PASS Protocol

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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

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Approved by:

PPD

Electronic signature is available at the end of the document

PASS INFORMATION

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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

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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

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CCI	
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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.

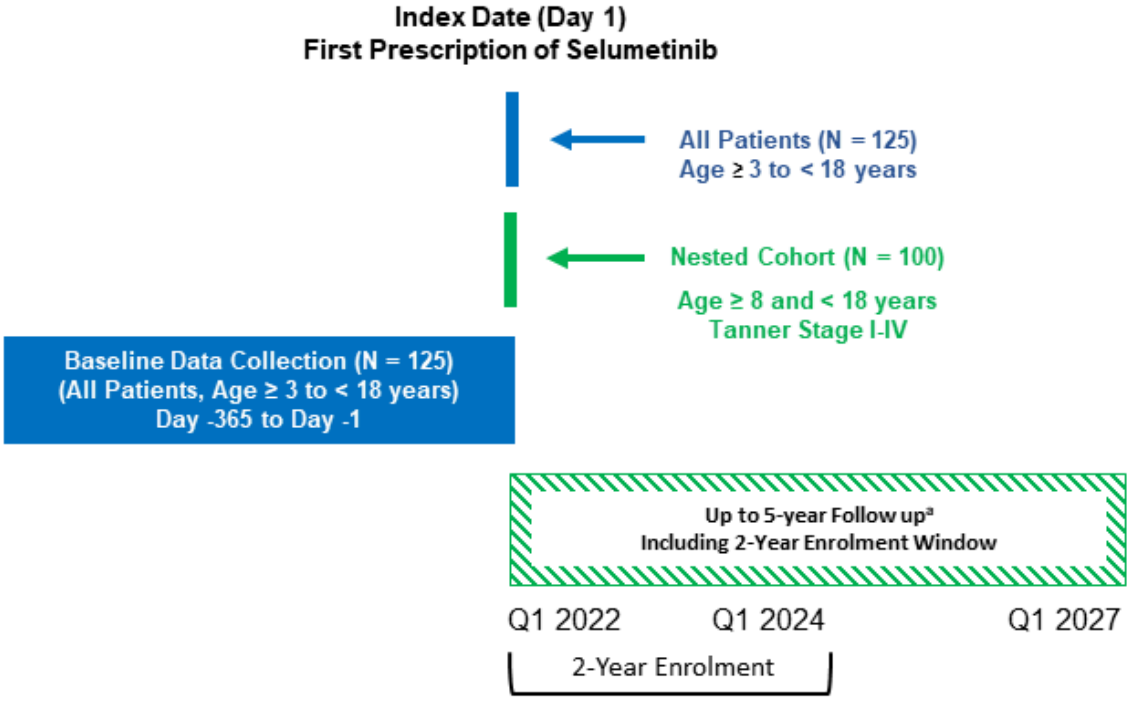
An eligible subset of patients (aged 8 to < 18 years who have not reached Tanner Stage V on the index date) will be enrolled in the Nested Prospective Cohort. Data will be collected following the first dose of selumetinib (Day 1) for the duration of the study and will focus on assessing the safety outcomes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

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