Title: A Phase 1/2 Study of the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity of the Oral ALK/EGFR Inhibitor AP26113

NCT Number: NCT01449461

SAP Approve Date: 14 April 2016

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STATISTICAL ANALYSIS PLAN

STUDY TITLE: A Phase 1/2 Study of the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity of the Oral ALK/EGFR Inhibitor AP26113

PROTOCOL NUMBER: AP26113-11-101

PROTOCOL DATE: 27 June 2011

PROTOCOL AMENDMENT DATE: 20 December 2013

SAP VERSION: Version 1.0

DATE: 14 April 2016

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PROTOCOL REVISION HISTORY:

Amendment Number	Protocol Version Number	Date
	Version 1.0	27 June 2011
Amendment 1	Version 2.0	22 July 2011
Amendment 2	Version 3.0	21 February 2012
Amendment 3	Version 4.0	17 September 2012
Amendment 4	Version 5.0	30 November 2012
Amendment 5	Version 6.0	22 May 2013
Amendment 6	Version 7.0	20 December 2013

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LIST OF ABBREVIATIONS (Excluding common laboratory tests)

Abbreviation	Term
AE	adverse event
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
AP26113	brigatinib
ARIAD	ARIAD Pharmaceuticals, Inc.
AUC	area under the curve
BOR	best overall response
CAT	computerized axial tomography
C_{max}	maximum plasma concentration
CMQ	Customized MedDRA Query
CNS	central nervous system
CR	complete response
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLCL	diffuse large-cell lymphoma
DLT	dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECG	electrocardiogram
EGFR	epidermal growth factor receptor
FISH	fluorescence in situ hybridization
HRQoL	health-related quality-of-life
ICH	International Conference on Harmonisation
IMT	inflammatory myofibroblastic tumors
IRC	independent review committee
ITT	Intention-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MMQ	Modified MedDRA query
MRI	magnetic resonance imaging
ms	milliseconds
MTD	maximum tolerated dose
NE	not evaluable – often reported for interpretable lab results not evaluated – reported when disease assessment scans cannot be read
non-CR/non-PD	not complete response and not progressive disease; also denoted ^CR/^PD
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response

Abbreviation	Term
PRO	patient-reported outcomes
PT	preferred term
QD	once-daily
QTcF	QT interval corrected (Fridericia)
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SMQ	Standardised MedDRA Query
SOC	System Organ Class
TKI	tyrosine kinase inhibitor
TTP	time to progression
ULN	upper limit of normal

1 INTRODUCTION

1.1 Purpose

This statistical analysis plan (SAP) will describe the statistical analyses performed by ARIAD Pharmaceuticals, Inc. for protocol AP26113-11-101.Though this is an ongoing study a clinical study report (CSR) will be prepared for regulatory submission using the following data extracts:

- The clinical database will be analyzed using a data cut dated 2015-11-16. The last date of patient contact included in this cut occurred on 2015-11-13.
- Intracranial central nervous system (CNS) response was assessed by an Independent Review Committee (IRC). IRC data are available from a data cut on 2016-01-28, from which the last observed scan was performed on 2015-10-08.

Subsequent data cuts and analyses will be performed to allow monitoring of the study, to address requests for information from regulatory agencies, and to facilitate periodic updates of the CSR.

1.1.1 Study Design

AP26113-11-1 is an open-label, multi-center, dose escalation study (3+3 design initial dose escalation cohort) with expansion into 5 cohorts (histologically and molecularly defined) after the recommended phase 2 dose (RP2D) is established.
The patient population of the initial dose escalation phase of the trial will include patients with advanced malignancies, all histologies other than leukemia, refractory to available therapies or for whom no standard or available curative treatments exist. The objectives will be to determine the safety, tolerability, pharmacokinetic profile, and the RP2D of orally administered AP26113 (brigatinib) in these patients. The RP2D is the maximum tolerated dose (MTD) or less. An RP2D less than the MTD may be chosen if aspects of tolerability not encompassed by the MTD determination suggest utilizing a lower dose.
The expansion phase will include 5 additional histologically and molecularly defined cohorts, with cohort 5 being limited to patients with active brain metastases. The dose and schedule for the expansion cohorts will be determined based on the RP2D and schedule determined in the dose escalation phase of the trial. The decision to open the expansion cohorts will be based on an assessment of safety and preliminary anti-tumor activity from the dose escalation cohort. The 5 expansion cohorts are as follows:

1) NSCLC patients with ALK rearrangements who are naive to prior ALK inhibitor therapy.
2) NSCLC patients with ALK rearrangements who are resistant to crizotinib.
3) NSCLC patients who are resistant to 1 prior EGFR TKI and have a documented EGFR-T790M mutation following disease progression on the most recent EGFR TKI therapy.
4) Patients with any cancers with abnormalities in ALK or other brigatinib targets (examples include, but are not limited to, ALCL, DLCL, IMT, and other cancers with ALK abnormalities, or tumors with ROS1 fusions).
5) NSCLC patients with ALK rearrangements who are either naive or resistant to crizotinib and who have active brain metastases.

The safety and tolerability of orally administered brigatinib will continue to be assessed in the expansion cohorts. However, the primary objective of the expansion component of the trial is to describe the preliminary efficacy of brigatinib in these patient populations. Overall response rate

will be the primary endpoint in expansion cohorts 1-4, and CNS response rate will be the primary endpoint in expansion cohort 5.

1.1.2 Study Objectives

The objectives of the study are:

1. To determine the safety profile of orally administered brigatinib including identification of the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs).
2. To determine the RP2D of orally administered brigatinib.
3. To examine the pharmacokinetic (PK) profile of brigatinib.
4. To describe the preliminary anti-tumor activity of brigatinib in NSCLC with ALK gene rearrangement or mutated EGFR, and other cancers with abnormal targets.

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1.1.3 Changes from analyses planned in the protocol:

- The following test results for a number of exploratory endpoints will not be available for inclusion in the analysis of the 2015-11-16 database extract and will not be included in the first version of the CSR:

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- Time to response analyses were specified to include progression as a competing risk (protocol section 8.5). Instead, all progression (as well as death prior to progression) will be

treated as censored follow-up intervals. Interpretation of competing risks models is difficult in a small, non-randomized study with heterogeneous diagnoses, prior treatment histories, and on-study treatment experiences.

- The exploration of covariates on the safety and efficacy profiles of brigatinib will not be included in the main CSR. Very little inferential modeling is planned, even on an exploratory basis. Where sufficient data are available results will be broken out by important baseline disease characteristics such as diagnosis, mutation history, prior anti-cancer therapy, and presence of CNS (brain) metastases, but consideration of these characteristics will be accomplished through presentations on subsets of similar patients rather than model-building exercises. Exploration of covariates will be included in a separate exposure response report.
- Separate primary endpoints were defined for the dose escalation cohort, expansion cohorts 1-4, and expansion cohort 5 (See section 1.2 above). The determination of RP2D remains the primary endpoint of the dose escalation phase. However, it is more informative to group all patients by important clinical characteristics such as tumor type and mutation history rather than the expansion cohort to which they were assigned in order to present primary efficacy estimates from the largest samples possible. Patients from the dose-escalation phase will be combined with those from across the expansion cohorts, according to starting dose regimen, in order to provide the best possible characterizations of systemic and intracranial CNS response rates as well as other efficacy endpoints. Section 8.1 of the protocol states that data from patients in the expansion phase cohorts will be summarized together with data from patients in the dose escalation cohorts, as appropriate.
- Time to progression (TTP) and time to treatment failure in patients who remain on brigatinib after initial progression (both in protocol section 8.2.2) will not be estimated. The clinical relevance of TTP is better captured by estimation of progression-free survival, which will be presented in the CSR for all analysis populations of interest. Evaluation of endpoints following progression is not consistent with RECIST 1.1 guidelines.
- Extra-CNS PFS will not be estimated in Cohort 5 patients (protocol section 8.2.2). The assessment of intracranial PFS was performed by an independent review committee (IRC) as defined by a charter, while no specific assessment was performed by the IRC to cover determination of extra-CNS disease burden. Robust analyses will be performed on investigator-performed whole-body disease assessments (RECIST 1.1) and the iCNS-specific assessments performed by the IRC. Investigation of progression excluding the CNS will best be accomplished by comparison of results of these analyses when performed as designed.
- A small number of patients were entered into the study without a measurable lesion at study entry, via a waiver of the relevant inclusion criteria. Such patients cannot be assessed as Partial Response (PR) or Stable Disease (SD) as defined by RECIST 1.1. They will be assessed as CR, defined as complete clearance of all lesions observed at baseline, or PD, defined as progression of the baseline lesions or the appearance of new lesions. Evaluable assessments that do not meet either of these definitions are reported as non-Complete Response/non-Progressive Disease or non-CR/non-PD.

1.2 Analysis Endpoints

1.2.1 Dose Escalation Phase

1.2.1.1 Primary Endpoint(s)

The primary endpoint of the dose escalation phase of the study is:

- The primary endpoint of the dose escalation component of the study is the RP2D of orally administered brigatinib.

1.2.1.2 Secondary Endpoint(s)

Secondary endpoints of the dose escalation component of the study include:

1. MTD of orally administered brigatinib
2. Safety, tolerability, and DLTs of brigatinib
3. Plasma PK parameters of single-dose and steady state brigatinib

1.2.2 Efficacy Analysis

1.2.2.1 Primary Endpoint(s)

The primary efficacy endpoints of the study as stated in the protocol are:

- The primary endpoint of expansion cohorts 1-4 is the overall response rate (using RECIST 1.1).
- The primary endpoint of expansion cohort 5 is CNS response rate (using RECIST 1.1).

Note: The definitions for the 5 expansion cohorts were not entirely mutually exclusive and allowed patients to qualify for more than one expansion cohort. Also, many of the patients enrolled in the dose-escalation phase also met the qualifications for one or more of the expansion cohorts. RECIST 1.1 evaluations were performed for every patient when possible, and therefore disease assessment data for every patient enrolled can enhance the characterization of the anti-tumor activity of brigatinib. Likewise, the intracranial CNS response was evaluated by independent review for every patient with available post-exposure brain scans. Therefore the analysis of efficacy endpoints has been simplified to present both systemic response using RECIST 1.1 (in all patients) and intracranial CNS response (in ALK+ NSCLC patients with intracranial CNS metastases at baseline), to the extent that data are available.

1.2.2.2 Secondary Endpoint(s)

Secondary endpoints of the expansion cohort component of the study as stated in the protocol include:

1. Safety and tolerability of brigatinib
2. Plasma PK parameters
3. Efficacy assessments include: best target lesion response, PFS, TTP, and time to treatment failure in patients who remain on study after RECIST 1.1 progression, but who continue to benefit according to the treating investigator. Overall survival (OS) will also be measured for up to 2 years following the first dose of brigatinib.

- For cohort 5: additional efficacy assessments include: overall response rate using RECIST 1.1, CNS PFS, and extra CNS PFS.

Note: TTP and time to treatment failure will not be analyzed since they are not likely to make meaningful contributions beyond what is covered by PFS (see section 1.1.3 above).

Progression free survival, duration of response and overall survival will be estimated using Kaplan-Meier methods.

1.2.2.3 Safety Endpoints

Safety will be characterized through the analysis of all relevant data including adverse events, laboratory measures, ECG, and vital signs as described starting in Section 4.4.9.

1.2.2.4 Pharmacokinetic Analysis

A non-compartmental pharmacokinetic (PK) analysis will be performed on the concentration of brigatinib in blood samples drawn in both the escalation (phase 1) and expansion (phase 2) phases of the study. The following PK parameters single dose and at steady state will be determined: Cmax, AUC 0-tau, AUC 0-inf, Tmax, Thalf, Cl/F, V/F. Summary statistics will be produced by dose cohort. Dose proportionality for AUC and Cmax will be explored using regression.

2 STATISTICAL CONSIDERATIONS

2.1 Sample Size

This is a phase 1/2 study uses a 3+3 dose escalation design for the phase 1 component. The number of patients is consistent with phase 1 dose finding studies and depends on the number of dose cohorts needed to reach the maximum tolerated dose (MTD). With a 3+3 design, the estimate of the rate of DLT at the MTD is in the range of 0.17 to 0.26. The estimate of the rate of DLT at the highest dose, which is 1 step above the MTD, is 0.33 (Ting, 2006).

The sample size for the phase 2 component of the study is determined based on clinical rather than statistical considerations. The histologically and molecularly defined expansion cohorts will facilitate obtaining preliminary estimates of clinical activity and the cohort sizes are consistent with an early phase 2 study.

2.2 Randomization and Masking

This is a non-randomized open label study.

2.3 Handling of Data

Overall RECIST response at each evaluation will be used as recorded by the investigator and will not be determined by programmatic processing of the individual data from target, non-target, and new lesions. Intracranial CNS response will be assessed by IRC and handled in the same way.

Some adverse events are recoded to reduce the possibility of underreporting as described in 4.4.8.

Date imputation is described in Appendix 3. Imputation of other data is not anticipated.

2.3.1 Baseline Values

The baseline value used in analysis will be the last valid value observed prior to first exposure to study drug.

2.3.2 Collapsed Treatment Group

Patients were assigned to 11 different regimens of brigatinib at study entry. Some displays will be presented broken out by all 11 groups but the primary interest in many cases is the focus on the doses selected for investigation in subsequent studies, the two RP2Ds, which are designated as the "90 mg QD" and the "90 mg=>180 mg QD" groups. To facilitate interpretation of results for these groups, as well as comparisons with other dose regimens, many tables will be broken out by "Collapsed Dose Group" which will do the following:

Description	Starting Dose(s)	Group Label
Starting doses lower than 90 mg QD	30 mg QD 60 mg QD	30 QD / 60 QD
Lower RP2D	90 mg QD	90 mg QD
Starting doses between the two RP2Ds	120 mg QD 60 mg BID	120 QD / 60 BID
Higher RP2D	90 mg QD for 7 days, then 180 mg QD	90 to 180 QD
Other starting dose groups at 180 mg per day	180 mg QD 90 mg BID	180 QD / 90 BID
Starting doses higher than 180 mg QD	240 mg QD 300 mg QD 120 mg BID	240 QD / 300 QD / 120 BID

2.3.3 Mutation History

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2.3.4 Prior Exposure to Crizotinib

Some analyses will be presented on patients who were, or were not, exposed to crizotinib prior to study entry. Subsets of patients based on crizotinib exposure will be drawn from the set of ALK+ NSCLC patients.

2.3.5 CNS Metastases

Some tables and figures will be presented on subsets of patients selected on the basis of:

- Presence or absence of CNS metastases at study entry
- Presence of measurable CNS lesions at study entry
- History of radiotherapy directed at CNS lesions

Subsets of patients based on CNS metastases criteria will be drawn from the set of ALK+ NSCLC patients unless otherwise specified.

3 POPULATIONS FOR ANALYSIS

3.1 All Patients

Since treatment assignment in the study was not performed through an intention-to-treat method, such as randomization, the definition of an ITT population is not relevant. In addition, since all patients received at least 1 dose of brigatinib at the intended starting dose the standard definitions of Safety and Efficacy populations both select every patient who entered the study. Therefore analyses that do not specify subsets of patients will be reported under the All Patients heading.

3.2 Pharmacokinetic (PK) population

All patients in the treated population with at least 1 PK concentration measurement.

4 STATISTICAL METHODS

4.1 Demographics, Baseline Characteristics, and Patient Disposition

Patient disposition will be tabulated by starting dose regimen and by categories as recorded by the investigator in the clinical database: ongoing, discontinued due to: Adverse Event, death, disease progression, lack of efficacy, physician decision, patient decision, and lost to follow up.

Demographic and baseline characteristics will be summarized overall and separately for each dose group. The following variables will be included: age, gender, race, weight, country/region, and disease characteristics (e.g., time since diagnosis, mutation status). Continuous variables will be summarized with descriptive statistics and categorical data will be presented in counts and percentages.

Baseline disease characteristics will include ECOG performance status, time since diagnosis, diagnostic characteristics, prior therapies, and presence of CNS metastases.

4.2 Study Drug Exposure

Study drug exposure will be summarized by number of doses, total cumulative dose, days from first dose to last dose), dose intensity (total dose/days from first to last dose) and maximum days of dose delay. Statistics will be produced for each starting dose regimen and overall. Compliance

will also be summarized, including percent compliance, and number of patients with a dose delay of 3 or more days or dose reduction.

4.3 Efficacy Analysis

4.3.1 Primary Efficacy Analysis

Patients will be assessed with scans every 8 weeks. Objective Response Rate (ORR), defined as complete response (CR) or partial response (PR) by RECIST 1.1 prior to the first occurrence of PD, is the primary efficacy analysis endpoint.

Objective response rate with exact binomial 95% confidence intervals will be computed overall and by collapsed dose group. For patients with data from independent review of brain metastasizes a second objective response will be determined by restricting the RECIST 1.1 criteria to brains lesions only (target, non-target and new lesions).

Time to first response will be analyzed using the Kaplan-Meier method. Patients who do not achieve response will be censored at the time of PD, if observed, or their last evaluable scan.

4.3.1.1 Determination of Intracranial CNS Response and Associated Endpoints

Assessment of anti-tumor activity in the brain has become an important aspect of TKI therapy in ALK+ NSCLC. Intracranial CNS response and progression will be evaluated for all patients determined to have brain metastases at baseline who have post-exposure CNS scans. Brain MRI scans were performed on all patients at Screening, but imaging assessments of the brain after initiating treatment with study drug were only performed for patients determined by the investigator to have brain metastases at Screening. All patients had their baseline MRI read by the IRC. Then, those who were identified as having baseline brain metastases had their on-study brain scans read. CT scans were not sent to the independent reviewers.

The assessment CNS response and progression requires special considerations that differ from RECIST 1.1. The first is that inclusion of target lesions in the brain is not required for RECIST 1.1 if there is sufficient burden of disease elsewhere in the body to fulfill the limitation of 5 target lesions. Another is that presence of measureable lesions outside the CNS combined with non-measurable lesions in the brain renders a patient evaluable by RECIST 1.1 but difficult to assess by the same standards when attempting a CNS-specific reading.

MRI scans were sent to an Independent Review Committee (IRC) for blinded assessment of intracranial CNS response. The review methods followed a modification of RECIST 1.1. All assessments for each patient were read by a single reader so no adjudication was employed.

The principal modifications to RECIST 1.1 were:

1) Reviewers only assessed MRI of the head, and no other body location were included in this review
2) Up to 5 target brain lesions were selected for following on subsequent scans. RECIST 1.1 allows 5 total target lesions but limits the number of target lesions in a single body system to 2.
3) For this review, the reviewers were not given any history as to whether the subject had prior CNS radiation therapy or if there had been progression in the field since completion of therapy. Selection of Target and Non-target lesions selection was therefore not based on this clinical history.

4) Reviews were not provided with steroid dose information or the neurologic status of the subject.

Target CNS lesions had to meet the same definitions of measurability as used for RECIST 1.1 response assessment. The process for selection of target, non-target and new lesions mirrored RECIST 1.1 as much as possible. Target lesions were to be measureable according to the same criteria as for systemic response and were tracked in the same way. Patients with no CNS lesions that could qualify as target lesions were tracked for progression or complete clearance of non-target lesions. Evaluation of new lesions was performed consistently with systemic disease assessment.

A special case in the selection of non-target lesions not described in RECIST 1.1 regards Leptomeningeal disease. It should be noted the presence of Leptomeningeal disease is an exclusion criteria for this study. However if in the opinion of the reviewer Leptomeningeal disease is present, it will be considered a non-target lesion.

Evaluation of response specific to target, non-target, and new lesions will proceed in the same manner as for RECIST, and the conversion of these three levels of response to time point response will also be the same. Conversion of timepoint response to other endpoints such as BOR or confirmed response will also be done in the same manner as for RECIST 1.1 response unless otherwise specified.

4.3.1.2 Data Handling Rules for Response Contemporaneous Scans.

Two or more scans may be taken within a few days. The scans may cover multiple anatomical regions and can be of different modalities (e.g. CAT scan and MRI). Scans within a +/- 2 day window scans will be "merged" lesion by lesion. If a lesion (target, non-target or new lesion) is on only 1 scan the evaluations of the multiple lesions will be combined. If a single target lesion appears on 2 or more scans the lesion measurements will be averaged. Any new lesion on any of the multiple scans will count as a new lesion. If a non-target lesion is present on multiple scans the 'worst' of the multiple evaluations, e.g. non-CR/non-PR and absent counts as non-CR/non-PR, progression and non-CR/non-PR counts as progression etc.

The handling of contemporaneous scans was performed in the data management process prior to export for programming and analysis.

4.4 Secondary Efficacy Analyses

Preliminary estimates of clinical activity including: progression free survival (PFS), duration of response, and time to response will be determined.

4.4.1 Best Overall Response (BOR).

Best overall response will be evaluated according to RECIST 1.1 criteria. For interim analyses patients who are still on study but have no follow up scans will be categorized as not evaluable.

Early, less than 26 days, scans showing stable disease (SD), PR or CR will not be evaluable for BOR. Early scans showing PD will be considered evaluable for BOR.

4.4.2 Confirmed Response

Patients who achieve PR or CR and who have subsequent RECIST 1.1 evaluations will be assessed for confirmation of response. To be considered the additional scans must be done on or

after Day 26 relative to the first scan showing response (defined as Day 1 in this context), with the exception that PD from a scan prior to Day 26 will define a response as unconfirmed. All scans after the first occurrence of PD will be excluded from consideration in the assessment of confirmed response.

Responses will be confirmed as follows:

- PR can be confirmed by another PR or a CR
- CR can only be confirmed by another CR

Scans assessed as Not Evaluated (NE) will not confirm a response. The first NE scan following the initial response can be ignored, but more than one NE scan in a row will cause the first response to be unconfirmed. In this case even though the first response was unconfirmed later responses will still be eligible for confirmation.

When confirming PR an assessment of SD will be treated as equivalent to NE. Therefore a single NE or SD will not cause failure to confirm the initial PR, but a subsequent scan of either type will render the initial PR to be unconfirmed.

Analysis of confirmed response will be done in the same manner as for ORR. Time to response will count the first response for each patient for whom response was confirmed. Censoring for patients who never responded will be the same as for ORR. Followup for patients with unconfirmed response will also be censored at the first occurrence of PD (when observed) or the last evaluable scan.

4.4.3 Best Confirmed Response

Best confirmed response is defined as the best response for each patient that met the definition of confirmed response. If a patient had scans of PR => CR => PD then:

- The patient's best overall response is CR
- The patient's best confirmed response is PR

4.4.4 Progression-Free Survival

A key secondary endpoint for this trial is PFS. PFS is defined as the time from the date of first dose to the date of the first documented evidence of progressive disease (PD) or death (whichever occurs first). PFS time will be censored at the last date for which the tumor assessment resulted in the absence of PD for patients who have not demonstrated objective tumor progression and are still on trial. For patients who withdraw consent for any reason before demonstrating evidence of tumor progression or recurrence, PFS time will be censored at the last date for which the tumor assessment resulted in the absence of PD. Patients are censored at the date of first dose of study treatment if no additional follow-up data are obtained.

Included below is a table that summarizes the data handling rules for the analysis of PFS. The assumptions for the data handling conventions are as follows:

- The assessment of tumor response will be based on the evaluations performed every 8 weeks after first dose of trial treatment. Evidence of PD may be obtained at these scheduled visits, or obtained from disease evaluations conducted between scheduled visits, prompted by symptoms.

- An adequate assessment will be defined as one where sufficiently clear radiological images are obtained so that changes in target lesions may be observed, or the presence of new lesions determined.
- All events are based on well-documented and verifiable progression events or death. Patients not experiencing a PD event are censored at the last date that the patient was known to be progression-free. The progression dates are based only on radiographic assessments. Clinical progression is not considered a disease progression event and therefore is not part of the PFS analysis.
- If one or more radiographic assessments are missing, the most recent date that a progression was documented will be used as the date of progression.
- The date of progression is defined as the earliest date when tumor progression is noted.
- For PFS, if PD is not documented, then the date of death will be defined as the date of progression.

Condition Date of progression or censoring

No progression		censored
One or more missed follow-up visits after which one of the following occurred: · Patient withdrew consent · Patient lost to follow-up	Date of last evaluable non-PD assessment	censored
New anticancer treatment started without evidence of PD prior to discontinuation of study treatment	Date of last evaluable non-PD assessment prior to starting new treatment	censored
Progression documented between scheduled visits	Date of radiographic assessment showing progression	progressed
Cancer-related surgery prior to documented progression	Date of surgery	censored
Treatment discontinuation for a reason other than documented disease progression or death	Follow patients until date of progression or death If no event occurs, censor at last evaluable non-PD assessment, prior to initiation of subsequent anticancer therapy	progressed censored
Death before first PD assessment Or Death between adequate assessment visits	Date of death	progressed
Death or progression after last valid scan for assessment of disease burden	Patients will be followed until date of death or end of study participation. Death within 126 days of last valid scan Death after 126 days of last valid scan	 progressed censored

4.4.5 Duration of Response

The analysis of response duration will only include patients with confirmed CR or PR based on disease assessment by the investigator.

Duration of response will be analyzed using the Kaplan-Meier method.The start of response will be the first date of observed response (PR or CR), and duration of response following response will use the censoring scheme described for PFS in the previous section. End of response will be observed if the response interval was ended by a PFS event, otherwise the response-time followup will be censored at the time of the last valid scan. The duration of response will be calculated as PFS Date – Response Date + 1.

4.4.6 Overall Survival

Overall survival (OS) will be determined by the number of days from first dose date to date of death. If the patient is lost to follow up, the time will be set to the last date that the patient was known to be alive and the observation will be censored. The same analytical methods will be applied to OS as were used for PFS.

4.4.7 Health-Related Quality of Life (HRQoL) Measurement

Quality of life assessments are not being collected.

4.4.8 Patient-Reported Outcomes (PRO)

Patient-reported outcomes are not being collected.

4.5 Safety Analyses

4.5.1 Adverse Events

4.5.1.1 Derivation of Treatment-Emergent Adverse Event Flag

Sites are instructed to "split" AEs that are ongoing as of first dose date into two records: one that ends as of first dose date and one that begins on first dose date. Therefore in some cases, what may at first appear as an AE that begins on first dose date is really a continuation of an AE that began prior to first dose date. If all of the following criteria are true for any two AE records then the two records should be considered as one event:

- The preferred term of the first AE = the preferred term of the second AE.
- The start date of the first AE is before the date of first dose.
- The end date of the first AE is one day before the date of first dose or equal to the date of first dose.
- The start date of the second AE = the date of first dose.
- The severity of the second AE <= the severity of the first AE.
- The relatedness of both the first and the second AEs is "Not Related".

After determining which records should be treated as a single event, the treatment-emergent flag can be determined as follows:

- All AEs with an onset date on or after the first dose date.
- In the case of missing onset date, impute using the rules defined in Appendix 3.

4.5.1.2 Synonym Recoding

Some preferred terms coding manifestations of similar medical conditions will be re-coded and re-grouped based on the synonym infrastructure determined through sponsor medical review (An example of such an infrastructure is provided in Appendix 2. The lists of terms recoded through this process are subject to change as new events occur and/or MedDRA versions change.). Such events will be identified as "Treatment-Emergent 'Synonym Recoded' Preferred Term" in the titles of tables in which they are presented.

In the summary tables, MedDRA preferred terms will be sorted in a descending order of incidence rate first then alphabetically in case of tied incidence rates. In the tables of treatment emergent AEs grouped by MedDRA System Organ Class (SOC), SOCs will first be sorted in a descending order of incidence of any event in the SOC, then SOCs will be sorted alphabetically in case of tied incidence rates.

4.5.1.3 AEs in Special Categories

Custom groupings of adverse events have been created to facilitate the analysis of areas of concern specific to brigatinib. Some of these groupings are Standardized MedDRA queries (SMQ) or Modified MedDRA queries (MMQ). Others were created through medical review of existing PTs by the ARIAD Medical Monitor and/or other sponsor personnel. Presentations of this type are identified by inclusion of the phrase "in Special Categories" in the table titles.

When more than one Special Category is presented in a table it is possible that a single PT will appear in more than one place on that table.

4.5.1.4 Analysis of Adverse Events

Tables for AEs will be presented for all patients and for ALK+ NSCLC patients and will include:

- A summary table with number of patients having any AE as well as any AE meeting criteria of interest such as relatedness, seriousness, severity, as well as combinations of these characteristics
- A table by System Organ Class (SOC) and Preferred Term (PT) for each treatment-emergent event, counting each patient once for each SOC and PT experienced, by:
    - All events
    - All serious events
    - All related events
    - All serious and related events
    - All Grade 3-5 events
    - All Grade 3-5 serious events
    - All Grade 3-5 related events
    - All Grade 3-5 serious and related events
    - AEs in special categories
    - Grade 3-5 AEs in special categories
    - Pulmonary AEs (pulmonary events are one of the special categories)
    - Grade 3-5 Pulmonary AEs
    - Pulmonary AEs within 7 days of first dose
    - Pulmonary AEs within 14 days of first dose
    - Grade 3-5 Pulmonary AEs within 7 days of first dose

- Grade 3-5 Pulmonary AEs within 14 days of first dose
- Pulmonary AEs within 7 days of dose escalation – Dose escalation is defined as an increase in the total mg of brigatinib from the maximum dose received in the previous 7 days
- Pulmonary AEs within 7 days of dose resumption – Dose resumption is defined as receipt of brigatinib after 7 or more days of no exposure to the drug

4.5.2 Laboratory Data

Laboratory data will be summarized as shift from baseline to highest on-study grade as defined by CTCAE 4.0. On-study grade will be defined using the minimum and/or maximum post-exposure result as appropriate. For example, glucose will be evaluated for hypoglycemia using the patient's minimum post-exposure value, and for hyperglycemia using the patient's maximum post-exposure value. Testosterone, INR, and Insulin will get cross tabulated baseline, low, normal, high by highest and lowest value on study (low, normal, high).

4.5.3 Vital Signs

Systolic and diastolic blood pressure will be summarized as shift from baseline to highest on-study grade as defined by CTCAE 4.0. On-study grade will be defined using the minimum and/or maximum post-exposure result as appropriate. Hypotension will be evaluated using the patient's minimum post-exposure value SBP and DBP, and hypertension using the patient's maximum post-exposure value.

4.5.4 QTcF Analysis

Descriptive statistics of maximum QTcF and change from baseline will be calculated following the ICH-E14 guidelines: the proportion of treated patients with at least one on-drug QTcF value > 450 ms, 480 ms, and 500 ms; proportion of treated patients with a maximum change in QTcF from baseline > 30 ms and > 60 ms. The Fridericia correction (QTcF) will be used throughout.

QTcF change from baseline and blood concentration will be analyzed using mixed effects models. A detailed QT analysis will be specified in a separate analysis plan.

4.5.5 Other Measures

On-study assessments not covered by other sections of this document will be presented in summary tables of observed values and/or changes from baseline.

Appendix 1 Notes from RECIST v1.1

Appendix 1.1 Measureable Disease vs. Non-measureable Disease

Measurable disease is defined by the presence of at least one lesion with a longest diameter > = 10 mm or a pathological lymph node with a short axis of > = 15 mm. Lesions with prior local treatment are usually not considered measurable unless there has been demonstrated progression in the lesion.

Non-measurable disease is defined as small lesions (longest diameter <10mm or pathological lymph nodes with > = 10 to < 15 mm short axis) or lesions truly non-measurable by reproducible imaging techniques.

Appendix 1.2 Target Lesions vs. Non-target Lesions vs. New Lesions

1. Target lesions
    a. A maximum of five total (and two per organ, maximum) of lesions or pathological lymph nodes will be identified at baseline to follow up to assess tumor burden in target lesions for response determination. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated as baseline or on-study sum diameters.
    b. Measurement of target lesions:
        - "Too small to measure" - In case that target lesions become very faint on CT scan and are reported as 'too small to measure': if it is the opinion of the radiologist that a lesion has likely disappeared, the measurement should be recorded as 0mm; if a lesion or lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned. This default value is derived from the 5mm CT slice thickness (but should not be changed with varying CT slice thickness). If the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5mm.
        - Lesions that split or coalesce on treatment - When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

c. Response criteria for target lesions:
   - Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
   - Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
   - Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the unequivocal appearance of one or more new lesions is also considered progression).
   - Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2. Non-target lesions
   a. All other lesions or pathological lymph nodes (or sites of disease) after the target lesions are chosen will be identified as non-target lesions and should also be recorded at baseline.
   b. Measurements are not required and these lesions will be assessed only qualitatively as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').
   c. Response criteria for non-target lesions
      - Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
      - Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumormarker level above the normal limits.
      - Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).
   d. Assessment of progression of non-target lesions
      - When the patient has measurable disease at baseline, the designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease is extremely rare. To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently and requires discontinuation of treatment.

- When the patient has only non-measurable disease at baseline, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. An unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is substantial and comparable in magnitude to the increase that would be required to declare PD form measurable disease: e.g., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion).

3. New lesions

   A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Appendix 1.3 Time Point Overall Response Status and Best Overall Response Status Calculation

Appendix Table 1 Summary of the Overall Response Status Calculation at each Time Point for Patients Who Have Target +/- Non-target Disease at Baseline

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Appendix Table 2 Summary of the Overall Response Status Calculation at each Time Point for Patients Who Have Non-measurable (Therefore Non-target) Disease only at Baseline

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

[a] 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Appendix Table 3 Summary of the Best Overall Response Status Calculation when Confirmation of CR and PR is Required

Overall response First time point	Overall response Subsequent time point	Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Appendix 2 Adverse Events Synonyms*

MedDRA Dictionary Preferred Term	MedDRA Dictionary System Organ Class	Recoded Preferred Term	Recoded System Organ Class
Thrombocytopaenia	Blood and Lymphatic System Disorders	platelet count decreased	Investigations
Thrombocytopenia	Blood and Lymphatic System Disorders	platelet count decreased	Investigations
Thrombocytosis	Blood and Lymphatic System Disorders	platelet count increased	Investigations
Thrombocythaemia	Blood and Lymphatic System Disorders	platelet count increased	Investigations
Thrombocythemia	Blood and Lymphatic System Disorders	platelet count increased	Investigations
Anemia	Blood and Lymphatic System Disorders	Anaemia	Blood and Lymphatic System Disorders
Haemoglobin decreased	Investigations	Anaemia	Blood and Lymphatic System Disorders
Hemoglobin decreased	Investigations	Anaemia	Blood and Lymphatic System Disorders
Haematocrit decreased	Investigations	Anaemia	Blood and Lymphatic System Disorders
Erythrocytosis	Blood and Lymphatic System Disorders	Hemoglobin increased	Investigations
Erythrocythemia	Blood and Lymphatic System Disorders	Hemoglobin increased	Investigations
Leukopenia	Blood and Lymphatic System Disorders	white blood cell count decreased	Investigations
white blood cell count increased	Investigations	Leukocytosis	Blood and Lymphatic System Disorders
Neutropenia	Blood and Lymphatic System Disorders	Neutrophil count decreased	Investigations
Lymphopaenia	Blood and Lymphatic System Disorders	Lymphocyte count decreased	Investigations
Lymphopenia	Blood and Lymphatic System Disorders	Lymphocyte count decreased	Investigations
eosinophil count increased	Investigations	Eosinophilia	Blood and Lymphatic System Disorders
basophil count increased	Investigations	Basophilia	Blood and Lymphatic System Disorders

blood glucose decreased	Investigations	Hypoglycaemia	Metabolism and Nutrition Disorders
Hypoglycemia	Metabolism and Nutrition Disorders	Hypoglycaemia	Metabolism and Nutrition Disorders
blood glucose increased	Investigations	Hyperglycaemia	Metabolism and Nutrition Disorders
Hyperglycemia	Metabolism and Nutrition Disorders	Hyperglycaemia	Metabolism and Nutrition Disorders
blood sodium decreased	Investigations	Hyponatraemia	Metabolism and Nutrition Disorders
Hyponatremia	Metabolism and Nutrition Disorders	Hyponatraemia	Metabolism and Nutrition Disorders
blood sodium increased	Investigations	Hypernatraemia	Metabolism and Nutrition Disorders
Hypernatremia	Metabolism and Nutrition Disorders	Hypernatraemia	Metabolism and Nutrition Disorders
blood potassium decreased	Investigations	Hypokalaemia	Metabolism and Nutrition Disorders
Hypokalemia	Metabolism and Nutrition Disorders	Hypokalaemia	Metabolism and Nutrition Disorders
blood potassium increased	Investigations	Hyperkalaemia	Metabolism and Nutrition Disorders
Hyperkalemia	Metabolism and Nutrition Disorders	Hyperkalaemia	Metabolism and Nutrition Disorders
blood calcium decreased	Investigations	Hypocalcaemia	Metabolism and Nutrition Disorders
Hypocalcemia	Metabolism and Nutrition Disorders	Hypocalcaemia	Metabolism and Nutrition Disorders
Hypercalcemia	Metabolism and Nutrition Disorders	Hypercalcaemia	Metabolism and Nutrition Disorders
blood calcium increased	Metabolism and Nutrition Disorders	Hypercalcaemia	Metabolism and Nutrition Disorders
blood magnesium decreased	Investigations	Hypomagnesaemia	Metabolism and Nutrition Disorders
Hypomagnesemia	Metabolism and Nutrition Disorders	Hypomagnesaemia	Metabolism and Nutrition Disorders
blood magnesium increased	Investigations	Hypermagnesaemia	Metabolism and Nutrition Disorders
Hypermagnesemia	Metabolism and Nutrition Disorders	Hypermagnesaemia	Metabolism and Nutrition Disorders

Blood Phosphorus decreased	Investigations	Hypophosphataemia	Metabolism and Nutrition Disorders
blood phosphate decreased	Investigations	Hypophosphataemia	Metabolism and Nutrition Disorders
Hypophosphatemia	Metabolism and Nutrition Disorders	Hypophosphataemia	Metabolism and Nutrition Disorders
blood phosphorous increased	Investigations	Hyperphosphataemia	Metabolism and Nutrition Disorders
Hyperphosphatemia	Metabolism and Nutrition Disorders	Hyperphosphataemia	Metabolism and Nutrition Disorders
blood triglycerides increased	Investigations	Hypertriglyceridaemia	Metabolism and Nutrition Disorders
Hypertriglyceridemia	Metabolism and Nutrition Disorders	Hypertriglyceridaemia	Metabolism and Nutrition Disorders
Hypercholesterolemia	Metabolism and Nutrition Disorders	Blood cholesterol increased	Investigations
Hypercholesterolaemia	Metabolism and Nutrition Disorders	Blood cholesterol increased	Investigations
blood albumin decreased	Investigations	Hypoalbuminaemia	Metabolism and Nutrition Disorders
Hypoalbuminemia	Metabolism and Nutrition Disorders	Hypoalbuminaemia	Metabolism and Nutrition Disorders
Hyperbilirubinaemia	Hepatobiliary Disorders	blood bilirubin increased	Investigations
Hyperbilirubinemia	Hepatobiliary Disorders	blood bilirubin increased	Investigations
Blood Lipase increased	Investigations	Lipase Increased	Investigations
Lipase	Investigations	Lipase Increased	Investigations
Blood Amylase	Investigations	Blood Amylase Increased	Investigations
Pancreatitis Acute	Gastrointestinal disorders	Pancreatitis	Gastrointestinal disorders
Rash erythematous	Skin and Subcutaneous Tissue Disorders	Rash	Skin and Subcutaneous Tissue Disorders
Rash Macular	Skin and Subcutaneous Tissue Disorders	Rash	Skin and Subcutaneous Tissue Disorders
Rash papular	Skin and Subcutaneous Tissue Disorders	Rash	Skin and Subcutaneous Tissue Disorders
rash maculo-papular	Skin and Subcutaneous Tissue Disorders	Rash	Skin and Subcutaneous Tissue Disorders

Troponin I increased	Investigations	Troponin increased	Investigations
painful defaecation	Gastrointestinal Disorders	proctalgia	Gastrointestinal Disorders
blood pressure increased	Investigations	hypertension	Vascular disorders
blood pressure decreased	Investigations	hypotension	Vascular disorders
escherichia bacteraemia	Infections and Infestations	bacteraemia	Infections and Infestations
staphylococcal bacteraemia	Infections and Infestations	bacteraemia	Infections and Infestations
abdominal pain upper	Gastrointestinal Disorders	abdominal pain	Gastrointestinal Disorders
abdominal pain lower	Gastrointestinal Disorders	abdominal pain	Gastrointestinal Disorders
stomach discomfort	Gastrointestinal Disorders	abdominal discomfort	Gastrointestinal Disorders
Myocardial Infarction	Cardiac Disorders	Acute Myocardial Infarction/Myocardial Infarction	Cardiac Disorders
Acute Myocardial Infarction	Cardiac Disorders	Acute Myocardial Infarction/Myocardial Infarction	Cardiac Disorders

*This list will be updated as new events occur and/or MedDRA versions change over the course of the study.

Appendix 3 Date Handling and Imputation

Calculation of Study Day

Study Day is defined as the date an event occurred – date of first dose of study drug +1.Unless otherwise specified other date calculations will be defined as the difference between the dates + 1.

Calculation of Months

Intervals expressed in days will be converted to months by # days / 30.4375.

Imputation Rules for Missing Initial Cancer Diagnosis Date and Start Date and Stop Date for Selected Prior Anti-Cancer Therapies

In general, a diagnosis date will be imputed first and then used to adjust the imputation of the corresponding prior treatment start date when necessary.

Initial Diagnosis Dates

- If day is missing but month and year are non-missing (UU-MMM-YYYY), impute as earliest of: 01-MMM-YYYY, randomization date.
- If day and month are missing (UU-UUU-YYYY), impute as earliest of: 01-JAN-YYYY, randomization date.
- No imputation for a completely missing date (UU-UUU- UUUU)
- Additional adjustment(s) may be applied depending on ARIAD medical's review on the prior anti-cancer therapies data

Prior Anti-Cancer Therapies Dates

Start Date

- If day is missing but month and year are non-missing (UU-MMM-YYYY), impute as earliest of: 01-MMM-YYYY, randomization date.
- If day and month are missing (UU-UUU-YYYY), impute as earliest of: 01-JAN-YYYY, randomization date.
- No imputation for a completely missing date (UU-UUU- UUUU)
- If an imputed prior treatment start date is before diagnosis date, re-impute as diagnosis date.

Stop Date

- If day is missing but month and year are non-missing (UU-MMM-YYYY), impute as the earliest of
    - 30-MMM-YYYY if month is April, June, September or November, 28-MMM-YYYY if month is February, 31-MMM-YYY otherwise
    - Randomization date
- If day and month are missing (UU-UUU-YYYY), impute as earliest of: 31-DEC-YYYY, randomization date.

If after applying above rules, any prior treatment stop dates are prior to corresponding prior treatment start date, impute as start date.

Duration of a selected prior anti-cancer therapy will be calculated using the following formula: duration = stop date – start date +1. Duration will be calculated with imputed dates when necessary. Total duration will be the sum of the individual durations.

Time since the stop date of a selected prior anti-cancer therapy to the first dose of study treatment will be calculated using the following formula: time since stop date = stop date – first dose date +1. Time since the stop date to the first dose date will be missing in the case of a completely missing stop date.

Imputation Rules for Missing Onset Date and Resolution Date of Adverse Events

In general the imputation will be conservative such that onset dates will be imputed to be as early as possible and resolution dates will be imputed to be as late as possible. Resolution date will be imputed first and then used to impute onset date.

Imputation for Resolution Date:

- If day is missing but month and year are non-missing (UU-MMM-YYYY), impute as the earliest of:
  - Last day of the month (28, 29, 30 or 31 depending on in which month the adverse event resolved)
  - Data cutoff date
  - Death date
- If day and month are missing (UU-UUU-YYYY), impute as the earliest of:
  - December 31 (31-DEC-YYYY)
  - Data cutoff date
  - Death date
- If date is completely missing (e.g., AE is ongoing), impute as earliest of:
  - Data cutoff date
  - Treatment discontinuation date + 30 days
  - Death date

Imputation for Onset Date:

- If day is missing but month and year are non-missing (UU-MMM-YYYY), impute as follows:
  - If year and month are the same as year and month of first dose date:
    - If resolution date (or imputed resolution date) is on or after first dose date, impute as first dose date
    - If resolution date (or imputed resolution date) is prior to first dose date, impute as latest of first day of the month or informed consent date
  - If year is the same as year of first dose date and month is **after** month of first dose date, impute as first date of month
  - If year is the same as year of first dose date and month is **before** month of first dose date, impute as latest of first day of the month or informed consent date
  - If year is **after** year of first dose date, impute as first day of month
  - If year is **before** year of first dose date, impute as latest of first day of the month or informed consent date
- If day and month are missing and year is non-missing (UU-UUU-YYYY), impute as follows:

  - If year is the same as year of first dose date:
    - If resolution date (or imputed resolution date) is on or after first dose date, impute as first dose date
    - If resolution date (or imputed resolution date) is prior to first dose date, impute as latest of first day of the month or informed consent date
  - If year is **after** year of first dose date, impute as January 1 (01-JAN-YYYY)
  - If year is **before** year of first dose date, impute as latest of first day of the year (01-JAN-YYYY) or informed consent date
- If date is completely missing:
  - If resolution date (or imputed resolution date) is on or after first dose date, impute as first dose date
  - If resolution date (or imputed resolution date) is prior to first dose date, impute as informed consent date.