NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Studyinformation

Title	Real World Data Collection Among Pediatric Neuroblastoma Patients Treated with Lorlatinib Through Expanded Access Program
Protocol number	B7461036
Protocol version identifier	Version 1.0
Date	23 February 2021
Active substance	Lorlatinib (L01XE44)
Medicinal product	Lorlatinib
Research question and objectives	The overall goal of this real-world data collection is to assess demographic, clinical characteristics and real-world effectiveness of pediatric neuroblastoma patients who initiated treatment with lorlatinib through expanded access programs.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALK	anaplastic lymphoma kinase
BSA	body surface area
DCT	data collection tool
DSU	drug safety unit
EDC	electronic data capture
HCP	healthcare professional
IEC	independent ethics committee
IRB	institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
NANT	New Agents in Neuroblastoma Therapy consortium
NB	neuroblastoma
OS	overall survival
RWD	real world data
SAE	serious adverse event
SD	standard deviation
SIOPEN	European SIOP Neuroblastoma Group
SQN	Syne Qua Non Limited
TKI	tyrosine kinase inhibitor
US	United States

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
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4. AMENDMENTS AND UPDATES

None

5. MILESTONES

Milestone	Planned date
Start of data collection	25 February 2021
Treatment completed population – data collection completion date	25 March 2021
Progress report – Treatment completed population	28 April 2021
Interim report 1 – Year 1	31 December 2021
Interim report 2 – Year 2	31 December 2022
End of data collection (Last patient added to real world data collection)	31 December 2023
Database lock	15 February 2024
Final study report	31 March 2024

6. RATIONALE AND BACKGROUND

Neuroblastoma (NB) is an aggressive solid tumor of childhood. Neuroblastoma is the third most common childhood cancer in the United States and accounts for 7-10% of pediatric cancers.[1] Estimated incidence of neuroblastoma is approximately 10-11 cases per million children under 15 years of age United States (US) and Europe.[2,3] Incidence in children <1 year is as high has 44.7 per million in Europe and 53 per million in US.[2] Neuroblastoma is most commonly diagnosed during the first year of life.[1,2] While 90% of cases are diagnosed before the age of 5, 30% of those are within the first year. The median age of diagnosis is 22 months. Rarely does it present in adolescence and adulthood, but outcomes are much poorer in this age group.[4] In addition, neuroblastoma accounts for approximately 12% of all cancer-related deaths in pediatric population.[5,6]

Five-year survival rates for infants with neuroblastoma range from 65% to 88% and overall survival has improved over time, likely due to therapeutic improvements.[1,3,5,7] However, improvements are attributable to improvement in patients with more low or intermediate-risk disease, mortality rates among children with high-risk neuroblastoma have shown modest improvement.[8]

Neuroblastoma is a complex disease but often results in treatment-resistant progression, metastasis and death.[8] Long-term survival rates for children with high-risk neuroblastoma are currently 40-50%.[8] Many patients (50-60%) with high-risk neuroblastoma will have either

refractory disease (responding poorly to therapy) or will relapse (experience disease recurrence). To date there are no well-established curative treatment regimens for these patients.[8,9] Median time to relapse is estimated to be approximately 13 months, and patients who relapsed between 6 and 18 months after diagnosis have the highest risk of death.[10]

Current treatment approach for high-risk patients include induction chemotherapy (reduce tumor burden by shrinking tumor), local control (delayed surgery to remove tumor), consolidation (myeloablative therapy with stem cell rescue performed in tandem) and maintenance therapy (GD2-directed therapy, which is painful and toxic).[11] A published meta-analysis of three European SIOP Neuroblastoma Group (SIOPEN) trials on standard backbone chemotherapy regimens showed poor outcomes in both relapsed and refractory neuroblastoma patients.[12] It is important to note that, unlike childhood leukemias, there is no standard approach for high-risk neuroblastoma patients who suffer a relapse and there is no known curative therapy. Response rates in clinical trials of relapsed/refractory neuroblastoma ranged from 20-64%.[12] After treatment, progression occurred in 54% of patients with refractory disease versus 87% of patients with relapsed disease.[12] Overall median OS was 16.1 months, with longer median OS for patients with refractory disease compared to relapsed disease.[12] Neuroblastoma has significant heterogeneity, therefore risk stratification has become an important factor in identifying novel biomarkers to inform treatment decisions.[9]

Initial reports of anaplastic lymphoma kinase (ALK) gene amplification and overexpression suggested a role of ALK in neuroblastoma.[13,14] Notably, ALK activating mutations were first discovered in the germline of families where the disease is inherited, and subsequently found to be present in somatic tissue in ~10% of patients at diagnosis.[15-18] The majority of patients with familial neuroblastoma have germline mutations in ALK.[18] Sporadic neuroblastoma tumors also occasionally harbor ALK abnormalities, including 4% of tumors with genomic amplification and approximately 10% with missense mutations.[14,17-19] Furthermore, the presence of ALK mutation correlates with worse prognosis in high and intermediate risk patients.[20] The detection of ALK mutations and/or amplifications in primary neuroblastomas, provides a molecular rational for targeted therapy of neuroblastoma.[16] It has been demonstrated that downregulation of ALK suppressed proliferation of neuroblastoma cells harboring mutated ALK.[15]

The identification of ALK as a critical factor in the development of neuroblastoma make it an attractive therapeutic target. Lorlatinib is a potent, brain-penetrant, third generation inhibitor of ALK.[21] Lorlatinib overcomes almost all known ALK resistance mutations observed with other ALK TKIs.[22] In preclinical models lorlatinib has exhibited superior potency towards ALK neuroblastoma tumor models.[23,24] In addition, lorlatinib shows strong activity toward all tested ALK neuroblastoma mutations.[23,24]

New Agents in Neuroblastoma Therapy (NANT) consortium has several ongoing clinical trials to identify best therapies and combination of therapies for treatment of pediatric patients with neuroblastoma. An on-going Phase 1 dose escalation clinical trial is assessing

the use of lorlatinib as a single agent in combination with chemotherapy in patients aged 1 to 90 years with relapsed/refractory neuroblastoma.[25] Recently presented results of this Phase 1 study showed inhibition of ALK driven neuroblastoma with lorlatinib occurred with manageable toxicity and objective anti-tumor activity was observed.[26]

Pediatric high-risk neuroblastoma remains an area of high unmet need and poor outcomes in young children. Along with the promising early clinical data from the NANT study, we have noted several pediatric neuroblastoma patients being treated through Pfizer's expanded access program. This protocol details the real world data collection of data to evaluate the real world effectiveness of lorlatinib in pediatric neuroblastoma patients. Generating real world evidence from expanded access programs is becoming increasingly valuable, as this data has the potential to supplement regulatory submissions.[27]

7. RESEARCH QUESTIONS AND OBJECTIVES

The primary goal of the Pfizer expanded access program is to provide access to lorlatinib to patients with a serious or immediately life-threatening disease/condition who have exhausted all other standards of care and are not eligible for a clinical trial. Treatment is delivered by the healthcare professional (HCP) as sponsor of the expanded access request and according to a treatment plan approved institutional review board/independent ethics committee as required by local laws and regulations or institutional requirements.

The overall goal of this real-world data collection is to assess demographic, clinical characteristics and real-world effectiveness of pediatric neuroblastoma patients who initiated treatment with lorlatinib through an expanded access program. Data will be collected to address the following specific objectives:

1. Describe the demographic and clinical characteristics of pediatric neuroblastoma patients who initiated treatment with lorlatinib through an expanded access program

2. Evaluate the effectiveness of treatment with lorlatinib in pediatric neuroblastoma patients in terms of duration of treatment, HCP reported response, and duration of response

3. Estimate progression free survival and overall survival

4. Collection of safety data

8. METHODOLOGY FOR REAL WORLD DATA COLLECTION

The real world data (RWD) evaluation will involve supplemental collection of de-identified data collected on patients treated with lorlatinib for pediatric neuroblastoma who initiated treatment through Pfizer's expanded access program. Pediatric patients with ALK-aberrant neuroblastoma who are prescribed lorlatinib by their healthcare professionals (HCPs) and have met Pfizer expanded access program criteria will be eligible for inclusion in data collection. Supplementary data will be collected in partnership with Bionical Emas.

Prior to initiation of data collection activities, Bionical Emas, in collaboration with Pfizer, will develop a customized data collection tool (DCT) to capture data on demographics, clinical characteristics and outcomes. The length of the DCT will be kept to a minimum to avoid burden on participating institutions. The DCT will be made available to participating institutions through a web-based, electronic data capture (EDC) system.

During data collection, Bionical Emas will review the data on an ongoing basis, with HCPs contacted for clarification as required. Bionical Emas in conjunction with their statistical partner Syne Qua Non Limited (SQN) will summarize and report the data at timepoints detailed in Section 5. Finally, a data collection report will be developed.

8.1. Design of data collection

Up to 50 pediatric patients with ALK-aberrant neuroblastoma who initiated treatment with lorlatinib as part of expanded access program will be included.

The real world data collection will be initiated after the patient has been approved for expanded access to lorlatinib per Pfizer's expanded access program and the treating HCP has agreed to participate in data collection. All assessments described in this protocol are performed as part of normal clinical practice or standard practice guidelines for the patient population and healthcare provider specialty in the countries where this data collection is being conducted. Data from patients who have completed treatment, patients receiving ongoing treatment and new patients will be captured. A progress report will be developed for the patients who have completed treatment, with a more comprehensive final report descriptive in nature produced for the total population.

8.2. Setting

Clinical practice and treatment of each patient will follow as determined by each treating HCP individually. There will be no interference from Pfizer with the HCP's diagnostic and treatment decisions. The decision to treat a patient with lorlatinib will be prior to and independent of participation in the real world data collection and according to the clinical judgement of their HCP. Therefore, the data collection will in no way influence prescribing patterns or treatment decisions. If eligible, the patient will receive treatment through Pfizer's expanded access program independent of involvement in the collection of real world data.

HCPs treating a patient approved to receive lorlatinib via Pfizer's expanded access program will be invited to take part in the real world data collection. Upon HCP agreement, they will receive access to the EDC, where they can enter data into the DCT.

The first pediatric neuroblastoma patient received lorlatinib in March 2017 as part of expanded access programs and the program is ongoing. Data collection is anticipated to initiate in January 2021 and is estimated to have last patient entered into real world dataset at

the end in December 2023. Database lock would occur in February 2024, as outlined in Section 5.

Data will be collected via DCT at multiple time points for patients who are receiving ongoing treatment. These timepoints will be determined by HCP standard practice for treatment and follow-up of their patients. Visits are anticipated to occur every 3-4 months, corresponding with re-supply of lorlatinib. Data will be collected on a continual basis until discontinuation of treatment with lorlatinib, death, loss to follow-up or end of study, whichever comes first.

8.2.1. Inclusion criteria

Patients must meet all the following inclusion criteria to be eligible for inclusion in the study:

1. Patient treatment with lorlatinib is initiated through Pfizer's expanded access program for treatment of ALK+ neuroblastoma.

2. HCP documentation of at least one tumor assessment of response after patient has had at least one dose of lorlatinib

3. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative, or a waiver of informed consent has been granted by the IRB/IEC) has been informed of all pertinent aspects of the study.

8.2.2. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1, Any patient who does not meet any of the inclusion criteria defined in the previous section.

8.3. Variables

Variables will include demographics at the start of lorlatinib treatment (age, gender, race, body surface area (BSA)), clinical characteristics (date of initial diagnosis, high risk at diagnosis, ALK aberration date of sample collection and testing, testing platform, ALK and other genetic mutations, ALK amplification, translocation or over-expression, and MYCN amplification, prior anti-cancer treatment, ALK inhibitor use, disease status), treatment start date, starting dose, resupply date(s), BSA, response assessment (date, disease status, HCP reported response, International Neuroblastoma Response Criteria (INRC) response assessment criteria[28] and assessment modality), last date of lorlatinib, patient alive, date of death, date of discontinuation of lorlatinib and reason for discontinuation of lorlatinib. Safety data will be collected in DCT as outlined in Section 10.

8.4. Data sources

The primary data source will be data collected through a DCT. Bionical Emas is the vendor responsible for facilitating capture of HCP responses in DCT via EDC. Bionical Emas is also responsible for de-identification of patient level information. Anonymized pathology reports

submitted as part of the initial lorlatinib request will be summarized and entered into the DCT by Pfizer to confirm information such as ALK aberration testing and status.

As part of Pfizer's expanded access program, HCPs report a full description of Adverse Events (AEs) to the local Pfizer Drug Safety Unit (DSU) using the expanded access adverse event report. AEs captured by the local Pfizer Drug Safety Unit (DSU)will be compared and reconciled to the AEs captured in the DCT and used to summarize the reported AEs. Upon resupply request the requesting HCP certifies that safety reporting has been done per Pfizer expanded access program requirements. Safety information will also be collected in the DCT as the HCP reviews the patient chart as outlined in Section 10.

8.5. Study size

With primary goal of the Pfizer expanded access program is to provide treatment access to patients with an unmet clinical need, no formal power calculations were conducted to determine sample size. Furthermore, the data collection does not involve hypotheses testing (via statistical testing) and it is primarily being conducted to understand treatment outcomes. Target sample size will comprise every patient fulfilling eligibility criteria above and providing informed consent for real world data collection.

8.6. Data management

Bionical Emas will implement Data Management practices for collating and managing the data. These include (1) HCP access management and training, (2) data review, and (3) database storage and retention.

HCP Access Management and Training:
Bionical Emas will add HCPs to the EDC using details obtained from Pfizer after confirmation of patient eligibility and HCP agreement. HCP information will include: HCP name, country, location.

Data Review:
Data review is iterative process to ensure integrity and quality of data. Bionical Emas will ensure data are complete, reliable and processed correctly.

8.6.1. Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record

As used in this protocol, the term DCT should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A DCT is required and should be completed for each included patient. The completed original DCT are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The HCP shall ensure that the DCTs

securely stored in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

The HCP has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the DCT and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The DCT must be electronically signed by the HCP or by an authorized staff member to attest that the data contained on the DCT are true. Any corrections to entries made in the DCT or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the HCP's chart. In these cases, data collected on the DCT must match those charts.

In some cases, the DCT may also serve as the source document. In these cases, a document should be available at the HCP site and at Pfizer that clearly identifies those data that will be recorded on the DCT, and for which the DCT will stand as the source document.

8.6.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the HCP agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., DCT and hospital records), all original signed informed consent/assent documents, copies of all DCT, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by the HCP according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The HCP must ensure that the records continue to be stored securely for so long as they are retained.

If the HCP becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another HCP, another institution, or to an independent third party arranged by Pfizer.

HCP records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The HCP must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

8.7. Data analysis

Bionical Emas in collaboration with Syne Qua Non Limited (SQN) will perform the data analyses described in this protocol using SAS statistical software. Statistical summaries, figures and listings will be produced using SAS (version 9.4 or later).

All development of data summaries and analyses will be documented and retained for traceability including dataset specifications and derivations, name of the programmed outputs and assigned program authors and reviewers.

All data outputs will be fully quality controlled including review of the logs and associated outputs.

No formal statistical testing is planned, and all data analyses will be descriptive and explorative.

8.7.1 Data Reporting Milestones

Data on patients who have completed treatment, patients receiving ongoing treatment and new patients will be captured. The plan is to report the data collectively and cumulatively with the first data reporting to provide an initial assessment of a group of patients having completed treatment. Patients who completed treatment by the time data collection is initiated (completed treatment prior to January 2021) will be those included in the initial progress report. Data reporting will be provided annually thereafter with a final report as outlined in Section 5.

8.7.2 Analysis Set

Data summaries and listings will be produced on all the data collected, regardless of patients fulfilling the inclusion and exclusion criteria detailed in Section 8.2.1 and Section 8.2.2.

8.7.3 Patient Disposition and Demography

Patient disposition will account for the number of patients receiving treatment, continued treatment and discontinued treatment at a specific milestone. Potential reasons for discontinuing treatment will include disease progression, adverse event excluding death, death, lost to follow up, and other.

Demographic and patient characteristics will include variables as noted in Section 8.3. Additional variables will be statistically derived and reported including time since initial diagnosis. Time since initial diagnosis, in months, will be derived as: 12*((Date of initial diagnosis) – (First Date of lorlatinib Treatment)+1)/365.25.

8.7.4 Safety endpoints

All adverse events collected on the DCT will be listed and summarized for all data reporting milestones. Adverse Events will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version. The version used will be indicated in the data summaries and listings.

All patients who discontinue treatment due to safety reasons such as AEs, will be captured and reported as a reason for discontinuation in the patient disposition summaries and listings.

All Adverse Event data captured will be listed. In addition a separate listing will be presented for Serious Adverse Events.

The number and percentage of patients reporting at least one Adverse Event will be summarized within the following categories:

- Adverse Events
- Treatment-related
- Serious
- Serious treatment-related

The following summary tables will also be presented:

- Number and percentage of patients and number of Adverse Events by MedDRA System Organ Class (SOC) and Preferred Term (PT);
- Serious Adverse Events by SOC and PT.

SOC and PT will be presented in decreasing frequency of the total number of patients with Adverse Events. If a patient experienced more than one Adverse Event, the patient will be counted once for each SOC and once for each PT.

8.7.5 Effectiveness endpoints

To assess the effectiveness of lorlatinib, the following endpoints will be collected via the DCT or derived:

Endpoint	Source Variable (if endpoint derived)	Description/Derivation
Objective tumor response of primary tumor (soft tissue), soft		Collected by the DCT at each visit. Outcomes include complete response (CR), partial response

<table>
<tr><td>tissue metastasis, and bone metastasis</td><td></td><td>(PR), stable disease (SD) and progressive disease (PD).</td></tr>
<tr><td>Bone marrow response</td><td></td><td>Collected by the DCT at each visit. Outcomes include CR, PD, minimal disease (MD) and SD.</td></tr>
<tr><td>HCP Reported Objective Response</td><td></td><td>Collected by the DCT at each visit. Outcomes include CR, PR, minor response (MR), SD and PD.</td></tr>
<tr><td>Derived Objective Response</td><td>Objective Tumor response components</td><td>Derived and compared for robustness to the HCP Reported Objective Response applying the following rules:
<table>
<tr><th>RESPONSE</th><th>CRITERIA</th></tr>
<tr><td>Complete Response (CR)</td><td>All components meet criteria for CR</td></tr>
<tr><td>Partial Response (PR)</td><td>PR in at least one component and all other components are either CR, MD (Bone marrow), PR (Soft tissue or Bone) or Not involved (NI); no component with PD.</td></tr>
<tr><td>Minor Response (MR)</td><td>PR or CR in at least one component but at least one other component with SD; no component with PD.</td></tr>
<tr><td>Stable Disease (SD)</td><td>SD in one component with no better than SD or NI in any other component; no component with PD.</td></tr>
<tr><td>Progressive Disease (PD)</td><td>Any component with PD</td></tr>
</table></td></tr>
<tr><td>Best Overall response</td><td>HCP Reported Response</td><td>Derived as the best overall response taking the HCP Reported Response observed up to the data cut-off date for a specific milestone. (The</td></tr>
</table>

	Repeated using Derived Objective Response	sequence order from best to worst is CR, PR, MR, SD, PD.)
Overall Response Rate (ORR)	Best Overall Response	Derived as Best overall response of CR+PR of the total population observed up to the data cut-off date for a specific milestone.
Duration of response	Treatment Start and HCP Reported Response Date	Derived as (Date of PD or death, whichever occurs first) – (Date of PR or CR, whichever occurs first) + 1
Progression free survival (PFS)	Treatment Start and HCP Reported PD/Death Date	Derived as (Date of PD or death (by any cause in the absence of PD)) – (Treatment start date) + 1
Duration of treatment	Treatment Start and Stop Dates	Derived as (Treatment stop date) – (Treatment start date) + 1
Overall survival (OS)	Treatment Start and Death Dates	Derived as (Date of death) – (Treatment start date) + 1

8.7.6 Statistical summaries

Demographic and clinical characteristics

The number and percentage of patients will be presented within each categorized variable. In addition, descriptive statistics for continuous variables will include the mean, standard deviation, median, interquartile range, minimum and maximum.

The demographics will also be presented by subgroups for any subgroups with more than 5 patients.

HCP's reported objective response

For each response component (with the exception of best response), the responses will be listed along with the date of the assessment. A derived objective response will be produced and compared to the HCP overall reported response for confirmation of robustness.

Best Overall Response (BOR) and Overall Response Rate (ORR)

For the BOR, the number and percentage of patients in each ordered category will be presented and summarized by baseline disease status. In addition, the ORR will be presented including the Clopper Pearson 95% Confidence interval.

Duration of response

The number and percentage of patients will be presented within each of the following categories for duration of response: 0 to <3 months; 3 months to <6 months; 6 months to <1 year; 1 to <2 years; 2 to <3 years >3 years; lost to follow-up. Kaplan-Meier (KM) estimates will be used to give the median, Q1 and Q3 duration of response, with 95% confidence limits. If a patient does not show symptoms of progressive disease, their duration of response will be censored at their last visit date prior to the data cut-off date.

Time to event

KM estimates will be presented, where possible, for duration of treatment, progression free survival and overall survival (i.e., time to death). The following censoring rules will be applied:

- Duration of treatment

  Patients who have not discontinued treatment at the data cut-off date will be censored based on the last recorded date when the patient was known to be continuing treatment prior to the data cut-off date.

- Progression free survival

  Patients who have not experienced PD or died at the data cut-off date will be censored at the date of last contact prior to the data cut-off date.

- Overall survival

  Any patient not known to have died at the data cut-off date will be censored based on the last recorded date on which the patient was known to be alive prior to the data cut-off date.

The KM curves will be used to estimate the median, Q1 and Q3 survival times, with 95% confidence limits. The proportion of patients with an event will also be estimated from the corresponding Kaplan-Meier curves with 95% confidence limits.

8.7.7 Subgroups

Subgroups of interest will be explored when a sufficient amount of data are available (n≥5) Examples of subgroups that may be investigated include, but not limited, to age, disease status at baseline, and prior anti-cancer treatment. The categories associated with these subgroups are tabulated below.

Subgroup	Categories
Age	Categorized based on the distribution of age in the study population, for example: ≤1 year; >1 to ≤12 years; >12 years
Disease status at baseline	Recurrent/Progressive; Refractory/Resistant;
Prior anti-cancer treatment	ALK Inhibitor; Chemotherapy; Immunotherapy; Transplant; Surgery; MIBG therapy; Radiation;

8.7.8 Missing data

Statistical summaries, figures and listings will be based on all available data, as observed. Missing data will not be imputed with the exception of partial dates as per below. However, the amount of missing data will be reported.

For the endpoints requiring date derivations such as duration of response, time to event, the following imputation for partial dates will be applied:

- Missing year: no imputation with date remaining as missing
- Missing month: impute as month 6 (June, mid-year approximately)
- Missing day: impute as 15 (mid month approximately)

8.8. Quality control

Programmed validation checks will be available in the EDC system. These will be triggered when the data is saved in the electronic DCT. Data Management will perform an aggregate review of the data, to look for outliers, patterns of inconsistent or missing data and any other identified key risk to the integrity of the data. During data collection, Bionical Emas will review the data on an ongoing basis, with sites contacted for clarification as required. Any issues identified from this review shall be flagged to Pfizer by Bionical Emas.

8.9. Limitations of the research methods

Patients included in this program represent a convenience sample such that supplemental data will be collected on patients of HCPs who are willing to participate in the data collection component and initiated treatment with lorlatinib through Pfizer's expanded access program.

All data captured in the DCT will be limited to information available to the HCP participating in the program. Information on health care services received outside the HCP's care setting will be unavailable.

Data will be entered directly by the participating HCP and therefore may be subject to entry errors and resulting inaccuracies in reporting. Although there will be data checks in place to improve internal consistency of the data, responses will not be validated against the patients' medical records by an independent reviewer.

8.10. Other aspects

Not applicable

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The HCP site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

9.2. Patient consent

The informed consent/assent documents and any patient recruitment materials must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the institutional review board (IRB)/independent ethics committee (IEC) before use, and available for inspection.

The HCP must ensure that each study patient or legal guardian, is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the patient's personal data. The HCP further must ensure that each study patient or legal guardian is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

Whenever consent is obtained from a patient's legal guardian, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/IEC. If the HCP determines that a patient's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/IEC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (e.g., minor, decisionally impaired adult), how the HCP determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (e.g., parent, spouse), and that the patient's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If the study includes minor patients who reach the age of majority during the study, as recognized under local law, they must re-consent as adults to remain in the study. If the enrollment of emancipated minors is permitted by the study age criteria, the IRB/IEC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The HCP, or a person designated by the HCP, will obtain written informed consent from each patient or the patient's legally acceptable representative, parent(s), or legal guardian and the patient's assent, when applicable, before any study-specific activity is performed unless a waiver of informed consent has been granted by an IRB/IEC. The HCP will retain the original of each patient's signed consent/assent document.

9.3. Patient withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the HCP or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document patient outcome, if applicable. The HCP would inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved adverse events.

If the patient withdraws from the data collection, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Treatment discontinuation or loss to follow-up do not constitute patient withdrawal, date of discontinuation or loss to follow-up will be considered last visit date for that patient.

9.4. Institutional review board (IRB)/Independent ethics committee (IEC)

It is the responsibility of the HCP to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained by the HCP. Copies of IRB/IEC approvals should be forwarded to Pfizer.

9.5. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in the Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, The ENCePP Code of Conduct for scientific independence and transparency in the conduct of pharmacoepidemiologic and pharmacovigilance studies, and the Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

REQUIREMENTS

The table below summarizes the requirements for recording safety events on the data collection tool and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure. These events are defined in the section “Definitions of safety events.”

Safety event	Recorded on the data collection tool	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	All
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE) Note: Any associated AE is reported together with the exposure scenario.

For each AE, the HCP must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE (refer to section "Serious Adverse Events" below).

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the HCP **regardless of whether the event is determined by the HCP to be related to lorlatinib**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the HCP does not become immediately aware of the occurrence of a safety event, the HCP must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the HCP is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an HCP may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the data collection tool. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of lorlatinib or the time of the patient's informed consent if s/he is being treated with lorlatinib at the start of the study, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (e.g., patient changes his/her mind about participation), the reporting period ends on the date of the decision to not enroll the patient.

If the HCP becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to lorlatinib, the SAE also must be reported to Pfizer Safety.

Causality assessment

The HCP is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the HCP to determine the causality of each AE. For AEs with a causal relationship to lorlatinib, follow-up by the HCP is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the HCP, and Pfizer concurs with that assessment.

An HCP's causality assessment is the determination of whether there exists a reasonable possibility that lorlatinib caused or contributed to an AE. If the HCP's final determination of causality is "unknown" and s/he cannot determine whether lorlatinib caused the event, the safety event must be reported within 24 hours.

If the HCP cannot determine the etiology of the event but s/he determines that lorlatinib did not cause the event, this should be clearly documented on the data collection tool and the NIS AEM Report Form.

DEFINITIONS OF SAFETY EVENTS

Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an AE);
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or

- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or

- Test result is considered to be an AE by the HCP or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Serious adverse events

A SAE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;

- Is life-threatening;

- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute AEs);

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as a SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as a SAE with severity Grade 5.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from

clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance (PV) personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol)

Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) lorlatinib, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to lorlatinib (maternal exposure).

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to lorlatinib prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with lorlatinib, this information must be submitted to Pfizer, irrespective of whether an AE has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to lorlatinib in a pregnant woman (e.g., a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a

live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the HCP assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);

- Confusion with regard to invented name (e.g., trade name, brand name).

The HCP must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.

- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:

  - An identifiable reporter;

  - A suspect product;

  - The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the HCP, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the HCP, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the HCP, irrespective of the presence of an associated AE/SAE.

REQUIREMENTS – BIONICAL EMAS

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AEs) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE,

but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.
The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the DCT and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All research staff members must complete the following Pfizer training requirements:

- *"YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)*".

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

10.1. Single reference safety document

The Core Data Sheet (CDS) will serve as the single reference safety document during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the HCP during the course of this study.

The product label should continue to be used by the HCP for prescribing purposes and guidance.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this data collection will be summarized in a report. This report will then be used to inform presentation and reporting of data collection results to regulatory authorities as needed. It is further planned to submit publications, at least one conference abstract and at least one manuscript based on the results of this data collection to a peer-reviewed journal.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the HCP is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the HCP will inform Pfizer immediately of any urgent safety measures taken by the HCP to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the HCP becomes aware of.

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ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ADDITIONAL INFORMATION

Not applicable