reduction	1(6.3)
Number of patients with at least one dose increase	2(12.5)
Number of patients who permanently discontinued treatment	1(6.3)

N Number of patients in cohort group.
[a]Patients may have more than one treatment interruption during the study.
[b]Percentage based on number of all treatment interruptions.

Table 10.6.1.1 Overview: Adverse events in any category
(Base Cohort)

AE category	Overall(N=33) Number	(%) of patients [a]	Event [b]
Any AE	20	(60.6)	97
Any AE with a reasonable possibility caused by Selumetinib	18	(54.5)	67
Any AE with outcome of death	0		0
Any AEs of CTCAE grade 3 or higher	3	(9.1)	4
Any AEs of CTCAE grade 3 or higher with a reasonable possibility caused by Selumetinib	1	(3.0)	1
Any SAEs (including events with outcome of death)	2	(6.1)	2
Any SAEs leading to permanent Selumetinib discontinuation	0		0
Any SAEs with a reasonable possibility caused by Selumetinib	0		0
Any AEs leading to permanent Selumetinib discontinuation	0		0
Any AEs leading to dose increase of Selumetinib	0		0
Any AEs leading to dose reduction of Selumetinib	3	(9.1)	4
Any AEs leading to dose interruption of Selumetinib	4	(12.1)	5
Any AESI	2	(6.1)	4
Any AESI of CTCAE grade 3 or higher	0		0
Any AESI with a reasonable possibility caused by Selumetinib	2	(6.1)	4

AE Adverse event. AESI AE of Special Interest (medical concepts for AESIs in this study are: cardiac toxicity, muscular toxicity, hepatotoxicity, ocular toxicity; in the pediatric population only: physeal dysplasia and choking on capsule).
N Number of patients in cohort group. SAE Serious AE .
[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
[b] Multiple events in the same category are counted multiple times in that category. Multiple events belonging to more than one category are counted multiple times in each of those categories. CTCAE Common Terminology Criteria for Adverse Events 5.0.

Program Name: t_adae_any_base.sas • Output Name: T_10_06_01_01.rtf • Execution Date: 28JUL2023:6:48 AM

Table 10.6.1.2 Overview: Adverse events in any category
(Nested Prospective Cohort)

AE category	Overall(N=16) Number (%) of patients [a]	Event [b]
Any AE	11 (68.8)	42
Any AE with a reasonable possibility caused by Selumetinib	10 (62.5)	31
Any AE with outcome of death	0	0
Any AEs of CTCAE grade 3 or higher	0	0
Any AEs of CTCAE grade 3 or higher with a reasonable possibility caused by Selumetinib	0	0
Any SAEs (including events with outcome of death)	0	0
Any SAEs leading to permanent Selumetinib discontinuation	0	0
Any SAEs with a reasonable possibility caused by Selumetinib	0	0
Any AEs leading to permanent Selumetinib discontinuation	0	0
Any AEs leading to dose increase of Selumetinib	0	0
Any AEs leading to dose reduction of Selumetinib	1 (6.3)	2
Any AEs leading to dose interruption of Selumetinib	2 (12.5)	3
Any AESI	1 (6.3)	3
Any AESI of CTCAE grade 3 or higher	0	0
Any AESI with a reasonable possibility caused by Selumetinib	1 (6.3)	3

AE Adverse event. AESI AE of Special Interest (medical concepts for AESIs in this study are: cardiac toxicity, muscular toxicity, hepatotoxicity, ocular toxicity; in the pediatric population only: physeal dysplasia and choking on capsule).
N Number of patients in cohort group. SAE Serious AE .
[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
[b] Multiple events in the same category are counted multiple times in that category. Multiple events belonging to more than one category are counted multiple times in each of those categories. CTCAE Common Terminology Criteria for Adverse Events 5.0.

Program Name: t_adae_any_nested.sas • Output Name: T_10_06_01_02.rtf • Execution Date: 28JUL2023:6:48 AM

Table 10.6.13.1 Serious adverse events - key patient information
(Base Cohort)

Country/Site	Patient identifier	Age*/Sex /Race	Event term <verbatim> as reported by the investigator	Adverse event (Preferred term)	Time from start of treatment to onset of AE (days)	Time from last dose prior to AE start date (days) [a]	Time from start of treatment to becoming serious (days)	Outcome	Action taken (with selumetinib)	Reasonable possibility AE caused by selumetinib [b]
PPD										

N No. Y Yes. M Male. F Female. DNC Dose not changed. DINC Dose increased. DR Dose reduced. DINT Dose interrupted. DPC Drug permanently discontinued. AI American Indian or Alaska native. A Asian. BA Black or African American. PI Native Hawaiian or Other Pacific Islander. W White. O Other. NR Not Reported. *Age at date of informed consent as collected in the eCRF.
[a]Calculated for AEs starting after the discontinuation of selumetinib.
[b]As assessed by the investigator.
MedDRA version 24.1

Program Name: t_adae_sae_base.sas • Output Name: T_10_06_13_01.rtf • Execution Date: 28JUL2023:6:48 AM

Table 10.6.13.2 Serious adverse events - key patient information
(Nested Prospective Cohort)

Country/Site	Patient identifier	Age*/Sex /Race	Event term <verbatim> as reported by the investigator	Adverse event (Preferred term)	Time from start of treatment to onset of AE (days)	Time from last dose prior to AE start date (days) [a]	Time from start of treatment to becoming serious (days)	Outcome	Action taken (with selumetinib)	Reasonable possibility AE caused by selumetinib [b]
There are no observations for this output										

N No. Y Yes. M Male. F Female. DNC Dose not changed. DINC Dose increased. DR Dose reduced. DINT Dose interrupted. DPC Drug permanently discontinued. AI American Indian or Alaska native. A Asian. BA Black or African American. PI Native Hawaiian or Other Pacific Islander. W White. O Other. NR Not Reported. *Age at date of informed consent as collected in the eCRF.
[a]Calculated for AEs starting after the discontinuation of selumetinib.
[b]As assessed by the investigator.
MedDRA version 24.1

Table 10.6.18 Listing of deaths
(Nested Prospective Cohort)

Country/Site	Patient identifier	Age/Sex/Race	Time from first dose (days)	Time from last dose to death (days)	Death Date	Primary cause of death investigator text	Primary cause MedDRA preferred term	Secondary cause of death investigator text	Secondary cause MedDRA preferred term
No event									

F Female. M Male. MedDRA Medical Dictionary for Regulatory Activities. N No. Y Yes. AI American Indian or Alaska native. A Asian. BA Black or African American. PI Native Hawaiian or Other Pacific Islander. W White. O Other. NR Not Reported. MedDRA version 24.1

Program Name: t_lis_death_nested.sas • Output Name: T_10_06_18.rtf • Execution Date: 28JUL2023:6:49 AM

Table of Contents

Listing 10.2.1 Discontinued patients
(Base Cohort)

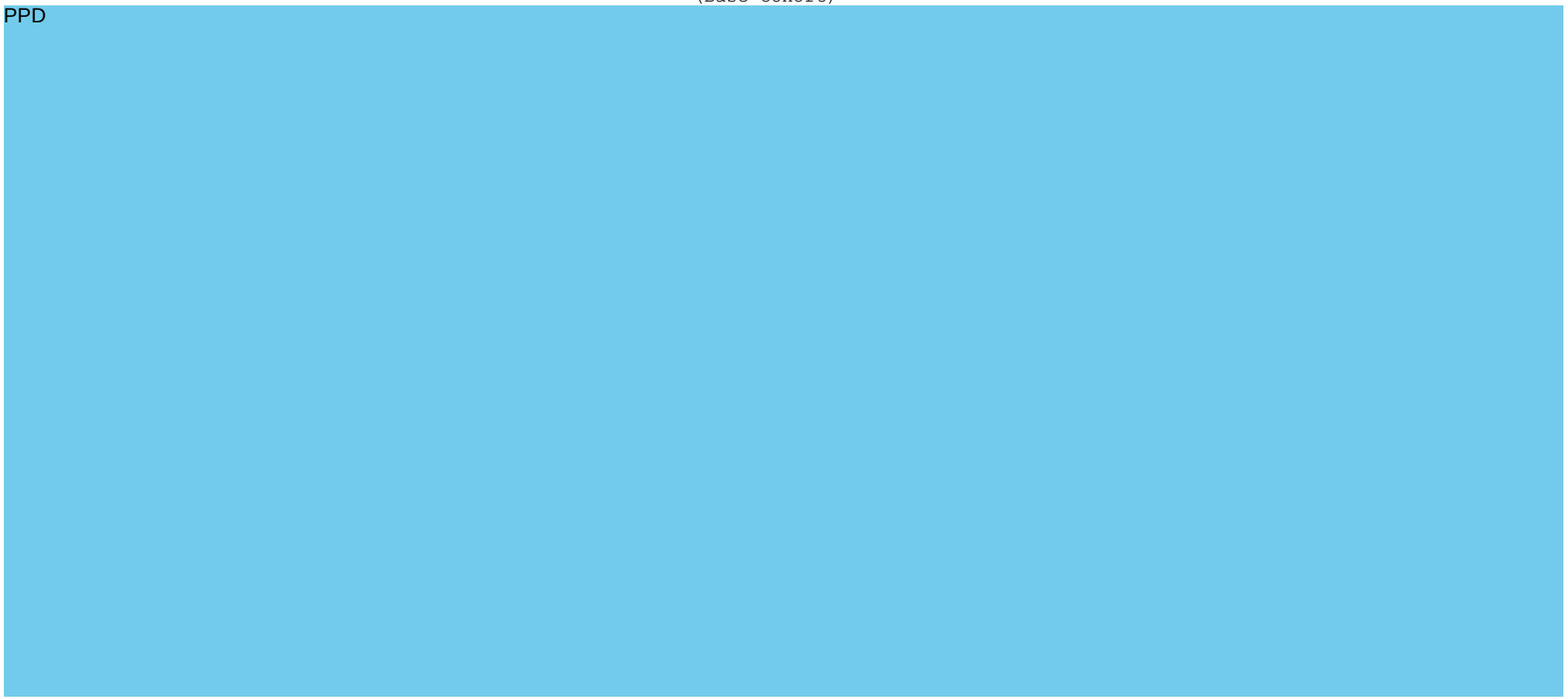
Listing 10.2.2.1 Demographic and anthropometric characteristics at baseline
(Base Cohort)

Listing 10.2.2.1 Demographic and anthropometric characteristics at baseline

PPD

Listing 10.5.1 Patient exposure to Selumetinib
(Base Cohort)

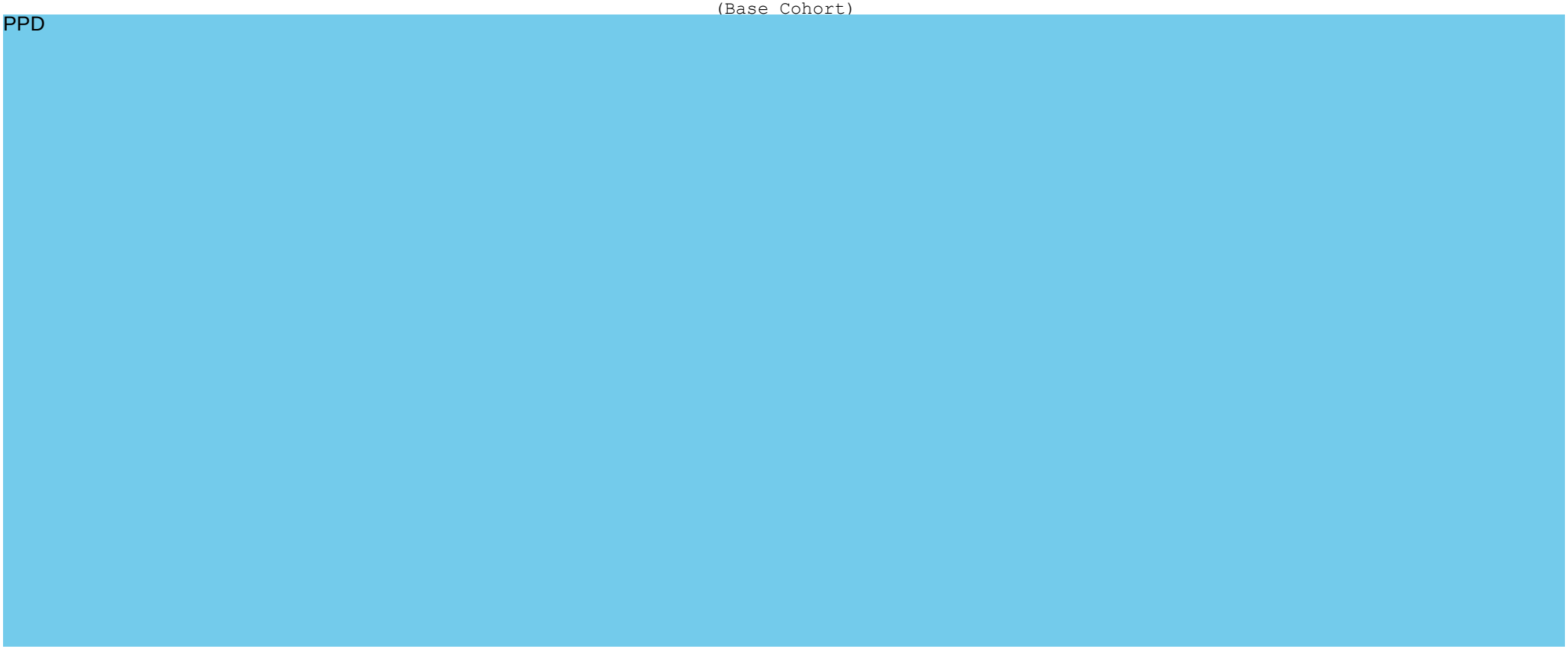
PPD



Listing 10.5.1 Patient exposure to Selumetinib

PPD

Listing 10.6.1 Adverse events
(Base Cohort)



Listing 10.6.1 Adverse events

PPD

Listing 10.6.1 Adverse events
(Base Cohort)

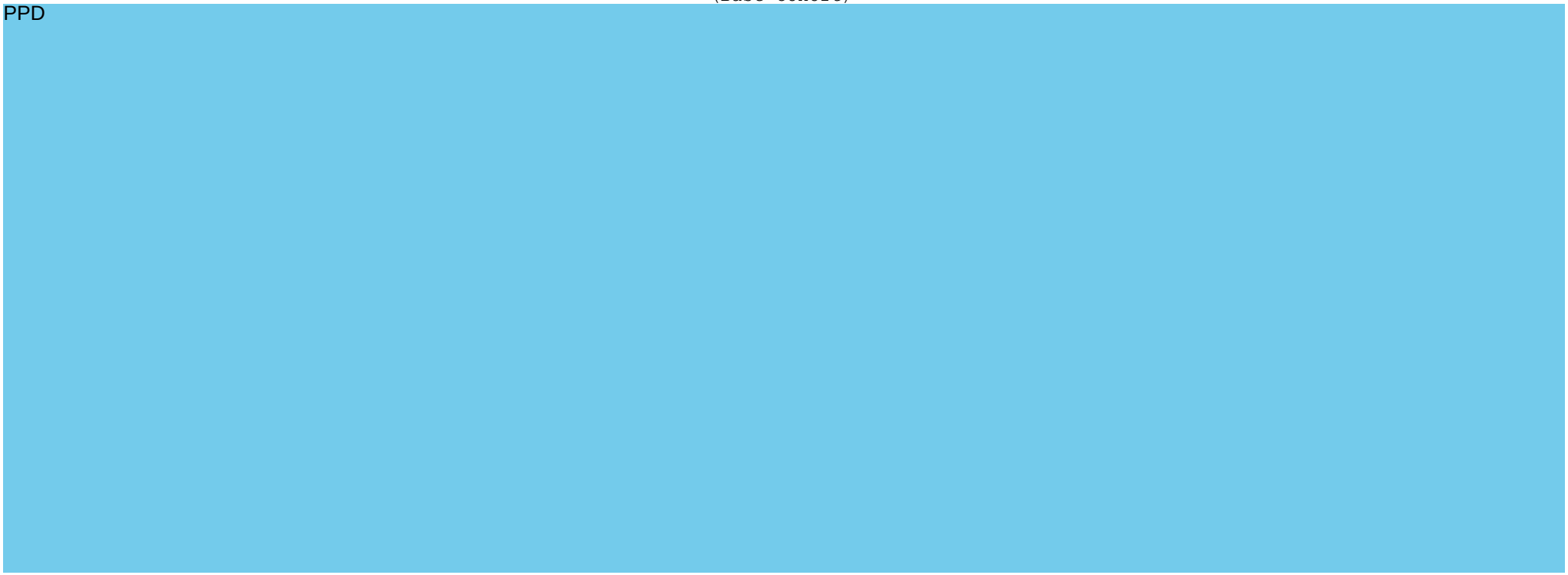
PPD

Listing 10.6.1 Adverse events
(Base Cohort)

PPD

Listing 10.6.1 Adverse events
(Base Cohort)

PPD



Listing 10.6.1 Adverse events

Listing 10.6.1 Adverse events

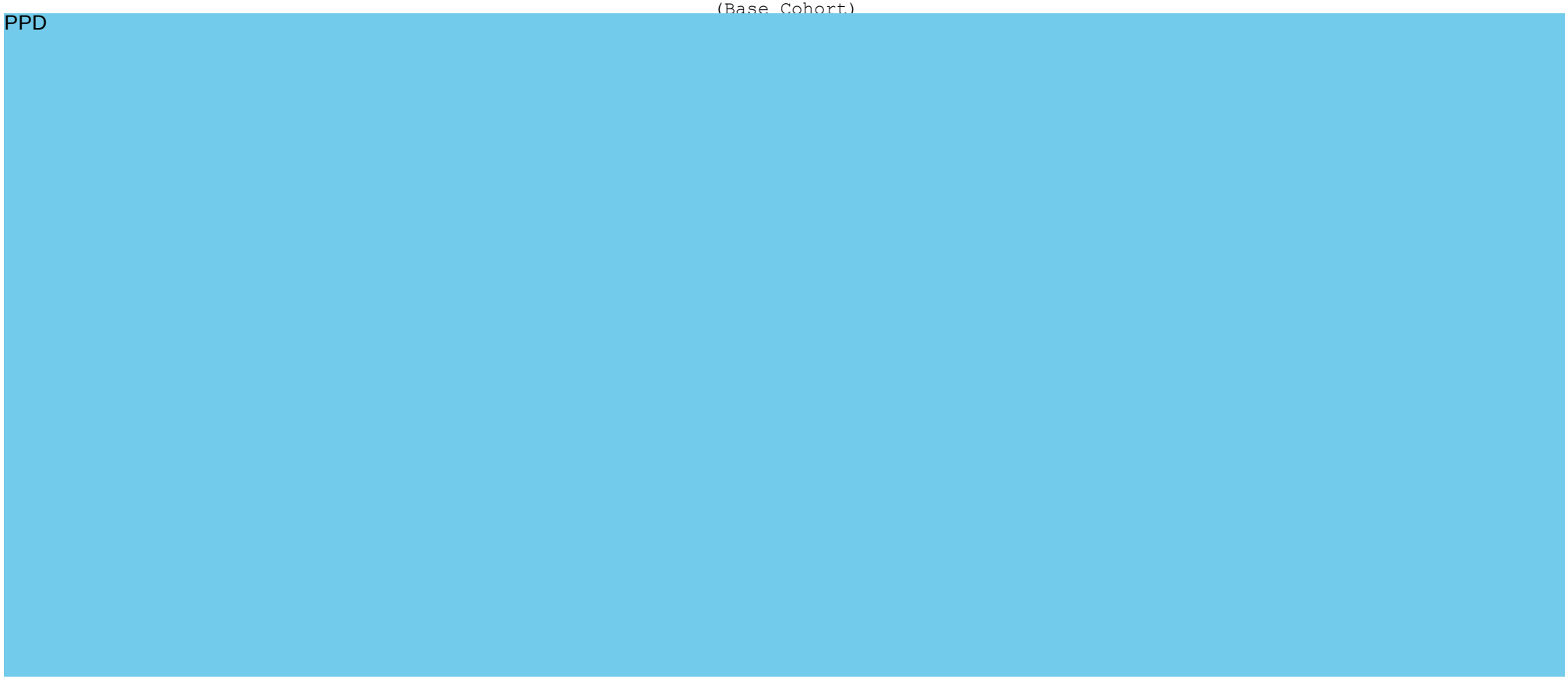
Listing 10.6.1 Adverse events
(Base Cohort)

PPD

Listing 10.6.1 Adverse events
(Base Cohort)

Listing 10.6.1 Adverse events
(Base Cohort)

PPD

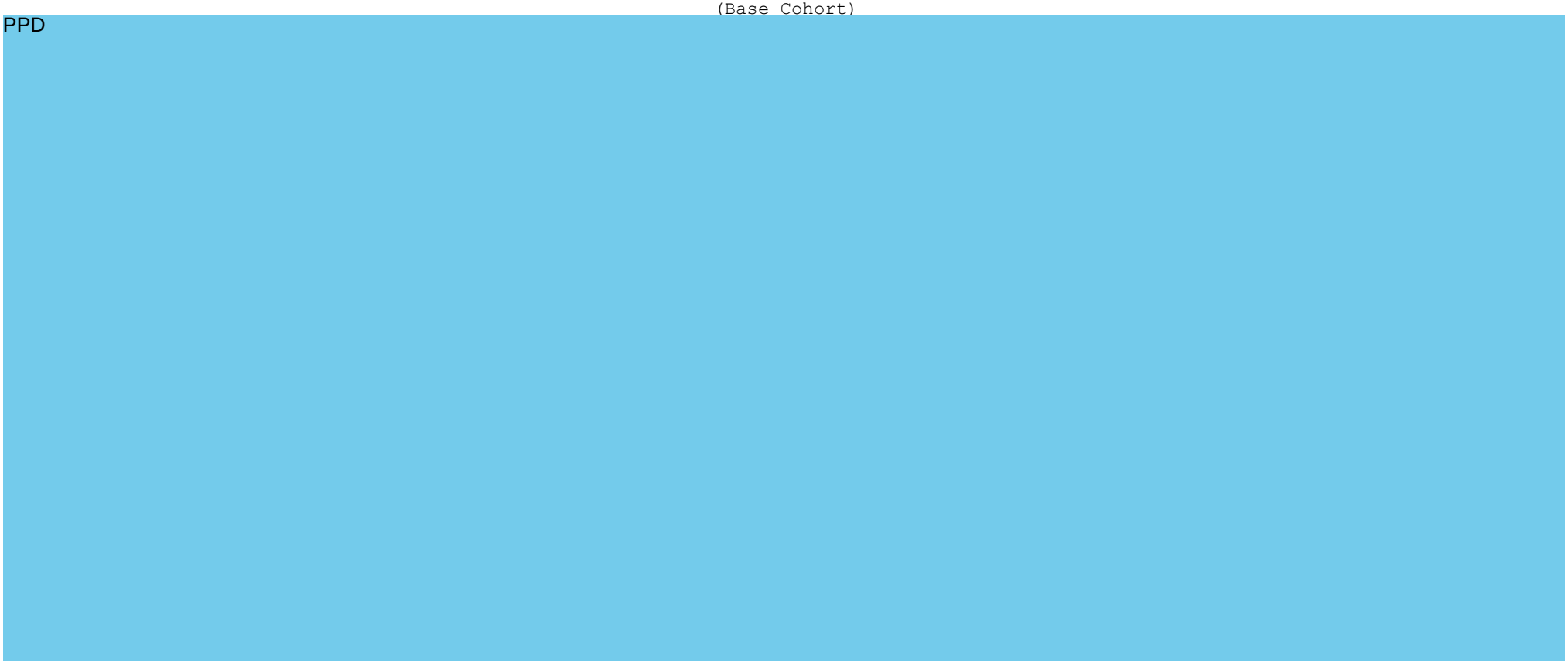


Listing 10.6.1 Adverse events
(Base Cohort)

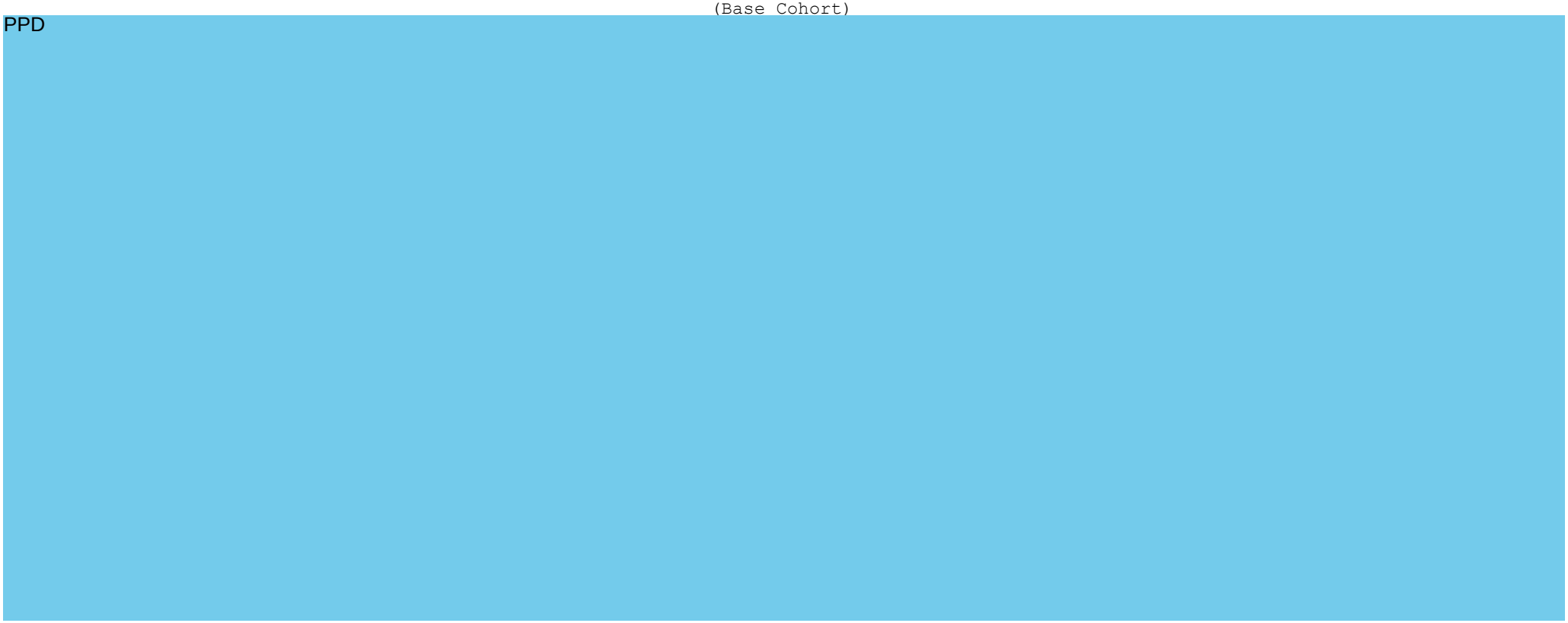
Listing 10.6.1 Adverse events

Listing 10.6.1 Adverse events
(Base Cohort)

PPD



Listing 10.6.1 Adverse events
(Base Cohort)



Listing 10.6.1 Adverse events
(Base Cohort)

Listing 10.6.1 Adverse events
(Base Cohort)

Listing 10.6.1 Adverse events
(Base Cohort)

Listing 10.6.1 Adverse events
(Base Cohort)

PPD

Listing 10.6.1 Adverse events
(Base Cohort)

PPD

Listing 10.6.1 Adverse events
(Base Cohort)

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d1346r00004-pass-clinical-study-report		
Document Title:	D1346R0004: Post-Authorisation Safety Study of Paediatric Patients Initiating Selumetinib: A Multiple-Country Prospective Cohort Study – Annual Progress Report 1	
Document ID:	Doc ID-005272763	
Version Label:	1.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
12-Sep-2023 07:56 UTC	PPD (Alexion)	Content Approval
12-Sep-2023 07:06 UTC	PPD (Alexion)	Author Approval

Notes: (1) Document details as stored in CCI, an AstraZeneca document management system.