NON-INTERVENTIONAL SAFETY STUDY
STUDY REPORT

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)
Version identifier of the study report	Version 1.0
Date of study report	03 March 2021
Active substance	[redacted]
Medicinal Product	ICLUSIG®
Sponsor	Takeda Pharmaceutical Company Ltd.
Research Question and Objectives	To assess the incidence, risk factors for, and outcomes of Vascular Occlusive Events (VOEs) for patients with chronic phase chronic myeloid leukemia (CP-CML), accelerated phase chronic myeloid leukemia (AP-CML), or blast phase chronic myeloid leukemia (BP-CML), or T315I-positive Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) treated with ICLUSIG with or without anticoagulant and/or antiplatelet agents in routine clinical practice in the US
Country of Study	United States of America
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3.0 SYNOPSIS

Title of 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)

Investigators/Study Centers: [redacted] (Hudson Valley Cancer Center), [redacted] (McFarland Clinic, P.C.), [redacted] (Swedish Cancer Institute – Seattle), [redacted] (Hackensack University Medical Center).

Publication (Reference): Not Applicable.

Study Period: This was a phase 4 study that had an anticipated duration of 2.5 years, including a planned enrollment period of approximately 1.5 years and a data collection period between 1 to 2.5 years. 3 patients were enrolled in total. The first patient signed the informed consent form (ICF) on 10 April 2018. The last patient enrolled by the Registry Coordinating Center signed the ICF on 19 February 2019.

Objectives: The primary objectives of this patient registry were to assess the incidences of Vascular Occlusive Events (VOEs), risk factors for development of VOEs, and the outcomes of VOEs in chronic phase (CP) chronic myeloid leukemia (CML), accelerated phase (AP) CML, blast phase (BP) CML, or T315I-positive Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) patients treated with ICLUSIG with or without anticoagulant and/or antiplatelet agents in routine clinical practice in the US (United States).

Methodology: The methodology of the study was divided into 3 parts:

- Pre-screening: Potential patients were recruited by a specialty pharmacy nurse who sent the patients study brochures and transferred the patient to the registry if the patient was interested in participating in OMNI. These potential patients were screened for eligibility by the OMNI Registry Coordinating Center's principal investigator (PI) or designee. It is noted that the registry and the PI or designee were managed and employed by the Clinical Research Organization (CRO) of the study. The CRO was United Biosource, LLC (UBC).
- Start of enrollment (Month 0): Per study protocol, it was planned that relevant medical and ICLUSIG dosing information would be taken from patients enrolled in the study, on or within 30 days before their day of enrollment.
- Post month 0: Relevant medical data were planned to be recorded by the CRO from participating Health Care Provider's (HCP) offices at three-month intervals.

Data from the study was planned to be stored within the Registry Coordinating Center's electronic case report forms (eCRFs). The sample CRF is included in Appendix 4.2.

Since study initiation, primarily due to various challenges in recruitment (articulated in the discussion), the study protocol underwent 4 amendments to bolster recruitment. A summary of protocol amendments is provided in Table 3.a. The original protocol and the protocol amendments are included in Appendix 4.1.

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Table 3.a Summarized Outline of OMNI Protocol Amendments

Protocol Amendment#/ Version #	Amendment Description
Protocol v1.0 (07 November 2014)	Original protocol.
Protocol Amendment 1.0/ Version 2.0/ (16 July 2015)	• Descriptions of methods that identified eligible patients and procedures for documenting reasons for non-participation. • Alignment of the protocol with the Statistical Analysis Plan (SAP), including the addition of a commitment to report tabulations of the numbers of candidate patients identified and evaluated for eligibility, the numbers of ineligible patients excluded with reasons for exclusion, and the numbers of eligible patients who agree to participate in this study. • Add commitment to report results of an analysis that compares baseline characteristics of eligible patients included and excluded from the study
Protocol Amendment 2.0/Version 3.0, (25 July 2016)	• Updated the inclusion criteria to include AP-CML, BP-CML, and Ph+ ALL patients to all protocol areas where only CP-CML patients were previously referenced. • Changed duration of study from 54 months to 30 months. • Updated the protocol from only requiring a site to identify prospective study subjects to allowing the specialty pharmacy to identify study subjects as well. Therefore, the study transitioned from a site-based observational study to a patient-centered prospective registry study operationalized by a CRO. • Changed the principal investigator to a single principal investigator as the responsible party at UBC. • Data collection changed to a call-center-based registry method where UBC will call a subject's HCP at 3-month intervals for registry data.
Protocol Amendment 3.0/ Version 4.0 (29 January 2018)	• Eliminated verbal consenting practices from the patient ICF process flow and replaced it with written consent, where applicable • Updated milestone dates for enrollment, data collection, and the final report.
Protocol Amendment 4.0/Version 5.0 (16 November 2018)	• Specialty pharmacy nurses allowed to transfer calls for interested patients directly to the registry coordinating center. • Added exposure-adjusted incidence rate and time to event analyses. • Added that a designee, in addition to the PI of the registry, could have confirmed the eligibility of a patient for enrollment.

Number of Subjects: The study targeted a total of 300 CP-CML, AP-CML, BP-CML, or Ph+ ALL enrolled patients in the registry. However, only 3 patients were enrolled and no ICLUSIG exposure data were accrued in the registry. Although the 3 patients were approved for study enrollment, the patients' individual HCP offices did not respond to requests for patient information. Thus, no patient data were collected.

Diagnosis and main criteria for inclusion: Adult patients 18 years or older diagnosed with CP-CML, AP-CML, BP-CML, or Ph+ ALL. These patients could not have taken a tyrosine

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kinase inhibitor (TKI) or investigational agent concurrently, nor should they have received ICLUSIG for any indication not approved in the US.

Test product, dose and mode of administration, batch number: Not Applicable. This was a non-interventional study that had no restrictions on the dose, mode of administration, and batch number of ICLUSIG.

Duration of Treatment: Not applicable since no patient data was ever collected. The duration of the study was to be between 1 and 2.5 years.

Discussion: Study AP24534-14-401 (OMNI) was a prospective, observational, voluntary patient registry aimed to further characterize the safety profile of ponatinib as used in routine clinical practice. The primary objectives of this patient registry were to assess the following for patients who had CP-CML, AP-CML, BP-CML, and Ph+ ALL treated with ICLUSIG with or without use of anticoagulants 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.

This patient registry study included patients who were over 18 years of age; and for whom the decision to initiate standard treatment with commercially available ICLUSIG had already been made. The patient registry was non-interventional, and all treatment decisions, including prophylactic or therapeutic use of anticoagulant and/or antiplatelet agents, were made at the discretion of the patient and the patients' HCP and were not mandated by the registry.

The protocol anticipated at least 300 patients to be enrolled and followed for the duration of the study or until patient withdrawal or death.

OMNI was originally designed as a site-based observational study. In December 2014, the CRO initiated site identification activities. Over 9 months, 373 sites were invited to participate in OMNI, and 6 sites agreed to participate. Only 4 sites were activated, and no patients were enrolled in 11 months.

Barriers to participation in OMNI, based on discussions with physicians, study nurses and expert investigators, included lack of interest from investigators and institutions in non-interventional observational studies, lack of institutional resources to support study/staffing requirements, and lack of operational feasibility at many study centers due to a limited number of patients to accrue to the study.

Consequently, the Sponsor developed a number of protocol amendments (Table 3.a), one of which Amendment 2.0 (Version 3.0) dated 12 October 2016, substantially modified the study from a site-based study to a registry-based observational study. It was operationalized by a CRO and with the principal investigator being a responsible party at the CRO.

Substantial effort had also been made in patient outreach, as the specialty pharmacy mailed study brochures with first drug shipment to 208 patients, and nurses offered to tell 320 patients about

OMNI. 123 patients agreed to hear about the study, but none of those patients called the coordinating center.

Sponsor Medical Science Liaisons (MSLs) had also been tasked to reach out to HCPs who had recently prescribed ICLUSIG to new patients, to tell them about OMNI and ask that they inform their patients of the registry. Between March 2018 and January 2019, MSLs had 258 interactions (via email, phone, teleconference, or face-to-face) with 220 HCPs. Of these interactions, 177 HCPs either did not respond or follow up, 30 were not interested, 2 indicated their patients were not eligible, and 10 could not be reached since their updated contact information was not available.

Despite the significant efforts made by the Sponsor including protocol amendments and several major patient or HCP outreach events to enhance enrollment, as of 30 September 2020, only 3 patients had been consented and enrolled. Given the lack of success in recruitment, the Sponsor decided to close the study.

Criteria for Evaluation:

Efficacy: Not applicable.

Safety: The study was designed to collect health information including adverse events (including VOEs), drug modifications, or health changes (concurrent medications, conditions, procedures, and surgeries) of patients post-ICLUSIG treatment. No data were collected.

Statistical Methods:

Statistical Analysis Plan: The SAP became effective on 01 August 2016. However, because no data from patients were collected, no statistical analyses were conducted.

Safety Analysis: The planned safety population included patients who would have received at least 1 dose of ICLUSIG and would have followed the safety assessments guidance described in the protocol amendment 4 (Appendix 4.1).

Conclusion: The Sponsor decided to close the OMNI study early due to accrual challenges and lack of data; therefore, no assessments for the study research objectives could be conducted.

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