Title: A Postmarketing Observational Registry to Evaluate the Incidence of and Risk Factors for Vascular Occlusive Events Associated With ICLUSIG® (ponatinib) in Routine Clinical Practice in the US (OMNI)

EUPAS Number: 9097

Protocol Approve Date: 15 January 2019

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally protected information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

A Postmarketing Observational Registry to Evaluate the Incidence of and Risk Factors for Vascular Occlusive Events Associated With ICLUSIG® (ponatinib) in Routine Clinical Practice in the US (OMNI)

Protocol Number:	AP24534-14-401
Version / Date	Amendment 4, Version 5.0 / 16 November 2018 Amendment 3, Version 4.0 / 29 January 2018 Amendment 2, Version 3.0 / 25 July 2016 Amendment 1, Version 2.0 / 16 July 2015 Original, Version 1.0 / 07 November 2014
Name of Test Drug:	ICLUSIG® (ponatinib) US: NDA 203469; IND 78,375
Sponsor:	ARIAD Pharmaceuticals, Inc. (a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited)
Responsible Medical Officer:	PPD

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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia
AOE	arterial occlusive event
AP	accelerated phase
BCR-ABL	Breakpoint Cluster Region-Abelson
BP	blast phase
CCyR	complete cytogenetic response
CFR	code of federal regulations
CI	confidence interval
CML	chronic myeloid leukemia
CP	chronic phase
CRO	Contract Research Organization
eCRF	electronic case report form
EDC	electronic data capture
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HCP	healthcare provider
HIPAA	Health Insurance Portability and Accountability Act
IRB	institutional review board
LTF	lost to follow-up
McyR	major cytogenetic response
MMR	major molecular response
Ph+	Philadelphia chromosome-positive
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
TKI	tyrosine kinase inhibitor
US	United States
USPI	United States Prescribing Information
VOE	vascular occlusive event
VTE	venous thromboembolic event

3 RESPONSIBLE PARTIES

This observational, voluntary, patient registry study will be conducted in the United States (US).

The Sponsor (ARIAD Pharmaceuticals, Inc. (a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited)) contact details are:

ARIAD Pharmaceuticals Inc. (a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited)
40 Landsdowne Street
Cambridge, MA 02139-4234
877-TAKEDA7 (877-825-3327)

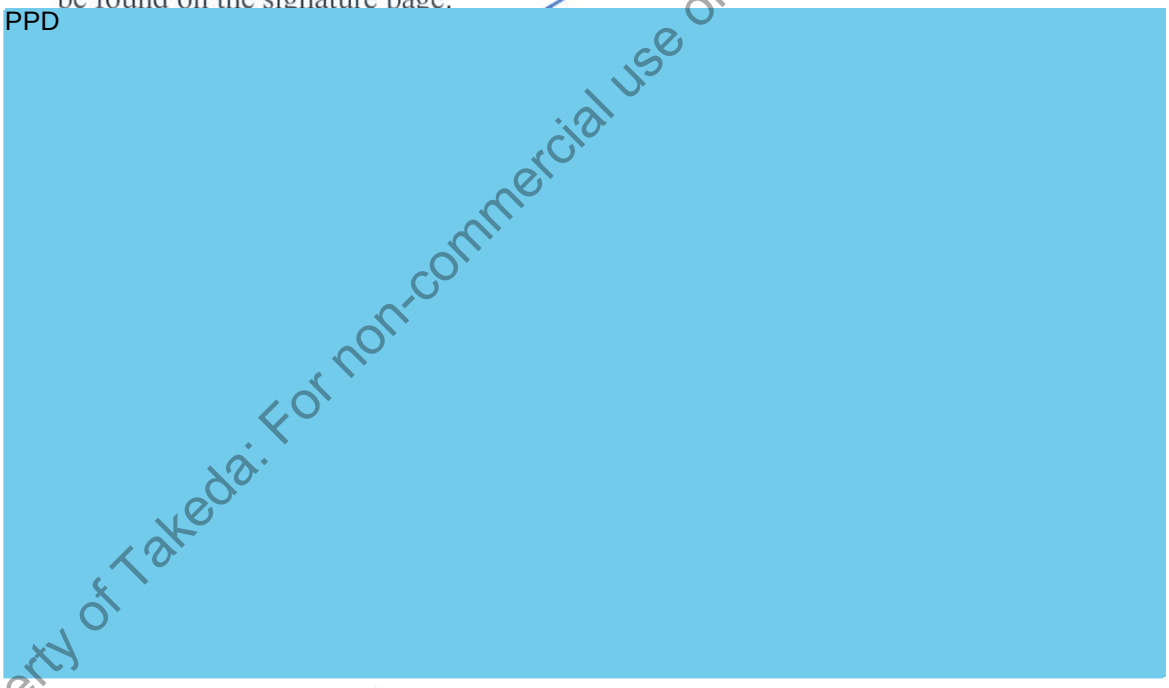
This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer and other signatories can be found on the signature page.

PPD



PRINCIPAL INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the package insert(s), and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events (SAEs) defined in Section 10.0 of this protocol.
- Responsibilities of the investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses of this protocol.

SIGNATURE

PPD

The investigator and contract research organization (CRO) contact details are:

PPD

4 SYNOPSIS

4.1 Title of Protocol

A Postmarketing Observational Registry to Evaluate the Incidence of and Risk Factors for Vascular Occlusive Events Associated with ICLUSIG® (ponatinib) in Routine Clinical Practice in the United States (OMNI).

4.2 Rationale and Background

Iclusig is indicated in the US for:

- Treatment of adult patients with T315I-positive chronic myeloid leukemia (CML) (in chronic phase [CP-CML], accelerated phase [AP-CML], or blast phase [BP-CML]) or T315I-positive Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL), or
- Treatment of adult patients with CP-CML, AP-CML, BP-CML, or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.

Iclusig was initially approved under 21 Code of Federal Regulations (CFR) 314 Subpart H in the US on 14 December 2012 with a Boxed Warning that included the risk of arterial thrombosis. The US Prescribing Information (USPI) includes data reflecting a cumulative incidence over time of vascular occlusive events (VOEs) (including arterial occlusive events [AOEs; comprising cardiovascular, cerebrovascular, and peripheral vascular events] and venous thromboembolic events [VTEs]). AOEs have occurred in at least 35% of Iclusig-treated patients in the phase 1 and phase 2 trials, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures (cerebrovascular, coronary, and peripheral arterial). Patients with and without cardiovascular risk factors, including patients less than 50 years old, experienced these events. In the Phase 2 Study AP24534-10-201, AOEs occurred in at least 150/449 Iclusig-treated patients (33%), with some patients experiencing events of more than one type. VTEs occurred in 25/449 Iclusig-treated patients (6%), including deep venous thrombosis (10 patients), pulmonary embolism (7 patients), superficial thrombophlebitis (3 patients), and retinal vein thrombosis (2 patients) with vision loss (Iclusig USPI).

Additional information is needed to characterize the safety profile of Iclusig as it is used in routine clinical practice in the US. This prospective, observational, voluntary patient registry study, a Food and Drug Administration (FDA)-mandated postmarketing requirement (PMR2113.2), will provide additional quantification and characterization of VOEs, their risk factors, and their outcomes in patients with CP-CML, AP-CML, BP-CML, or Ph+ ALL treated with Iclusig with or without anticoagulant and/or antiplatelet agents.

The patient registry will include patients who are diagnosed with CP-CML, AP-CML, BP-CML, or Ph+ ALL; who are over 18 years of age; and for whom the decision to initiate standard treatment with commercially available Iclusig has already been made. The patient registry is non-interventional; all treatment decisions, including prophylactic or therapeutic use of anticoagulant and/or antiplatelet agents, are made at the discretion of the patient's healthcare provider (HCP) and are not mandated by the registry. HCPs prescribing Iclusig to patients for the first time may be asked to provide registry study information to the patient.

As all prescriptions are filled through specialty pharmacies which distribute Iclusig in the US, additional patients who may be eligible to participate in this registry will be further identified through prescriptions dispensed by specialty pharmacies. The specialty pharmacies will provide patients with registry study information and those who are interested in participating will be connected with and / or provided contact information for the Registry Coordinating Center to enroll, based on patient preference.

The Registry Coordinating Center will obtain written informed consent from these patients and will review the Inclusion/Exclusion criteria for eligibility. The registry enrollment date is the date the written informed consent is given by the patient. The Registry Coordinating Center will collect registry study data on enrolled patients every 3 months for the duration of the study.

4.3 Research Objectives

The primary objectives of this patient registry are to assess the following for patients with CP-CML, AP-CML, BP-CML, or Ph+ ALL treated with Iclusig with or without anticoagulant and/or antiplatelet agents in routine clinical practice in the US:

- the incidence of VOEs
- the risk factors for development of VOEs
- the outcomes of VOEs

4.4 Study Design

This is a prospective, observational registry study of eligible patients with CP-CML, AP-CML, BP-CML, or Ph+ ALL who are being treated with Iclusig with or without anticoagulant and/or antiplatelet agents in the US. The study is non-interventional; all treatment decisions, including the prophylactic or therapeutic use of anticoagulant and/or antiplatelet agents, are made at the discretion of the patient's HCP and are not mandated by the study design or protocol.

The total registry duration is anticipated to be approximately 30 months, including an enrollment period of approximately 18 months followed by data collection on all patients for a period of 12 months from the date of last patient enrollment. The registry will provide 12 to 30 months of exposure in these Iclusig-naïve patients, providing an adequate amount of time to accumulate additional data on VOEs. Any VOEs occurring after study closeout will be captured in the standard ARIAD post-marketing pharmacovigilance database. At least 300 patients will be enrolled and followed for the duration of the study or until patient withdrawal or death, whichever occurs first.

A schema of the patient enrollment procedure is provided in Figure 1. The roles of the HCP, specialty pharmacy, Registry Coordinating Center, and Principal Investigator (PI) are defined in the following text.

HCP: The HCP will make the decision to start Iclusig independent of this registry and will notify the specialty pharmacy to initiate dispensing as per their standard process. The HCP may provide the patient with an IRB-approved information sheet about the registry and may instruct the patient to contact the Registry Coordinating Center for questions about the patient registry and/or to enroll in the patient registry.

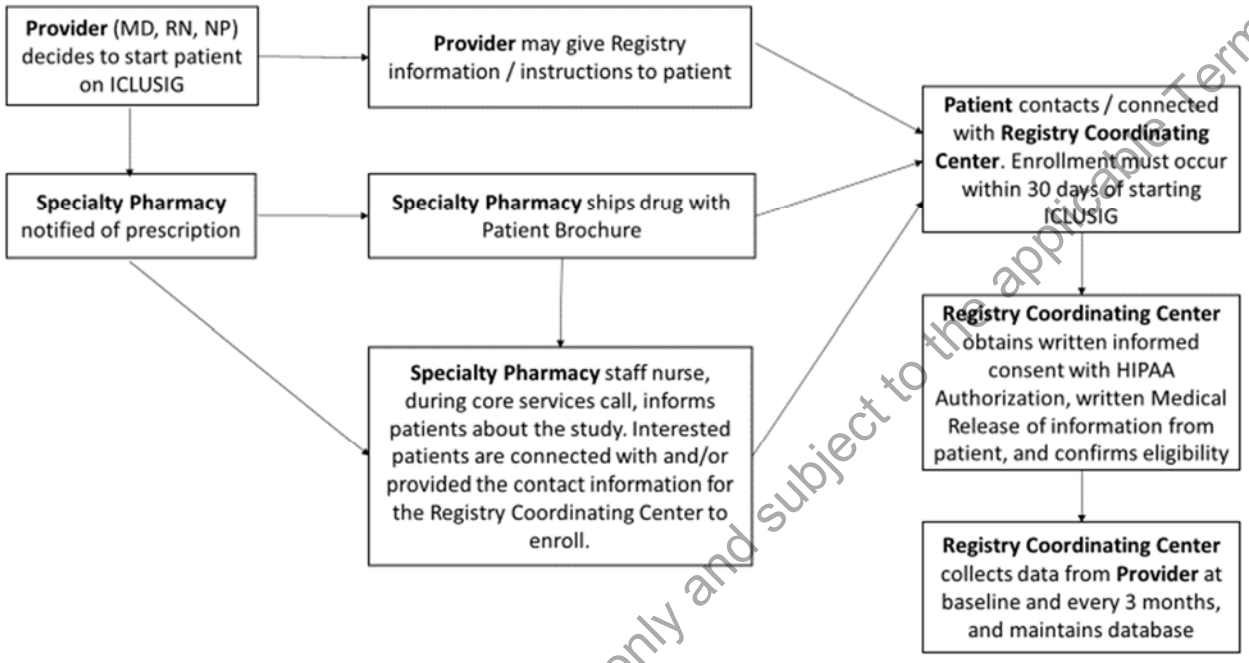
Specialty pharmacy: Patients who are initiating treatment with Iclusig will receive a brochure about the registry with their first prescription dispensed by the Specialty pharmacy, The brochure directs patients to contact the Registry Coordinating Center to receive information about the registry and how to enroll, if they are interested. As part of the routine procedures by the specialty pharmacy, patients will also receive a call from a nurse on staff at the specialty pharmacy. During this core services call made as a routine commercial practice for every ICLUSIG prescription, the specialty pharmacy nurse will inform patients about the study. Patients who are interested in participating will be connected with and / or provided contact information for the Registry Coordinating Center to enroll, based on patient preference. Patients must enroll in the registry study within 30 days after initiating treatment with Iclusig.

Registry Coordinating Center and PI: The Registry Coordinating Center will discuss the registry with the patient, confirm their eligibility, and send them a consent form, HIPAA statement, and a Medical Release of Information (MRI) form. Once the Registry Coordinating Center receives all signed documents back from the patient, the PI from the Registry Coordinating Center (or designee) will confirm that the patient can be enrolled.

Once the patient is enrolled, the Registry Coordinating Center will mail the HCP (Iclusig prescriber) the MRI form and will then call the HCP at patient enrollment and at approximately 3-month intervals to collect registry study data on enrolled patients. The Registry Coordinating Center will also track the number of patients who inquire about the registry, the number who provided informed consent as well as any reasons why those patients were not enrolled in the patient registry, and those patients who agreed to participate, but their HCPs did not agree to

provide their data. No data will be collected, analyzed, or reported for patients who do not consent to participate in this registry.

Figure 1 Registry Study Schema



Abbreviations: HIPAA=Health Insurance Portability and Accountability Act; MD=medical doctor; NP=nurse practitioner; RN=registered nurse.

4.5 Population

The target registry population will include adult patients in the US who are diagnosed with CP-CML, AP-CML, BP-CML, or Ph+ ALL; who are over 18 years of age; and for whom the decision to initiate treatment with commercially available Iclusig has already been made. Inclusion criteria are broad and exclusion criteria are limited so as to include a representative population of patients being treated with Iclusig in routine clinical practice for one of the current approved indications.

4.6 Data Variables

Data collection will include documentation of informed consent, inclusion/exclusion criteria, demographics, medical history and concurrent conditions, adverse events, incidence of VOEs, and details of Iclusig treatment (see Section 8.5 for details). VOEs are the adverse events (AEs) of special interest (AESIs) to be identified for this patient registry, including AOEs and VTEs. AEs and VOEs are further described in Section 6.1 and Section 8.5.7.

4.7 Data Sources

Data collection forms are designed to gather the protocol-specified data that have been documented as part of the routine care. There are no protocol-mandated clinic visits, treatments,

procedures, or diagnostic tests required. Data will be collected from the treating HCP at approximately 3-month intervals.

4.8 Registry Size

Approximately 300 patients will be enrolled.

4.9 Data Analysis

Complete analytical specifications, including tables and listings, will be included in the Statistical Analysis Plan (SAP), which will be prepared separately.

The primary analyses will be performed 12 months after the last patient has been enrolled and will present estimates of the incidence of VOEs and exposure-adjusted incidence rate (EAIR), and 95% confidence intervals (CIs) for patients enrolled in the registry. Data will be presented using descriptive statistics, with number and percent for categorical endpoints, n, mean, standard deviation (SD), standard error (SE) of the mean, median, minimum (min), and maximum (max) for continuous endpoints.

Exploratory analyses will also be performed to better understand any differences in patients who experience any AESIs (VOEs) versus those who do not. The exploratory analyses will be performed using logistic regression, including factors such as patient demographic characteristics, dose and duration of Iclusig, and concomitant medications including but not limited to the use of anticoagulant and/or antiplatelet agents. Time to event analysis may also be performed to describe the effect of the above factors on event-free survival.

Historical estimates (from published data or ARIAD study data) of the expected rates of VOEs will be used as benchmarks for assessing potential excess risk of VOEs among Iclusig patients (see Section 8.7 for further details). No formal statistical tests of the difference in VOE rates with regard to risk factors are planned.

Finally, ARIAD will report baseline demographic characteristics and medical history analysis of patients included in the observational patient registry (see Section 8.5 for further details).

5 MILESTONES

Milestone	Planned Date
Enrollment (18 months)	March 2018 – September 2019
Start of data collection	Upon enrollment of first patient
End of data collection (12 months from the date of last patient enrolled)	~September 2020
Final report of registry results (6 months from date of last data collection	March 2021

6 RATIONALE AND BACKGROUND

Iclusig is a novel, synthetic, orally active multi-target TKI. The primary target for Iclusig is Breakpoint Cluster Region-Abelson (BCR-ABL), an abnormal tyrosine kinase that is the hallmark of CML. Iclusig was designed to inhibit the enzymatic activity of BCR-ABL with very high potency and inhibit mutated forms of the protein that confer resistance to treatment with existing TKIs, including the T315I mutant for which no effective therapy exists. Iclusig exhibits broad-spectrum inhibition of BCR-ABL mutants and is considered a pan-BCR-ABL inhibitor. In the heavily pretreated phase 2 trial population (58% ≥ 3 prior TKIs), major cytogenetic response (MCyR), complete cytogenetic response (CCyR), and major molecular response (MMR) were observed in 158/267 patients [59.2%], 142/267 patients [53.2%], and 102/267 patients [38.2%] of CP-CML patients, respectively, after a median of 2 years of follow-up.

Iclusig was initially approved in the US on 14 December 2012 with a Boxed Warning that included the risk of arterial thrombosis. Data from the phase 2 trial, with longer follow-up after product approval, demonstrated a cumulative incidence of arterial thrombosis (including cardiovascular, cerebrovascular, peripheral vascular events) and VTEs that was higher than reported at the time of initial approval. Following a temporary marketing suspension implemented on 31 October 2013 (to further assess incidence of VOEs), the FDA approved a revised label and a Risk Evaluation and Mitigation Strategy (REMS) for Iclusig on 20 December 2013, and commercial distribution of Iclusig resumed on 17 January 2014. The revised US Prescribing Information (USPI) for Iclusig carries a Boxed Warning for arterial and venous thrombosis and occlusions (collectively referred to as VOEs), with VTEs reported to have occurred in 6%, and AOEs reported to have occurred in at least 35% of Iclusig-treated patients from the phase 1 and 2 trials, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients less than 50 years old, experienced these events (Iclusig USPI).

Additional information is needed to characterize the safety profile of Iclusig as it is used in routine clinical practice in the US. This observational, voluntary patient registry study, an FDA-mandated postmarketing requirement (PMR 2113-2), will provide additional quantification and characterization of VOEs, and their outcomes in patients treated with Iclusig. The patient registry will include at least 300 adult patients who are diagnosed with CP-CML, AP-CML, BP-CML, or Ph+ ALL; are initiating treatment with Iclusig with or without anticoagulant and/or antiplatelet agents; and who agree to participate in the registry.

6.1 Risks of Iclusig

The risks associated with Iclusig use, as listed in the Warnings and Precautions and Adverse Reactions sections of the USPI, include vascular occlusion, heart failure, hepatotoxicity, hypertension, pancreatitis, neuropathy, ocular toxicity, hemorrhage, fluid retention, cardiac arrhythmias, myelosuppression, tumor lysis syndrome, compromised wound healing and gastrointestinal perforation, and embryo-fetal toxicity. As per the PMR (PMR 2113-2), this registry will focus on estimating the risk of VOEs.

6.1.1 Vascular Occlusive Events (VOEs)

Arterial and venous thrombosis and occlusions, both serious and non-serious, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures have occurred in at least 27% of Iclusig-treated patients who participated in the phase 1 and phase 2 clinical trials. Iclusig can also cause recurrent or multi-site vascular occlusion.

In the phase 2 Study AP24534-10-201, 110/449 Iclusig-treated patients (24%) experienced a VOE of any grade. Fatal and life-threatening vascular occlusion has occurred within 2 weeks of starting Iclusig treatment. The starting dose of Iclusig is 45 mg per day with dose reductions as required to manage AEs. Fatal and life-threatening vascular occlusion has been observed in patients treated with average daily dose intensities as low as 15 mg per day. In the phase 1 dose escalation Study AP24534-07-101, the median time to onset of the first vascular occlusion event was 5 months. Patients with and without cardiovascular risk factors have experienced vascular occlusion; although, these events were more frequent with increasing age and in patients with prior history of ischemia, hypertension, diabetes, or hyperlipidemia. It is recommended to interrupt or stop Iclusig immediately in patients who develop VOEs. Benefit-risk considerations should guide the decision to restart Iclusig therapy. Refer to Section 5.1 of the USPI for further details.

7 RESEARCH OBJECTIVES

The primary objectives of this registry are to assess, for patients treated with Iclusig with or without anticoagulant and/or antiplatelet agents in routine clinical practice in the US:

- the incidence of VOEs
- the risk factors for development of VOEs
- the outcomes of VOEs

8 RESEARCH METHODS

8.1 Study Design

This is a prospective, observational, voluntary, patient registry study of patients who are diagnosed with CP-CML, AP-CML, BP-CML, or Ph+ ALL; who are over 18 years of age; and for whom the decision to initiate standard treatment with commercially available Iclusig has already been made. The patient registry is non-interventional; all treatment decisions, including prophylactic or therapeutic use of anticoagulant and/or antiplatelet agents, are made at the discretion of the patient and the patient's HCP and are not mandated by the registry.

Eligible, consenting patients initiating treatment with Iclusig will be enrolled into the registry. Approximately 300 patients will be enrolled.

Data variables to be collected are described in Section 4.6, with details provided in Section 8.5. Data will be collected during the patient registry at approximately 3-month intervals for each patient (see Section 8.5.1).

Because this is an observational registry of real-world treatment practices and outcomes, no medication will be provided as a part of this registry. Iclusig will be obtained through usual commercial channels for prescription medicines and will not be provided free of charge by the sponsor (ARIAD). HCPs and their enrolled patients will make all treatment decisions according to their routine practices; the HCPs will provide prescriptions for their patients, as appropriate. HCPs will make the decision to treat the patient with Iclusig prior to the decision to enter the patient into the registry. All dosing decisions will be made by the HCP. The only addition to routine practice is the reporting of data to ARIAD. There are no protocol-mandated procedures or diagnostic tests.

8.2 Healthcare Provider Setup and Management

ARIAD is the sponsor of this registry, however some sponsor responsibilities are delegated to the Contract Research Organization (CRO), which is documented in the trial master file (TMF). The CRO manages the Registry Coordinating Center, which will contact HCPs to collect the protocol-specified data at approximately 3-month intervals after patient enrollment.

8.3 Study Duration

The total registry study duration is anticipated to be approximately 30 months, including an enrollment period of approximately 18 months followed by data collection on all patients for a period of 12 from the date of last patient enrollment. Therefore, the data collection period will range from 30 months (first patient in) to 12 months (last patient in). Any VOEs occurring after study closeout will be captured in the standard ARIAD post-marketing Pharmacovigilance database.

Patients may continue Iclusig per HCP discretion after the registry data collection period ends. Iclusig may be discontinued at the request of the patient and his/her HCP at any time during the registry. In the case of treatment discontinuation at any time, data collection will continue for a minimum of 12 months up to 30 months (total registry duration) from the patient's date of enrollment.

8.4 Setting

The target registry population will include adult patients diagnosed with CP-CML, AP-CML, BP-CML, or Ph+ ALL and for whom the decision to initiate treatment with commercially available Iclusig has already been made. This will include both patients who are and those who are not taking concomitant anticoagulant and/or antiplatelet agents. Patients who may be eligible to participate in this registry will be identified through prescriptions dispensed by the specialty pharmacies which distribute Iclusig in the US. This will allow for the identification of all patients potentially eligible for participation in the registry. The registry enrollment date is the date the written informed consent is provided by the patient.

Patients who are excluded from the registry will be patients who do not meet the registry eligibility criteria, patients who decline to provide written informed consent, or patients whose HCPs refuse to participate. Inclusion criteria are broad and exclusion criteria are limited so as to include a representative population of patients taking Iclusig for treatment of CP-CML, AP-CML, BP-CML, or Ph+ ALL in routine clinical practice in the US.

8.4.1 Inclusion Criteria

Patients must meet all of the following criteria to be eligible for the registry:

1. Adult patients (age ≥18 years) who are diagnosed with CP-CML, AP-CML, BP-CML, or Ph+ ALL
2. Patients who are initiating Iclusig therapy for the first time, or for whom Iclusig therapy was initiated within 30 days before registry enrollment.
3. The decision to prescribe Iclusig must have been made prior to enrollment in the registry and based upon approved US indications.
4. Patients who have the ability to understand the requirements of the registry, and provide written informed consent to comply with the registry data collection procedures.

8.4.2 Exclusion Criteria

Patients are not eligible for participation in the registry if they meet any of the following exclusion criteria:

1. Patients previously treated with investigational Iclusig.
2. Patients receiving any investigational agent (eg, any drug or biologic agent or medical device that has not received approval in the US) or receiving Iclusig for any indication not currently approved in the US.
3. Concurrent treatment with another TKI.

8.4.3 Withdrawal from the Registry

Patients may withdraw from the registry at any time either at their own request or in consultation with their HCP. Patients who withdraw from the registry may continue Iclusig per HCP discretion. Note: discontinuation of Iclusig treatment does not necessitate withdrawal from the registry.

If the patient withdraws consent for disclosure of future information, no further information will be collected beyond that point. The registry may retain and continue to use any data collected before withdrawal of consent in accordance with the patient consent.

8.5 Data Variables

8.5.1 Data Collection Schedule

Data collection is designed to minimize the burden on participating HCPs. Data collection forms are designed to gather data that have been documented as part of routine patient care in addition to medical history used to better categorize cardiovascular risk. There are no protocol-mandated procedures or diagnostic tests. The data collection schedule is provided in Table 1.

Table 1 Data Collection Schedule

	Enrollment[a]	Data Collection[b]									
Months	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**
Inclusion/Exclusion Criteria	X										
Informed Consent	X										
Demographics and Medical History / Concurrent Conditions	X										
Prior Medications	X[c]										
Concomitant Medications	X[d]	X	X	X	X	X	X	X	X	X	X
Adverse Events (including Vascular Occlusive Events)	X[e]	X	X	X	X	X	X	X	X	X	X
Iclusig Treatment	X[f,g]	X	X	X	X	X	X	X	X	X	X
Procedures and Surgeries	X[h]	X	X	X	X	X	X	X	X	X	X
Stem Cell Transplant	X[i]	X	X	X	X	X	X	X	X	X	X

a The enrollment period will be up to 18 months. Patients must enroll in the patient registry within 30 days after initiating treatment with Iclusig.

b At Month 0 (date of enrollment in the study), the Registry Coordinating Center will begin retrospective data collection from the HCP, including baseline demographic characteristics, medical history and prior/ongoing medications, and Iclusig dosing information. Data collection will continue at approximately 3–month intervals after initiation of Iclusig treatment, for a minimum of 12 months up to 30 months (total registry duration) or until the patient dies, withdraws from the study, or is lost to follow-up, whichever occurs first.

c Prior medications include all medications taken within approximately 30 days before starting Iclusig.

d Concomitant medications include all medications taken after starting Iclusig treatment. Concomitant medication data collection at the enrollment time point is only for patients who started taking Iclusig within the 30-day period prior to enrolling in the registry. During the data collection period, concomitant medication data collection will be done on all patients.

e VOE data collection at the enrollment time point is only for patients who started taking Iclusig within the 30-day period prior to enrolling in the registry. During the data collection period, VOE data will be collected on all patients.

f Iclusig may be discontinued at the request of the patient and his/her HCP at any time during the registry. In the case of treatment discontinuation at any time, discontinuation reason will be captured, and data collection will continue on discontinued patients for a minimum of 12 months up to 30 months (total registry duration) from the patient's date of enrollment.

g Details of Iclusig treatment at the enrollment time point is only for patients who started Iclusig prior to enrolling in the registry. During the data collection period, details of Iclusig treatment will be recorded on all patients.

h Collect recent surgeries/procedures done 3 months prior to Iclusig therapy and while on registry.

i Collect prior and on study stem cell transplant

8.5.2 Informed Consent

- Date of informed consent

8.5.3 Inclusion/Exclusion Criteria

- Documentation that the patient meets all inclusion criteria and does not meet any exclusion criteria

8.5.4 Demographics

- Patient contact information (including secondary contacts and HCP)
- Patient demographic information
  - Date of birth
  - Sex
  - Race and ethnicity

8.5.5 Medical History and Concurrent Conditions

- Smoking history: the approximate number of years and Yes/No with regard to whether the patient is still a smoker
- Ph + Leukemia history (CP-CML, AP-CML, BP-CML, or Ph+ALL) including diagnosis dates and mutation status
- Treatment history (all prior TKIs and non-TKI therapies, including hematopoietic stem cell transplantation)
- History of cardiac disease (non-vascular), cardiovascular, cerebrovascular, or peripheral vascular arterial disease (the approximate year of diagnosis only), such as, but not limited to the following:
  - Myocardial infarction
  - Angina
  - Coronary artery disease
  - Congestive heart failure
  - Atrial arrhythmia
  - Ventricular arrhythmia
  - Cerebrovascular accident or transient ischemic attack
  - Peripheral vascular disease
  - Retinal artery occlusion
  - Revascularization procedures
  - Renal artery stenosis
- History of VTEs (the approximate year of the event only), such as, but not limited to the following:
  - Pulmonary embolism
  - Deep vein thrombosis
  - Retinal vein thrombosis
- History of VOE risk factors (the approximate year of occurrence), such as, but not limited to the following:
  - Any prior radiation therapy to the chest
  - Thrombophilia (eg, Protein C or S deficiency; Factor V Leiden)
  - Prolonged immobilization
  - Recent surgery
- History of Type I or Type II Diabetes (the approximate year of diagnosis and Type only)

- History of hypertension, hypercholesterolemia, and/or hyperlipidemia (the year of diagnosis only)
- Relevant family history (Yes/No/Relationship to Patient), such as, but not limited to:
    - Arterial or venous thromboembolic disease
    - Risk factors for VOEs, as described previously

8.5.6 Prior and Concomitant Medications

Prior medications are defined as those taken within approximately 30 days before starting Iclusig therapy; concomitant medications are defined as those started or ongoing on the same date as initiating Iclusig therapy. All prescription and non-prescription medications and supplements will be recorded.

Data collection will include the name of the medication as recorded in the patient's records (trade or generic names), start and stop dates (if known), route of administration, and indication for the medication.

Concomitant medications of special interest in this patient registry include use of anticoagulant agents and/or antiplatelet agents and use of prophylactic and therapeutic substances for:

- Non-vascular cardiac disease
- Cardiovascular disease
- Hypertension
- Diabetes
- Hypercholesterolemia or hyperlipidemia

8.5.7 Adverse Events

All AEs, regardless of seriousness, causality, or expectedness, will be recorded on the AE eCRF from the time that patients provide informed consent until they have completed study participation.

8.5.7.1 Adverse Events of Special Interest

The AESIs for this program are VOEs (AOEs and VTEs). VOEs are further described in Section 10.1.7.

Longitudinal data on VOEs will be collected regardless of grade or severity. For any enrolled patient, VOEs are to be recorded continuously from the first dose of Iclusig and throughout the entire data collection period. See Section 10.1.7 for further information on VOEs. Data to be collected regarding VOEs include:

- Specific event diagnosis, including diagnostic procedures and results
- New risk factors associated with VOEs, including:
    - New chemotherapy added to the patient's regimen
    - Events that were not present at enrollment and occur while the patient is taking Iclusig
    - Any new diagnosis associated with those listed in Section 8.5.5
- Hospitalizations
    - Length of stay (approximate start and stop dates)
    - Reason for hospitalization

- Treatments for the VOE (prophylactic and therapeutic) and other interventions
- Outcome (resolved, resolved with sequelae, or ongoing)
- Serious adverse event (SAE: Yes/No)
- Severity: (mild, moderate, severe, life threatening, or death)
- Relationship (not related; related)

Note: VOE data collection at the enrollment time point is only for patients who started Iclusig prior to enrolling in the registry. During the data collection period (minimum of 12 months up to 30 months or until the patient dies, withdraws from the study, or is lost to follow-up, whichever occurs first), data on whether a VOE occurred will be collected for all patients.

8.5.8 Iclusig Treatment Details

Longitudinal data will be collected at approximately 3-month intervals.

- Starting date and dose
- Changes in treatment, including:
  - Dose reductions: Yes/No; date dose reduced; new dose
  - Dose interruptions: Yes/No; number of days interrupted
  - Discontinuation of Iclusig (if applicable): date
  - Reason(s) for any of the dose modifications or discontinuation, if applicable

8.5.9 Minimizing Patients Lost to Follow-Up

If a patient does not return to the provider 6 months after the last data collection time point, the HCP will be asked to contact the patient and determine the patient's reason for not returning. The treating HCP will also be asked to contact the patient's designated secondary contacts, if needed, including the patient's primary HCP and next of kin or out-of-household contacts. Patients who cannot be contacted after at least 4 attempts over a 4-week period will be considered lost to follow-up (LTF). However, if the patient later returns to the provider, he/she will continue in the registry.

If the patient's vital status remains unknown at the end of the study, vital statistics records and other sources of information (e.g., National Death Index [NDI]), may be used to determine vital status. If the patient's care is transferred to another HCP, the treating HCP (or designee) at the site where the patient was originally enrolled will be contacted by the Registry Coordinating Center to provide the new HCP information and the patient will be contacted to sign a new Release of Medical Information form so that data can be obtained from the new provider.

8.6 Registry Size

The patient registry will enroll approximately 300 patients who are initiating treatment with Iclusig with or without anticoagulant and/or antiplatelet agents. The population includes patients with a diagnosis of CP-CML, AP-CML, BP-CML, or Ph+ALL. The sample size is based on practical considerations. If VOE rates are comparable to those observed in clinical trials (ranging from 1% to 25%), CIs such as those listed in Table 2 would be observed. The CIs are exact binomial 95% CIs.

Table 2 Precision of Observed AESI Rates with a Sample Size of 300 (2-sided 95% Confidence Interval)

Observed Rate (%)	95% Confidence Interval
1%	0.2, 2.9
2%	0.7, 4.3
5%	2.8, 8.1
10%	6.8, 14.0
15%	11.2, 19.6
20%	15.6, 25.0
25%	20.2, 30.3

The median duration of exposure from the phase 2 study, AP24534-10-201, was 17 months. Assuming a comparable duration of exposure in this registry, and with a lost to follow-up(LTF) rate of 2% to 5% per year, there will be approximately 425 person years of exposure accrued in the registry.

8.7 Historical Estimates of Expected VOE Rates

Published estimates and results of previous data analyses conducted by ARIAD will be used to estimate the expected incidence rates of VOEs for benchmarking purposes. A systematic review of the literature, including published manuscripts, conference abstracts and posters, and other reports will be undertaken to identify reported estimates of VOE rates among patients with or without TKI therapy. Relevant estimates will be selected based on comparability to the current registry with respect to the registry population, definition of outcomes, period of follow-up, and completeness of reporting. No formal statistical tests of the difference in VOE rates are planned.

8.8 Data Handling and Record Keeping

8.8.1 Case Report Forms and Registry Records

Registry-specific electronic case report forms (eCRFs) will be used by the Registry Coordinating Center. Registry data will be collected via either phone call or written questionnaire with the HCP, and entered into the eCRFs by the Registry Coordinating Center or participating site staff.

8.9 Data Analysis

Complete analytical specifications, including tables and listings, will be included in the SAP, which will be prepared separately. Analyses will include tabulations of the number of candidate patients identified through the specialty pharmacy database. The Registry Coordinating Center will provide data on the number of patients who provide written informed consent, the number of ineligible patients excluded from the registry (with the reasons for exclusion), and the number of eligible patients per the inclusion/exclusion criteria. Baseline demographic and medical history data will be presented using descriptive statistics, with number and percent for categorical endpoints, n, mean, SD, SE of the mean, median, minimum (min), and maximum (max) for continuous endpoints. The primary analyses will also present 95% CIs. No data will be collected, analyzed, or reported for patients who do not consent to participate in this registry.

Exploratory analyses will also be performed to better understand any differences in patients who experience any of the AESIs (VOEs) versus those who do not. The exploratory analyses will be

performed using logistic regression, including factors such as patient demographic characteristics, risk factors, dose and duration of Iclusig treatment, and concomitant medications, including but not limited to prophylactic and/or therapeutic use of anticoagulant and/or antiplatelet agents.

8.10 Quality Control

8.10.1 Training and Initiation of Registry Coordinating Center

The CRO trains the Registry Coordinating Center on the registry requirements and use of the electronic data capture (EDC) system. Ongoing Registry Coordinating Center management will occur throughout the entire duration of the registry. Additional outreach and training will occur if needed to address quality control concerns prior to analysis.

8.10.2 Data Quality Assurance

8.10.2.1 HCP Monitoring

Central monitoring will be performed by the CRO. All inbound calls from providers will be triaged immediately and all calls (inbound and outbound) will be tracked, including inquiry type, HCP/provider ID registry number, query resolution, and feedback by the Registry Coordinating Center.

8.11 Limitations of the Research Methods

8.11.1 Comparison Population

This protocol has been designed as a patient registry study without a comparator; the patients who are eligible for participation will be representative of the target population for whom Iclusig is indicated, which is generally patients for whom no other TKI is indicated or patients who carry the T315I mutation (USPI). As described in Section 8.9, ARIAD will not collect, analyze, or report any data for patients who do not provide written informed consent.

8.11.2 Hawthorne Effect

The Hawthorne Effect is the tendency of people to act atypically when they know they are being observed. Efforts to minimise the Hawthorne Effect (Roethlisberger et al, 1939) are warranted given that the main outcomes of interest are to evaluate the safety of Iclusig in routine care. Properly implemented, a naturalistic design (such as this prospective, non-interventional, observational study) can decrease the impact of the Hawthorne Effect. It will be emphasized to HCPs that the study protocol should not interfere with routine care and treatment of patients, and that a critical review of HCP practice is not an objective of the project.

8.11.3 Selection Bias

Patient-selection bias is a consideration, as motivation to consent to join the registry study can vary between patients for different reasons. However, as Iclusig is dispensed from a central specialty pharmacy, , this patient-centered registry allows access to the registry for all patients who will receive Iclusig treatment for the first time in the US, minimizing the selection bias.

With a patient-centered registry study, the selection bias is significantly reduced compared to a site-based study with a limited number of participating HCPs.

8.12 Other Aspects

8.12.1 Regulatory Authorities

The protocol and any amendments will be submitted to the FDA in accordance with the post-marketing requirement.

8.12.2 Protocol Modifications

Amendments to the protocol may only be made by ARIAD and/or the CRO, with ARIAD review and approval. All protocol amendments must be signed and dated by the CRO, who will serve as the principal investigator. Prior to implementation, the registry protocol will be submitted to and approved by a central Institutional Review Board (IRB).

8.12.3 Records Retention

The CRO and Registry Coordinating Center must maintain all essential documents until notified by ARIAD and in accordance with all local laws and regulations.

ARIAD, the CRO and Registry Coordinating Center will follow their applicable Standard Operating Procedures (SOPs) regarding retention of records.

8.12.4 Compensation to Healthcare Providers

HCPs or their designee will be compensated for time spent in completing patient registry requirements. This compensation schedule will be determined in accordance with fair market value for the work performed.

9 PROTECTION OF HUMAN SUBJECTS

9.1 Informed Consent

Prior to any data collection under this protocol, written informed consent must be provided by the patient. Information about the registry will be explained to the patient by the Registry Coordinating Center. The consent includes a request for the patient's Social Security number in order to match against the National Death Index (NDI), if necessary, designated as optional information, and information on the patient's secondary contacts in order to minimize loss to follow-up. A written Medical Release of Information will be obtained by the Registry Coordinating Center, and signed and dated by the patient, and given to the patient and HCP. The informed consent text must not be altered without the prior agreement of the relevant IRB and ARIAD Pharmaceuticals, Inc. (a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited).

9.2 Patient Confidentiality

In order to ensure patient confidentiality, patients will be assigned a unique identifying number by the EDC system. The key matching identification numbers with patient names will be maintained by the Registry Coordinating Center, and only the unique identifier will be entered on the EDC forms with the patient initials. Upon enrollment, patients may be asked to provide their name, telephone number and e-mail contact information, and similar information on secondary contacts as well as the patient's Social Security number (optional). This information will be stored separately from the registry clinical database. This information will only be used to obtain patient vital status and disposition if the patient becomes lost to follow-up.

In any presentations or in publications of the results of the registry, the patients' and their secondary contacts' identities will remain anonymous and confidential. ARIAD Pharmaceuticals, Inc. (a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited), its designee(s), and the FDA or other foreign health agencies may inspect the records of the registry. Every effort will be made to keep the patients' personal medical data confidential.

9.3 Institutional Review Board Review

Prior to the collection of any registry related data, IRB approval of the protocol, informed consent, and all patient enrollment materials will be obtained, as applicable.

The registry will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki, applicable privacy laws, and local regulations for each participating site. This non-interventional registry will be conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology.

10 MANAGEMENT AND REPORTING OF ADVERSE EVENTS

All AEs, regardless of seriousness, causality, or expectedness, Special Situation Reports (SSRs) and Product Quality Issues (PQIs) will be recorded on the AE eCRF from the time that patients provide informed consent until they have completed study participation.

10.1 Definitions

10.1.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, a new disease or worsening in severity or frequency of a concomitant disease, temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE
- A laboratory test result that requires the subject/patient to receive specific corrective therapy
- A laboratory abnormality that leads to discontinuation of therapy
- A laboratory abnormality that the health care provider considers to be clinically significant

10.1.2 Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death. Note that death is an outcome of an event. The event(s) causing death should be recorded.
- In the view of the Health care provider, places the subject/patient at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- An SAE may also be any other medically important event that, in the opinion of the Health care provider, may jeopardize the subject/patient or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an

emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

10.1.3 Adverse Drug Reactions

An adverse drug reaction (ADR) is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

10.1.4 Product Quality Issues

A Product Quality Issue (PQI) refers to defects related to the safety, identity, strength, quality, or purity of the product or with the physical characteristics, packaging, labeling, or design of the product.

10.1.5 Special Situation Reports

A Special Situation Report (SSR) includes any of the following events:

- Pregnancy: Any case in which a pregnancy patient is exposed to an ARIAD Product or in which a female patient or female partner of a male patient becomes pregnant following treatment with an ARIAD Product. Exposure is considered either through maternal exposure or via semen following paternal exposure.
- Breastfeeding: Infant exposure from breast milk
- Overdose: All information of any accidental or intentional overdose
- Drug abuse, misuse or medication error: All information on medicinal product abuse, misuse or medication error (potential or actual)
- Suspected transmission of an infectious agent: All information on a suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product.
- Lack of efficacy of ARIAD Product
- Occupational exposure
- Use outside the terms of the marketing authorization, also known as “off-label”
- Use of falsified medicinal product

A SSR should be reported even if there is no associated AE.

10.1.6 Hospitalizations

Adverse events that require hospitalization or prolongation of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a health care facility meets these criteria. Adverse events that require emergency room care that do not result in hospital admission are not SAEs unless assessed by the treating HCP to be an important medical event. Hospitalization does not include the following:

- Hospice facilities

- Respite care
- Skilled nursing facilities
- Nursing homes
- Routine emergency room admissions, and
- Same day surgeries (as outpatient/same day/ambulatory procedure)

Hospitalization or prolongation of hospitalization in the absence of a precipitating AE is not in itself an SAE. Examples include:

- Social admission (e.g., patient has no place to sleep)
- Optional admission not associated with a precipitating AE (e.g., for elective cosmetic surgery that was planned prior to registry enrollment [appropriate documentation is required for these cases])
- Hospitalization or prolongation of hospitalization for scheduled therapy of the target malignancy of the registry is not considered an SAE

10.1.7 Adverse Events of Special Interest (AESI) Definition

VOEs have been identified as AESIs for Iclusig. These include arterial and venous thrombotic and occlusive AEs that meet the criteria for SAEs, defined above in Section 10.1.2, and those AEs that do not meet the SAE criteria.

AESIs require ongoing monitoring by treating HCPs and rapid identification and communication by the treating HCP to ARIAD. All AESIs, whether SAEs or not, must be reported immediately (within 24 hours of becoming aware of the event) to ARIAD or its designated representative. ARIAD has determined that the events listed below (whether considered serious or nonserious by the treating HCP) should be considered AESIs and therefore should be reported within 24 hours.

A. Myocardial infarction: The Third Universal Definition of Myocardial Infarction (Thygesen et al, 2012) is used to define MI
B. Angina (newly diagnosed or worsening of existing angina or unstable angina)
C. Coronary artery disease (CAD) (newly diagnosed or worsening of existing CAD) or symptoms that may reflect cardiovascular disease (Thygesen et al, 2012)
D. Cerebrovascular ischemic disease including ischemic or hemorrhagic stroke, vascular stenosis, transient ischemic accident (TIA), cerebrovascular occlusive disease documented on diagnostic neuroimaging, or symptoms that may reflect cerebrovascular disease (Easton et al, 2009)
E. New onset or worsening of peripheral artery occlusive disease (eg, renal artery, mesenteric artery, femoral artery) or symptoms that may reflect peripheral vascular disease
F. Retinal vascular thrombosis, both venous and arterial
G. Venous thromboembolism where significant compromise of organ function or other significant consequences could result (eg, pulmonary embolism, portal vein thrombosis, renal vein thrombosis) or symptoms that may reflect venous thrombosis

10.1.8 AESIs That May be Non-Serious

Signs/symptoms of vascular occlusive disease that are not fatal or life-threatening, do not require hospitalization or prolong hospitalization, and do not meet the definition above of SAEs, and ***that require medical evaluation***, are also considered VOEs and must be reported to ARIAD, or its designated representative as an AESI.

10.2 Reporting Adverse Events, Special Situation Reports and Product Quality Issues

All AEs, regardless of seriousness, causality, or expectedness, will be recorded from the time that patients provide informed consent until they have completed study participation. The occurrence of any reportable events in patients after registry completion will be collected and reported through routine Pharmacovigilance reporting.

The Registry Coordinating Center will notify ARIAD Pharmacovigilance and Risk Management, or its designated representative, **immediately (within 24 hours)** after becoming aware of an SAE or AESI (VOE) (serious and non-serious). This is typically achieved by the Registry Coordinating Center completing the adverse event report pages of the electronic CRF or by submitting an AE Report Form to ARIAD Pharmacovigilance and Risk Management. This timeframe also applies to additional new information (follow-up) on previously reported SAEs, AESIs. ARIAD Pharmacovigilance and Risk Management will obtain follow-up information regarding any SAE or AESIs and will report them to the health authorities as appropriate.

The Investigator may be contacted to obtain additional information on the event or for data clarification. The investigator shall make her or his best effort to provide the requested additional information, **within 1 working day of obtaining the additional information for SAEs and AESIs (VOEs).**

10.3 Severity

The principal investigator at the site or CRO will determine the severity of an AE based on the following definitions:

- Mild: The AE/VOE is noticeable to the patient, but does not interfere with routine activity.
- Moderate: The AE/VOE interferes with routine activity, but responds to symptomatic therapy or rest.
- Severe: The AE/VOE significantly limits the patient's ability to perform routine activities despite symptomatic therapy.
- Life Threatening: The patient is at immediate risk of death.
- Death: The patient dies as a directed result of the complication induced by the AE/VOE.

10.4 Relationship

The relationship of Iclusig to an AE will be determined by the treating HCP. Treating HCPs should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an AE is considered to be related to Iclusig, indicating "yes" or "no" accordingly. ARIAD Pharmacovigilance and Risk Management will obtain follow-up information regarding any SAEs or AESIs and will also perform a sponsor causality assessment which may differ from that of the treating HCP.

Not Related: The AE is not related to Iclusig if there is evidence that clearly indicates an alternative explanation, such as, if the timing of the exposure to Iclusig and the onset of the AE are not reasonably related in time, or if other facts, evidence, or arguments exist that strongly suggest an alternative explanation, then the AE is not related.

Related: The administration of Iclusig and the AE are considered reasonably related in time and the AE could be explained either by exposure to Iclusig or by other causes, or no alternative explanation has been identified. The following factors should be taken into consideration:

- Temporal relationship of event onset to the initiation of Iclusig.
- Course of the event, considering especially the effects of dose reduction.
- Discontinuation of Iclusig, or reintroduction of Iclusig (where applicable).
- Known association of the event with Iclusig or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

11 PHARMACOVIGILANCE CONTACT DETAILS

The Registry Coordinating Center will complete the adverse event report pages of the electronic CRF. If the EDC is unavailable, an AE Report Form should be submitted as outlined below:

Adverse Events, SSRs, ADRs, SAEs

PPD

Product Complaints

PPD

12 PLANS FOR DISSEMINATING AND COMMUNICATING REGISTRY RESULTS

12.1 Reporting to Regulatory Agencies

All reports will be submitted to relevant heath agencies based on agreed upon timeframes.

12.2 Use of Information and Publications

All data generated from this registry are the property of ARIAD. ARIAD shall have the right to publish such data and information without approval from the HCPs. ARIAD will establish a uniform procedure for analyzing, publishing, and disseminating findings from this registry. Co-authors of publications may include participating HCPs, ARIAD, and/or other relevant thought leaders who contribute substantially to the registry design and publication. Publications will adhere to the International Committee of Medical Journal Editors (ICMJE) guidelines (December, 2015) and Good Publications Practices 3 (GPP3) (Battisti et al 2015).

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