Study information

Title	Lorlatinib in Patients with Advanced Non-Small Cell Lung Cancer Who Progress on First- and Second- Generation Tyrosine Kinase Inhibitor: A Real-world Evidence among Taiwanese Population, Non-Interventional Study
Protocol number	B7461028
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Medicinal product	Lorlatinib
Research question and objectives	The primary objective of this study is to evaluate real-world systemic treatment patterns and clinical outcome among advanced non-small cell lung cancer (NSCLC) patients treated in Lorlatinib who were progressed on chemotherapy, first- and second- generation TKI
Author	PPD

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AEM	Adverse Event Monitoring
ADR	Adverse Drug Reaction
ALK	Anaplastic Lymphoma Kinase
ATP	Adenosine Triphosphate
CRF	Case Report Form
CRO	Clinical Research Organization
CSA	Clinical Study Agreement
CR	Complete Response
CUP	Compassionate Use Program
DCT	Data Collection Tools
EC	Ethics Committee
EML4	Echinoderm Microtubule-Associated Protein-Like 4
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practices
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
IEC	Independent Ethics Committee
IRB	Institutional Review Board
NIS	Non-interventional Study
NSCLC	Non-Small-Cell Lung Cancer

ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
ROS-1	Receptor Tyrosine Kinase C-Ros Oncogene I
PR	Partial Response
RTK	Receptor Tyrosine Kinase
SAP	Statistical Analysis Plan
SD	Stable Disease
TKI	Tyrosine Kinase Inhibitor
TTF	Time to Treatment Failure
YRR	Your Reporting Responsibilities

3. RESPONSIBLE PARTIES

The contact details of all main responsible parties and the list of all investigators will be kept in a stand-alone document and listed in Annex 1.

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
PPD MD	PPD	PPD	PPD

ABSTRACT

Study Title: Lorlatinib in Patients with Advanced Non-Small Cell Lung Cancer Who Progress on First- and Second- Generation Tyrosine Kinase Inhibitor: A Real-world Evidence among Taiwanese Population, Non-Interventional Study

Rationale and Background:

Non-small cell lung cancer (NSCLC; 80–85% of all lung cancers) remains the most common cause of cancer-related mortality globally, most often diagnosed in advanced stages. Targeted drugs are currently the most often used therapies for advanced NSCLC patients that harbor molecular alterations, including the echinoderm microtubule-associated protein like 4 (EML4)-anaplastic lymphoma kinase (ALK) translocation [1]. For ALK-positive NSCLC patients, crizotinib, ceritinib, alectinib, and brigatinib, are the first- and second-generation tyrosine kinase inhibitors (TKIs). Although the benefit of them has been demonstrated in series of pivotal clinical trials, most patients who initially derive the benefit latterly develop resistance due to secondary mutations [2, 3]. Lorlatinib, a third-generation inhibitor, is a TKI of ALK and Receptor Tyrosine Kinase C-Ros Oncogene I (ROS-1). It is also a potent TKI that is effectively against known resistant mutants that mediate resistance to first- and second-generation ALK-TKIs [2, 4]. Despite the efficacy and safety data derived from the pivotal phase 1/2 clinical trial, there are limited data describing the use of lorlatinib and its outcomes in real-world practice settings outside the highly controlled environs of clinical trials. The objective of this study is therefore to evaluate real-world systemic treatment patterns, clinical outcome, therapeutic effect, safety profile of Lorlatinib in advanced NSCLC patients, and also factors associated with clinical outcome in those Lorlatinib treated patients.

Research Question and Objectives:

Primary Objective

- To evaluate real-world systemic treatment patterns among advanced non-small cell lung cancer (NSCLC) patients treated with Lorlatinib who were progressed on chemotherapy, first- and second- generation TKI among Taiwanese population.

Secondary Objective

- To summarize the therapeutic effect and safety profile of Lorlatinib-treated patients with advanced NSCLC

CCI

- CCI

Study Design

This is a retro- and prospective, multi-center, observational study.

Population

All subjects will be enrolled from Lorlatinib Compassionate Use Program (CUP) and should be entered into this observational study at the physician's discretion.

Variables

Variable	Role	Operational definition
Demographic characteristics	Baseline characteristics	Gender, age, smoking history, Hepatitis B Virus (HBV)/Hepatitis C Virus (HCV) infection status, prescription and diagnose record for NSCLC history and etc. at first dose of Lorlatinib used.
NSCLC History	Baseline Characteristics, study outcome	NSCLC diagnose from initial diagnose to current status and NSCLC related gene mutation.
Treatment of NSCLC	TKI Exposure Treatment Duration Study outcome	CT/TKI exposure, treatment duration and persistence by standard of care medical practice.
Tumor assessment for NSCLC	Study outcome	1) Best response of pre-Lorlatinib NSCLC treatment will be presented as four ORR categories by physician clinical judgement 2) NSCLC related gene mutation status before and after Lorlatinib Treatment 3) ORR in intracranial, extracranial and overall response of Lorlatinib. 4) OS, PFS, 1-year OS rate and Time to Treatment Failure (TTF) of each treatment and TTF of Lorlatinib.
Lorlatinib related adverse drug reaction (ADR)	Study outcome	Lorlatinib related ADR to be recorded from first dose of Lorlatinib until study closed. For any ongoing Lorlatinib related ADR at the end of study, the reporting process will follow local regulations and Pfizer Spontaneous reporting related SOPs and the data will not be included in study data pool.
Drug and non-drug treatment from first dose of Lorlatinib to study completion	Study outcome	Medications and procedures for NSCLC, comorbidities/complications and Lorlatinib ADR

Data Source

The data will be collected through medical record review including the followings:

- Subject demographic characteristics
- HBV and HCV infection status
- Prescription and diagnose record for NSCLC
- NSCLC related gene examination result
- Prescription and diagnose record for Lorlatinib related ADR
- Tumor Assessment for NSCLC from initial diagnose.

Study Size

Given this is an observational study rather than a clinical research of comparison, the sample size is limited by actual patients fulfill the inclusion criteria and without any situation listed in exclusion criteria treated in Taiwan during the data collection period; calculated sample number is not applicable for present setting. However, attempt will be made to ensure around 90 subjects with comprehensive data can be enrolled to provide valuable clinical information.

Data Analysis

Kaplan-Meier estimates of survival curves will compute for overall survival (OS) progression free survival (PFS), 1-year OS rate, time to treatment Failure (TTF) and will be analyzed by the log rank test. Multivariate analyses will be carried out and variables include sex, smoking status, pathology, stage, and the potential interactions of any two factors used by fitting multiple Cox's proportional hazard models to predict patient's hazard rates of duration of response. In statistical testing, two-sided $P \leqq 0.05$ was considered statistically significant.

Milestones

Milestone	Planned date
Completion of feasibility assessment	31 Aug 2019
Start of data collection	31 May 2020
End of data collection	30 Sep 2020
Final study report	31 Dec 2020

4. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
NA				

5. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	31 Aug 2019
Start of data collection	31 May 2020
End of data collection	30 Sep 2020
Final study report	31 Dec 2020

6. RATIONALE AND BACKGROUND

Non-small cell lung cancer (NSCLC; 80–85% of all lung cancers) remains the most common cause of cancer-related mortality globally, most often diagnosed in advanced stages. Platinum-based chemotherapy, with or without radiotherapy or immunotherapy, used to be the main treatment method for advanced NSCLC. With the development of gene sequencing technology, molecular target therapy has become a first-line treatment option for populations with therapy-sensitive mutations in lung cancer driver gene. [1]. The most common targeted drugs are tyrosine kinase inhibitors (TKIs) which act by binding and inhibiting receptor tyrosine kinases (RTKs) and thus lead to inhibition of signaling pathways that induce abnormal growth and proliferation of tumor cells. Although targeted therapies have been successfully used in the treatment for NSCLC, the 3-year overall survival is only about 11.3% and 14.9% for advanced-stage NSCLC patients who received TKIs as first-line and second-line treatments [5]. The unsatisfactory results highlight the need for novel therapies and treatment regimens.

Targeted therapies work differently from the specificity of molecular targets, consequently it often works for patients with specific driven mutation only. For anaplastic lymphoma kinase (ALK)-positive NSCLC, crizotinib is the first approved TKI and it is also one of the first-line agents in current clinical practice. For most ALK-positive NSCLC patients (90%), the benefit from crizotinib has been shown both in clinical studies and real-world reports [6, 7]. Regardless of the satisfaction, some ALK-positive NSCLC patients have limited benefit from the treatment (intrinsic resistance), as well as most patients who initially derive the benefit latterly develop resistance (acquired resistance) due to secondary mutations in ALK [2, 3]. In response to the failure of crizotinib treatment, next-generation ALK-TKIs are developed.

The second-generation ALK-TKIs includes ceritinib, alectinib, and brigatinib, which have demonstrated their activity in a crizotinib refractory or resistant treatment setting and have shown the potential for even greater activity in treatment-naïve patients [8-10]. However, ALK resistance mutation were present in over one-half of patients progressing on second-generation ALK inhibitors while ALK G1202R is the most notably resistance mutation after treatment with second-generation ALK inhibitor [2, 4].

Lorlatinib, a selective, brain-penetrant and new generation TKI, is reversible, potent adenosine triphosphate (ATP)-competitive small molecule inhibitor of ALK and Receptor Tyrosine Kinase C-Ros Oncogene I (ROS-1) and is also a potent ALK-TKI that is

effectively against all known resistant mutants, including certain mutations that are the most difficult to inhibit such as the ALK G1202R mutation. The potential of lorlatinib to improve progression-free survival (PFS) of the treatment-naïve advanced ALK-positive NSCLC patients and patients who had progressed on crizotinib and second-generation ALK-TKIs has demonstrated by clinical trials [11, 12]. The broad coverage and the mechanism of lorlatinib against all known single point mutations that mediate resistance to first- and second-generation ALK-TKIs is also elucidated by trials and studies [2, 4].

Currently, there are limited data describing the use of lorlatinib and its outcomes in real-world practice settings outside the highly controlled environs of clinical trials. The objective of this study is therefore to evaluate real-world systemic treatment patterns, clinical outcome, therapeutic effect, safety profile of Lorlatinib in advanced NSCLC patients, and also factors associated with clinical outcome in those Lorlatinib treated patients.

7. RESEARCH QUESTION AND OBJECTIVES

7.1 Study Objective

Primary Objective

- To evaluate real-world systemic treatment patterns among advanced NSCLC patients treated in Lorlatinib who were progressed on chemotherapy, first- and second- generation TKI among Taiwanese population.

Secondary Objective

- To summarize the clinical outcome and safety profile of Lorlatinib patients with advanced NSCLC

CCI [redacted]

- CCI [redacted]

7.2 Study Endpoint

Clinical Effect Endpoint

- The treatment pattern from initial diagnose to current Lorlatinib treatment
- Objective response rate (ORR), Overall Survival (OS), PFS, 1-year OS rate, Time to Treatment Failure (TTF) for all NSCLC treatment and TTF of Lorlatinib based on investigator's final assessment

Safety Endpoint

- The clinical nature, incidence, duration, and severity of Lorlatinib related adverse drug reaction; outcome and possible causality will be recorded.

CCI [redacted]

- CCI [redacted]

8. RESEARCH METHODS

8.1. Study design

This is a retro- and prospective, multi-center, observational study with patients who are treated by Lorlatinib for advanced NSCLC after failure of chemotherapy, first- or second-generation TKI. Approximately 90 patients from Lorlatinib compassionate use program (CUP), who 1) approved joining Lorlatinib CUP on / before 31 Jul 2019; 2) initiate Lorlatinib treatment before 30 Sep 2019, are expected to be enrolled in the study in Taiwan. Prior to study entry, each eligible patient shall provide his/her written informed consent, except retrospective patients who died before this study approved by Institutional Review Board (IRB).

All enrolled subjects will be followed until study completion on 30 Sep 2020 to make sure all subjects are followed at least 1 year from first dose of Lorlatinib. The data to be captured from this group of patients includes advanced NSCLC diagnosis, gene mutation status, tumor assessment, Lorlatinib Adverse Drug Reaction (ADR) and prescription records during usage of Lorlatinib.

The list below is the information, prior the first dose of Lorlatinib, to be captured as disease history.

1. Prescription and diagnose record of NSCLC from initial NSCLC diagnose
2. Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) infection status
3. NSCLC related gene examination result,
4. Best tumor response in four categories, including complete response (CR), partial response (PR), stable disease (SD) and progression disease (PD), for all pre-Lorlatinib NSCLC treatment

8.2. Setting

Advanced NSCLC patients enrolled from Lorlatinib CUP after failure of chemotherapy, 1st and 2nd generation TKI.

The site staff will collect patient data from medical record according to the schedule below.

Procedure/ Assessment	Baseline visit (V1)	Follow-up Data Collection
Day	D1	Every 12 to 14 weeks until 30 Sep 2020
Informed consent	X*	
Inclusion/Exclusion Criteria	X	
Demographic data	X	
HBV/HCV Infection Status		
NSCLC Related Genetic Examination Result		
NSCLC specific medical/ treatment history	X	
Primary diagnose at Lorlatinib prescription	X	
Tumor assessment record	X	X
Lorlatinib related ADR	X	→
Drug and non-drug treatment from fist dose Lorlatinib to study completion	X	→

* Informed consent process will be waived for subjects who died before the study approved by IRB.

The investigator may schedule clinic visits in addition to those listed in the schedule of activities table according to clinical standard of care practice.

8.2.1. Inclusion criteria

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

1. Age ≥ 20 years old

2. Patients who were approved to join Lorlatinib CUP on or before 31 Jul 2019 while initiate Lorlatinib treatment before 30 Sep 2019,

    i. Joining in Lorlatinib CUP, or

    ii. Ever joined in Lorlatinib CUP since Mar 2018

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

    *For retrospective subjects, the informed consent process is not required for patients who died before the study approved by IRB.

8.2.2. Exclusion criteria

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

1. Patient treated Lorlatinib other than CUP.

8.3. Variables

Variable	Role	Data source(s)	Operational definition
Demographic characteristics	Baseline characteristics	Medical records	Gender, age, smoking history, HBV/HCV infection status and etc. at first dose of Lorlatinib used.
NSCLC History	Baseline Characteristics, study outcome	Medical records	NSCLC diagnose from initial diagnose to current status and NSCLC related gene mutation.
Treatment of NSCLC	Chemotherapy (CT) Exposure TKI Exposure Treatment Duration Study outcome	Medical records	CT/TKI exposure, treatment duration and persistence by standard of care medical practice.
Tumor assessment for NSCLC	Study outcome	Medical records	1) Best response of pre-Lorlatinib NSCLC treatment will be presented as four ORR categories by physician clinical judgement 2) NSCLC related gene mutation status before and after Lorlatinib Treatment 3) ORR in intracranial, extracranial and overall response of Lorlatinib. 4) OS, PFS, 1-year OS rate of and TTF of each treatment and TTF of Lorlatinib.
Lorlatinib related ADR	Study outcome	Medical records	Lorlatinib related ADR to be recorded from first dose of Lorlatinib until study closed. For any ongoing Lorlatinib related ADR at the end of study, the reporting process will follow local regulations and Pfizer Spontaneous

			reporting related SOPs and the data will not be included in study data pool.
Drug and non-drug treatment from first dose of Lorlatinib to study completion	Study outcome	Medical records	Medications and procedures for NSCLC, comorbidities/ complications and Lorlatinib ADR

Detailed instruction regarding the variables will be included in Case Report Form (CRF) and statistical analysis plan.

8.4. Data sources

The data will be collected through medical record review.

All demographic information, HBV/HCV Infection status, NSCLC related genetic examination result, NSCLC related medical history, Lorlatinib related ADR, Pre-Lorlatinib NSCLC drug/non-drug treatment, tumor assessment, Lorlatinib concurrent drug/non-drug treatment and post-Lorlatinib drug/non-drug treatment will be collected from medical record to Case Report Form.

The demographic characteristic as baseline information will collect the data at the time of first dose of Lorlatinib administered. The Lorlatinib related ADR, Lorlatinib concurrent drug/non-drug treatment and post-Lorlatinib drug/non-drug treatment will be record from first dose of Lorlatinib until end of data collection.

8.5. Study size

This is a descriptive study rather than a clinical research of comparison. The sample size is limited by actual patients fulfill the inclusion criteria and without any situation listed in exclusion criteria in Taiwan during the specific period. A calculated sample number is not applicable for present setting.

According to current Lorlatinib CUP in Taiwan, the estimated recruiting number is 90. All eligible subjects who signed and agree to the informed consent or not available to provide the informed consent will constitute the cohort to be analyzed for this observational study.

8.6. Data management

Study data will be collected via medical record review, the source documents are the subject medical records at study sites. Data collected on the CRFs must match the data in the source documents.

The collected data will be entered into a validated database. Pfizer/CRO data management will be responsible for data processing, in accordance with the data management procedure. Database lock will occur once quality assurance procedures have been completed.

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

As used in this protocol, the term CRF[/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 CRF[/DCT] is required and should be completed for each included patient. The completed original CRFs[/DCTs] 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 investigator shall ensure that the CRFs[/DCTs] are securely stored at the study site in paper form and will be secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs[/DCTs] 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 CRFs[/DCTs] must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs[/DCTs] are true. Any corrections to entries made in the CRFs[/DCTs] or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs[/DCTs] must match those charts.

8.6.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs[/DCTs] and hospital records), all original signed informed consent/assent documents, copies of all CRFs[/DCTs], 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 investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator 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 investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

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

8.7. Data analysis

Descriptive statistics will be used to summarize the proportion of gene mutations in all patients, demographics, smoking history, clinical characteristics, treatments pattern, as well as response rate and duration of response under different treatment pattern.

The treatment pattern will be analyzed into following subpopulations:

1) Lorlatinib treatment after one prior ALK TKI different from crizotinib in ALK gene mutation subject;

2) Lorlatinib treatment after two prior ALK TKI in ALK gene mutation subject;

3) Lorlatinib treatment after at more than two prior ALK TKI in ALK gene mutation subject;

4) Lorlatinib treatment in ROS-1 gene mutation subject with any pretreatment.

Key outcome variables include OS, PFS, 1-year OS rate, and TTF for all NSCLC treatment and TTF of Lorlatinib will be summarized by using Kaplan-Meier method and analyzed by the log rank test. Multivariate analyses will be carried out and variables include first-line ALK TKI prescribed, sex, pathology, stage, and the potential interactions of any two factors used by fitting multiple Cox's proportional hazard models to predict patient's hazard rates of treatment response.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

8.8. Quality control

Pfizer or its agent will conduct monitoring visits during study conduct for studies conducted at investigator sites, to ensure that the protocol and Good Clinica Practice (GCPs) and/or Good Pharmacoepidemiology Practices (GPP), as relevant, are being followed. The monitors may review source document to confirm that the data recorded on CRFs[/DCTs] are accurate. The investigator and institution will allow Pfizer monitors/ auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/Ethics Committee (EC). It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits and that sufficient time is devoted to the process.

8.9. Limitations of the research methods

As the study only to describe the real-world treatment pattern and treatment outcome, the size of sample might not guarantee to ensure a representative distribution of the Taiwanese advanced NSCLC population.

The secondary limitation of the research is related to subject population. Subject who die after IRB approval but before clinic visit to join this study will not be able to be enrolled. IRB will only approve to waive informed consent process for subject who die before IRB approve the study.

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 paper form and will be secured in a locked room 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 investigator 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

Informed consent is required per IRB requirements and local regulation and below requirements should be followed:

The informed consent form must be in compliance with local regulatory requirements and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/Independent Ethics Committee (IEC) and Pfizer before use.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

For patients completed Lorlatinib treatment before study start and not able to be contacted, the informed consent process will be waived. Only retrospective data will be collected from this group of patients.

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 investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events.

If the patient withdraws from the study, 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.

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

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must 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 Good practices for real‐world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR‐ISPE Special Task Force on real‐world evidence in health care decision making.

(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5639372/).

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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 paper Case Report Form 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.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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 investigator 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.

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13. LIST OF TABLES

Not applicable

14. LIST OF FIGURES

Not applicable

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Document reference number	Date	Title
B7461028-001	Contact Detail of Study Personnel		

ANNEX 2. ADDITIONAL INFORMATION

Not applicable