Title: AGRYLIN Capsules 0.5mg Drug Use Results Survey

NCT Number: NCT03625895

Protocol Approve Date: 27-MAR-2019

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

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- Patient identifiers within the text, tables, or figures or in by-patient data listings.
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Note; This document was translated into English as the language on original version was Japanese.

SHP422-406

Protocol of drug use-result survey

Shire Japan KK

Ammendment3, 27 Mar 2019

Ammendment2, 01 Apr 2018

Amendment 1, 25 May 2017

(Replaces Original, 30 Oct 2014)

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1 Purpose of the Survey

The objectives of this survey are to collect data to evaluate the safety and efficacy of Agrylin (anagrelide hydrochloride) in the post-marketing phase in patients diagnosed with Essential Thrombocythemia (ET).

Data will be collected to address the following specifications:

- Safety data from real life experience.
- Efficacy in real life experience

2 Safety issue

Use of Agrylin in patients with cardiac disorders, QT/QTc prolongation, blood toxicity, thrombohaemorrhagic events, interstitial lung disease, headache and use in patients with hepatic function disorders.

3 Estimated Number of Patients and Rationale

3.1 Target number of cases and rationale

Target number of cases: 474 cases

It is estimated that there will be 474 patients prescribed this drug at the end of the second year of marketing which is adequate to potentially observe with 95% confidence interval common events that occur classified as important investigation items in this all-case survey except less common events such as ILD or some cardiac disorders (e.g. Torsade de pointes).

4 Target patient population

- All cases who received treatment with Agrylin.

5 Dosage and Administration

Appropriately administer the drug in accordance with description of package insert.

6 Planned number of centers (departments) which will take part in the survey

All treatment centers who prescribe Agrylin will be approached to participate on the survey.

Hematology centers: 450 sites
Hematology Oncology centers: 286 of 450 sites
Internal Medicine centers: 633 sites
Total 1083 treatment centers

7 Surveying method

Study methods employ a central enrollment system. The following steps will be completed:

7.1. Request for investigation to Medical institutions

(1) Medical representatives will explain the purpose of the survey, targeted patients, investigation method, issues to be investigated, and the survey period etc. to the investigators at the medical institutions where Agrylin will be used, and make a request to the principal at the respective institutions (e.g. head of the hospital) to conduct the investigation. A written contract must be executed.

As a rule, Agrylin will be delivered to the medical institutions after the execution of the contract. If there is an urgent need for Agrylin to be administrated to the patient, and if Agrylin is delivered before the execution of the contract, the medical institution must comply with our request for a contract even after administration.

(2) This survey shall comply with "Good post-marketing study practice (GPSP)" ordinance at all times during the implementation of the investigation after the contract entered into with each medical institution.

7.2. Collection for the registration form and Case Report Forms (CRFs)

(1) Registration form

The investigation method is an all-case surveillance system. The investigators must populate the Registration Form with all required items (name of institution, name of department, name of investigator, patient identified number, start (expected) date of Agrylin) for all the patients who have been or will be prescribed Agrylin and, as a rule, the form must be sent to the registration center by FAX within 7 days from the start date of Agrylin.

If there are patients who have already been prescribed Agrylin at the time the contract is executed, the investigator must register all cases and investigations retrospectively.

Registration center

FAX PPD
(Within the office of IQVIA Services Japan K.K.)

Address 4-10-18 Takanawa, Minato-ku, Tokyo 108-0074 Japan
TEL : PPD

(2) CRFs

At dates 6 months and 12 months (the end of the survey or discontinuation of the survey) after the initiating treatment with Agrylin, the investigator completes the CRFs for all registered cases and promptly provides these to the Medical representatives. If a case is discontinued the survey cause of death etc, the investigator must record information until this point and promptly provide CRF to the Medical representatives.

(3) Confirmation that all cases are registered

After the registration period, the investigator must confirm that he/she completed registration forms for all cases who were administered Agrylin and complete the "All Cases Registered Confirmation Form" and provide it to the Medical representatives. This form is required once a year for confirmation of the registered patient in previous year.

7.3. Report Adverse Events

If adverse events (Adverse drug reactions/infections, subjective/objective symptoms, aggregated complications) occur after initiation of treatment with Agrylin, the investigator must contact the Medical representatives and record the details of the adverse event in the AE section of the CRF. The investigator must attempt to follow the case until the event is resolved and must confirm the outcome of the event.

7.4. Schedule

	Registration Form	Book 1			Book 2	
		Registration	Additional Visit	6 Month visit	Additional Visit	12 Month visit
Patient identified number	●	●				
Patient initials	●					
Date of birth (Age)	●	●				
Sex	●	●				
Race		●				
Diagnosis of ET		●				
JAK2 status		●				
Testing for pathogenetic mutations		●				
Bone marrow biopsies		●				
Testing to rule out other hematological malignancies		●				
Prior treatments for ET		●				
Medical history/Complication		●				
Echocardiogram (If Applicable)		●	●	●	●	●
Electrocardiogram (If Applicable)		●	●	●	●	●
Vital signs (Blood Pressure, Pulse)		●	●	●	●	●
Height		●				
Weight		●	●	●	●	●
Pregnancy status (Urinalysis)		●	●	●	●	●
Administration status		●	●	●	●	●
Concomitant therapy		●	●	●	●	●
Safety (Adverse Event)		●	●	●	●	●
Efficacy (Platelet count)		●	●	●	●	●
Date of Discontinuation/ Reason for Discontinuation			●	●	●	●

Important Items for investigation (Cardiac disorders, QT/QTc prolongation, Thrombohaemorrhage events, Interstitial lung disease)		●	●	●	●	●

8 Estimated duration of the survey

Planned implementation period of this survey is as follows

1. Implementation period: from the approval to the approval condition regarding to all case survey is removed.
2. Patient registration: from the approval to the approval condition regarding to all case survey is removed. However, for all patients who were prescribed Agrylin prior to 31 May, 2015 , all CRFs must be completed and included in the analysis. Patients who were prescribed Agrylin after 31 May, 2015, should be included in the analysis if CRF has already been completed. After 31 May, 2015, it is planned that only patient registration will continue until the approval condition is removed. All CRFs will be collected and fixed by 31, Dec, 2017.
3. Observation period: efficacy and safety will be observed for 1 year.

9 What is investigated in the survey

Safety and efficacy data that are available as part of routine clinical practices related to the treatment with anagrelide.

9.1 Items for investigation

a. Information for patient identification (at survey entry)

- Patient identified number
- Patient initials

b. Patient background

- Date of birth
- Sex
- Race
- Diagnosis of ET
- *JAK-2* status
- Testing for pathogenetic mutations
- Bone marrow biopsies
- Testing to rule out other hematological malignancies
- Prior treatments for ET (including refractory or intolerant response)
- Medical history/Complication (including hepatic impairment, renal impairment, cardiac disorders, QT/QTc prolongation, thrombohaemorrhagic events and interstitial lung disease)

- Echocardiogram (If Applicable)
- Electrocardiogram (If Applicable)
- Vital signs (Blood Pressure, Pulse)
- Height
- Weight
- Pregnancy status (Urinalysis)

c. Each visit

- Echocardiogram (If Applicable)
- Electrocardiogram (If Applicable)
- Vital signs (Blood Pressure, Pulse)
- Weight
- Pregnancy status (Urinalysis)

d. Administration status

- Record the details of the initial dose and every time the dose amount is adjusted: Start and stop date of each new dosage administration, indication/purpose of use
- Reason for change (adverse event or platelet optimization)

e. Concomitant therapy

- Presence or absence of concomitant therapy
- Names of concomitant drugs including anti-platelet therapies, anti-coagulant or Thrombolytic agents
- Indication/purpose of use, start and stop date

f. Safety

- Presence or absence of Adverse event
- Name of Adverse event
- Start date and stop date
- Severity
- Relationship to Agrylin
- Outcome
- Action Taken regarding Agrylin
- Seriousness
- Treatment received for the AE

Collected safety assessments include all adverse events (AEs) occurring following initiation of treatment with anagrelide regardless of the seriousness or relationship to anagrelide. Vital signs and abnormal laboratory assessments associated with AE will be collected. Laboratory assessments include any parameters the physician deems to be associated with and pertinent to the adverse event in question including hematology, biochemistry, urinalysis, and other relevant tests e.g. cardiac testing including ECG and echocardiograms. Relationship of AE to Agrylin, underlying disease, concomitant drug, concomitant medical condition or other will be collected.

An adverse reaction or adverse event is a serious adverse reaction or serious adverse event, respectively, if the reaction or event results in any of the following seriousness criteria:

- results in death
- life-threatening (NOTE: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or results in prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- a congenital anomaly/birth defect
- a medically important event or reaction

g. Efficacy

- Platelet count

h. Survey Discontinuation

- Date of discontinuation, reason for discontinuation if the subject has discontinued

9.2 Important items for investigation

Cardiac disorders, QT/QTc prolongation, thrombohaemorrhagic events and interstitial lung disease

10 Items for analysis and the analysis method

10.1. Items for analyses

a. Items on patient constitution

- Number of cases enrolled
- Number of cases collected CRF
- Number of cases evaluable for safety
- Number of cases evaluable for efficacy
- Number of cases excluded from the survey with reason

b. Safety issues

- Adverse reactions (including unknown events), as well as adverse events by severity, incidence, etc.
- Adverse reactions as well as adverse events according to the background factor
- Serious adverse reactions as well as adverse events by type of event (by system order class)

c. Efficacy issues

- Absolute value and change from registration visit platelet count

- Clinical efficacy (as defined by absolute value and change from registration visit platelet count) in patients with special backgrounds; pediatric, elderly, hepatically impaired, renally impaired, pregnant, treatment-naïve

d. Important items for investigation

- Cardiac disorders, QT/QTc prolongation, thrombohaemorrhagic events and interstitial lung disease

10.2. Analysis method

Safety will be assessed through the recording of adverse events and any abnormal clinical laboratory tests including ECGs. Summaries of patient background including prior treatment for ET, prior history of hepatic impairment, anti-aggregatory, anti-coagulant or Thrombolytic agents prior and concomitant therapies as well as patient drug usage, especially at higher doses as well as treatment emergent adverse events (TEAEs), serious adverse events, TEAEs considered related to anagrelide, TEAEs leading to withdrawal (dose discontinuation), and TEAEs by severity and relationship to anagrelide will be presented. All patients who receive any dose of anagrelide, and provide any post-registration data, will be included in the Safety Population.

The primary efficacy variable is platelet count, for which the absolute value and the change from the registration visit will be summarized, by visit, using descriptive statistics (number of observations, mean, standard deviation, median, minimum, and maximum values). In addition, the two-sided 95% confidence intervals (CIs) for the parameters of interest will be estimated as appropriate. No formal statistical tests will be performed.

The safety data will be presented periodically for regulatory submissions per the regulation of the Safety Periodic Reporting System. In addition, summaries of the accumulating data including efficacy data may be assessed during the conduct of the study for exploratory and administrative purposes, if deemed necessary. The statistical analysis methods will be prospectively specified in detail in the statistical analysis plan.

11 Organization for implementing the survey

The same as shown in the Risk Management Plan section 6.3.

12 Name and address of trustee

Contractor for the operations 1 (From April, 2019)
Takeda Pharmaceutical Company Limited
4-1-1 Dosho-machi Chuo-ku, Osaka

Request the site to conduct the survey, Contract with the site, Status management of the survey, AE information collection, CRF and/or DCF collection

Contractor for the operations 2

IQVIA Services Japan K.K.
4-10-18 Takanawa, Minato-ku, Tokyo 108-0074 Japan
Anticipated scope of services: Operation of specified use-result survey (Request to hospitals/clinics, making contracts with hospitals/clinics, enrollment of patients, collection of CRFs and review/follow-up, progress management, information collection of adverse reactions/infections, data compilation/analyses).

13 Additional measures which may be taken depending on the outcome of the survey and the decision criteria for initiating the measures

Depending on the outcomes of DURS, if new safety issues or risks are identified the additional pharmacovigilance and risk minimization measures will be taken.

14 Milestones for the implementation of the survey and the assessment of the results, or reporting to the PMDA, and the justification

- At the time of Periodic safety report
- Interim analysis: Since entire observation period (12 months) of the statistical subjects (patients who were prescribed Agrylin prior to 31, May, 2015) has already completed, only final analysis will be conducted. Initially planned interim analysis will not be conducted.
- Final Report: The final report will be submitted in Apr, 2018, which is 4 months after data collection and fixing (database lock) at the end of December, 2017.

Additional drug results utilization survey may be considered after the time of final results are final.

15 Other necessary items

Reference documents

- Contract
- Guideline for implementation of the use-result survey
- Registration form for the use-result survey
- Questionnaire for the use-result survey
- All Cases Registered Confirmation Form

Appendix 1 Version History

Document	Date	Global/Country/Site Specific	Reason for Amendment
Original Protocol	30 Oct 2014	Country	NA
Version 2 (Amendment 1)	25 May 2017	Country	Change milestones and schedule for report completion
Version 2.1 (Amendment 2)	1 Apr 2018	Country	Change name of CRO
Version 3.0 (Amendment 3)	27 Mar 2019	Country	Additional outsource