Title: AGRYLIN Capsules 0.5mg Drug Use Results Survey

NCT Number: NCT03625895

Statistical analysis plan Approve Date: 26-SEP-2019

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Note; This document was translated into English as the language on original version was Japanese.

STATISTICAL ANALYSIS PLAN

Protocol No.:	SHP422-406
Protocol Title:	AGRYLIN Capsules 0.5mg Drug Use Results Survey
Drug:	AGRYLIN Capsules 0.5mg
Sponsor:	Shire Japan KK Tekko Building 21 F 1-8-1 Marunouchi, Chiyoda-ku Tokyo 1000005 Japan
Version No. and Date	Version 3.0, Date 26SEP2019

Version No:	Document History Description of Update	Author(s)	Effective Date
1.0	N/A	PPD	13AUG2015
2.0	Add new subject population sets. Add Final Analysis Efficacy. Add important items for investigation.	PPD	11JAN2018
3.0	Updated MedDRA version. Updated SAS version.	PPD	26SEP2019

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ABBREVIATIONS

AE	adverse event
BMI	body mass index
CRF	case report form
CI	confidence interval
DURS	Drug Use Results Survey
ECG	electrocardiogram
ECHO	Echocardiogram
ET	essential thrombocythemia
ILD	interstitial lung disease
MedDRA	Medical Dictionary for Regulatory Activities
PMDA	Pharmaceuticals and Medical Devices Agency
PT	preferred term
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy and safety data as described in the final protocol version 3.0 (Japanese version dated 27 March 2019; English version dated 27 March 2019).

2. SURVEY DESIGN

2.1 General Survey Design

This is a Drug Use Results Survey (DURS) of Agrylin (anagrelide hydrochloride) in the post-marketing phase in patients diagnosed with Essential Thrombocythemia (ET).

Planned implementation period of this survey is as follows:

1. Implementation period: from product approval until the approval condition regarding implementation of the all case survey is removed.[1]

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:

All patients who received treatment with Agrylin will be included in this survey and will be observed for 1 year.

2.2 Randomization

Not applicable to this survey.

2.3 Blinding

Not applicable to this survey.

[1] The implementation period is from the launch of XAGRID in Japan to receipt of approval from the Pharmaceuticals and Medical Devices Agency (PMDA) to discontinue the survey. At least 474 subjects must be registered and followed for 1-year before the PMDA can be petitioned to end the survey.

2.4 Schedule of Assessments

Safety and efficacy data that are available as part of routine clinical practice related to the treatment with Agrylin will be investigated.

Table 1: Schedule of Assessments

	Registration Form	Book 1			Book 2	
		Registration	Additional Visit	6 Month visit	Additional Visit	12 Month visit
Patient identification 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)		●	●	●	●	●

ET=essential thrombocytemia; JAK=Janus-Activated Kinase; QTc=corrected QT interval

2.5 Determination of Sample Size

Target Patient Population

All cases who received treatment with Agrylin.

Target number of cases: 474 cases

It is estimated that 474 patients will be prescribed Agrylin at the end of the second year of marketing in Japan. This number suffices to potentially observe with 95% confidence interval (CI) (exact binomial CI estimated by Clopper & Pearson method) common adverse events that are classified as important investigation items in this all-case survey; less common events such as interstitial lung disease (ILD) or some cardiac disorders (e.g., Torsade de pointes) might not be captured.

2.6 Multiplicity Adjustments for Type I Error Control

No adjustments for multiplicity are being made.

3. OBJECTIVES

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

Data will be collected to address the following specifications:

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

4. SUBJECT POPULATION SETS

The following populations are defined:

4.1 Enrolled Sets

The following two types of Enrolled Set are created.

4.1.1 The Pre-Data Lock Point Enrolled Set

The Pre-Data Lock Point (DLP) Enrolled Set will consist of all subjects in the Overall Enrolled Set who started treatment with Agrylin before May 31, 2015.

4.1.2 The Overall Enrolled Set

The Overall Enrolled Set will consist of all subjects who are enrolled in this survey.

4.2 Safety Analysis Sets

4.2.1 The Pre-Data Lock Point Safety Analysis Set

The Pre-DLP Safety Analysis Set will consist of all subjects in the Pre-DLP Enrolled Set (Section 4.1.1) who started treatment with Agrylin before May 31, 2015 and have provided any post-registration data.

4.2.2 The Overall Safety Analysis Set

The Overall Safety Analysis Set will consist of all subjects in the Overall Enrolled Set (Section 4.1.2) who have received at least one dose of Agrylin and have provided any post-registration data.

4.3 Efficacy Analysis Sets

4.3.1 The Pre-Data Lock Point Efficacy Analysis Set

The Pre-DLP Efficacy Analysis Set will consist of all subjects in the Pre-DLP Safety Analysis Set (Section 4.2.1) who started treatment with Agrylin before May 31, 2015 and have at least one post-baseline platelet count assessment.

4.3.2 The Overall Efficacy Analysis Set

The Overall Efficacy Analysis Set will consist of all subjects in the Overall Safety Analysis Set (Section 4.2.2) who have at least one post-baseline platelet count assessment.

5. SUBJECT DISPOSITION

The number of subjects included in each subject population (i.e., Pre-DLP Enrolled Set, Overall Enrolled Set, Overall Safety Analysis Set, Pre-DLP Safety Analysis Set, Overall Efficacy Analysis Set, and Pre-DLP Efficacy Analysis Set) will be summarized.

Additionally, subjects with case report forms and completion status will be summarized by each part of CRF and overall.

Subject disposition will be listed for the Enrolled Set.

6. PROTOCOL DEVIATIONS

Not applicable to this survey.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Continuous variables such as age, weight, and height will be summarized using the number of observations, mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables such as age category and sex will be summarized using the number of observations and percentages.

Descriptive summaries of demographic and baseline characteristics will be presented for the Pre-DLP Safety Analysis Set (Section 4.2.1) and Overall Safety Analysis Set (Section 4.2.2).

The following demographic characteristics will be summarized in the tables: sex, age (years), age category and time since ET diagnosis (years) (calculated by [start date of Agrylin administration - date of ET diagnosis]/365.25).

In addition, the following baseline characteristics will be summarized in the tables: JAK-2 status (positive, negative, not done), prior thrombocythaemia therapy (no, yes, with subcategories anti-platelet therapy, ant-coagulant therapy, thrombolytic agent, and response [refractory/intolerant/other] for each subcategories and overall), weight (kg), height (m), body mass index (BMI, calculated by weight(kg) / height(m)^2), BMI category, platelet counts, platelet counts category, and pregnancy test result (positive, negative, not applicable) at baseline (registration visit).

Medical histories and complications will be coded using the Medical Dictionary for Regulatory Activities (MedDRA Ver22.0) and will be summarized by the following CRF-specified categories:

- Hepatic impairment (no, yes, missing, with categories of severity)
- Renal impairment (no, yes, missing, with categories of severity)
- Cardiac disorders (no, yes, missing)
- QT/QTc prolongation (no, yes, missing)
- Thrombohemorrhagic events (no, yes, missing)
- Interstitial lung disease (no, yes, missing)
- Others (no, yes, missing)

All demographic and other baseline characteristics will be listed.

8. EXTENT OF EXPOSURE

8.1 Exposure to Agrylin

Exposure to Agrylin will be summarized for the Pre-DLP Safety Analysis Set (Section 4.2.1) and Overall Safety Analysis Set (Section 4.2.2) in terms of following parameters. Descriptive statistics (n, mean, SD, minimum, median, and maximum) will be presented.

- Duration of exposure (days): the stop date of Agrylin administration - the start date of Agrylin administration + 1.
- Total dose (g): summation (over the different intervals of total daily doses) of ([stop date of Agrylin administration - start date of Agrylin administration + 1] x total daily dose (mg))/1000
- Average daily dose (mg/day): total dose (g) / duration of exposure (days) x 1000.

Subjects in the Overall and Pre-DLP Safety Analysis Sets whose total daily dose of Agrylin exceeded 7mg/day will be similarly summarized.

The number and percentage of subjects who met each of these criteria will also be displayed.

9. CONCOMITANT MEDICATION

Concomitant medication is defined as any medication with a start date prior to the start date of Agrylin administration and continuing after the start date of Agrylin administration or with a start date between the dates of the start date and the stop date of Agrylin administration, inclusive. Any medication with the end date before the start date of Agrylin administration or the start date after the stop date of Agrylin administration will not be considered a concomitant medication.

Additional details related to missing or incomplete dates are addressed in Section 17.

Concomitant medication usage for the Pre-DLP Safety Analysis Set (Section 4.2.1) and Overall and Safety Analysis Set (Section 4.2.2) will be summarized by the number and proportion of subjects receiving each medication within each type of medication (anti-platelet therapies, anti-coagulant, thrombolytic agents, others) and generic name. Multiple medication usage by a subject in the same category will be counted only once.

All concomitant medication will be listed.

10. EFFICACY ANALYSES

All efficacy analyses will be based on the Pre-DLP Efficacy Analysis Set (Section 4.3.1) and Overall Efficacy Analysis Set (Section 4.3.2). Baseline for all efficacy analyses is defined as the value for the efficacy assessment at the registration visit. Platelet count is the only efficacy parameter.

Descriptive statistics, consisting of the number of observations, the mean, the standard deviation, the median, and the minimum, and maximum values, will be presented, but no statistical tests will be performed.

10.1 Primary Efficacy Endpoint(s) and Analysis

The primary efficacy variable is platelet count, for which the absolute value will be summarized, by visit (Baseline, 1 Months, 3 Months, 6 Months, 9 Months, 12 Months), using descriptive statistics for the Efficacy Analysis Set.

10.2 Exploratory Efficacy Endpoint(s) and Analyses

Platelet counts will be similarly summarized for the Overall and Pre-DLP Efficacy Analysis Sets by age group (<= 17 [pediatric], 18 – 64, >= 65 [elderly]), baseline hepatic impairment group (yes, no, missing), baseline renal impairment group (yes, no, missing), baseline urine pregnancy test group (positive, negative), and by prior thrombocythemia therapy group (yes, no).

10.3 For Final Analysis Efficacy Endpoint(s) and Analyses

The control rate of platelet count will be summarized using the number of observations and percentages. The control rate of the platelet count is determined as follows.

Baseline	Survey data after 91 days (3 months) after Agrylin administration	The control rate of the platelet count (600,000 / uL)
600,000 / uL or more	less than 600,000 / uL	Achieved
600,000 / uL or more	600,000 / uL or more	Not achieved
less than 600,000 / uL	less than 600,000 / uL	Undecidable
less than 600,000 / uL	600,000 / uL or more	Undecidable

Baseline	Survey data after 91 days (3 months) after Agrylin administration	The control rate of the platelet count (400,000 / uL)
400,000 / uL or more	less than 400,000 / uL	Achieved
400,000 / uL or more	400,000 / uL or more	Not achieved

less than 400,000 / uL	less than 400,000 / uL	Undecidable
less than 400,000 / uL	400,000 / uL or more	Undecidable

Rate of change (After Agrylin administration - Baseline) /Baseline * 100	The control rate of the platelet count (50% decrease)
-50% or less	Achieved
more than -50%	Not achieved

11. SAFETY ANALYSES

The safety analysis will be performed using the Pre-DLP Safety Analysis Set (Section 4.2.1) and Overall Safety Analysis Set (Section 4.2.2). Safety parameters include adverse events (AEs), vital signs, and electrocardiogram (ECG) parameters. For each safety parameter, the registration visit value will be used as the baseline value.

11.1 Adverse Events

Adverse events will be coded using the MedDRA (appropriate version).

An AE (classified by PT) that occurs during the observation period will be considered a treatment-emergent adverse event (TEAE) if it has a start date on or after the start date of Agrylin administration or if it has a start date before the start date of Agrylin administration, but increases in severity on or after the start date of Agrylin administration. If more than 1 AE with the same PT is reported before the start date of Agrylin administration, then the AE with the greatest severity will be used as the benchmark for comparison to the AEs occurring during observation period under the PT. If a TEAE is determined to be related to Agrylin, it is classified as an Adverse Drug Reaction (ADR).

An overall summary of the number of subjects with TEAEs will be presented, including the number and percentage of subjects with any TEAEs, serious TEAEs, TEAEs related to Agrylin, TEAEs leading to dose interruption and TEAEs leading to drug withdrawal. The number and percentage of subjects reporting TEAEs will be tabulated by system organ class (SOC) and PT; by SOC, PT, and maximum severity. TEAEs considered related to Agrylin (ADRs) and serious TEAEs will also be summarized by SOC and PT. If more than 1 AE occurs with the same PT for the same subject, then the subject will be counted only once for that PT using the most severe and most related occurrence for the summarization by severity and by relationship with Agrylin.

The number of subjects in the Overall and Pre-DLP Safety Analysis Sets with any TEAEs will also be summarized by Outcome.

The number and percentage of subjects in the Overall and Pre-DLP Safety Analysis Sets with any TEAEs will also be summarized by the following background or baseline factors:

- SEX
- Age category (<= 17 [pediatric], 18 – 64, >= 65 [elderly])

  (<= 17, 18 - 44, 45 - 54, 55 - 64, 65 - 74, 75 - 84, >= 85)
- Baseline Hepatic impairment (yes, no, missing)
- Baseline Renal impairment (yes, no, missing)
- Baseline urine pregnancy test (positive, negative, missing)

- Prior thrombocythaemia therapy (yes, no, missing)
- Other factors judged necessary (Details are described in TLF Shells)

In addition, the number and percentage of subjects reporting TEAEs will be tabulated by PT for each of the background or baseline factors listed below.

- Children (Aged Under 18 Years), Elderly (Aged 65 or Older)
- Pregnant
- Important Items for investigation (Hepatic Impairment, Renal desorder, Cardiac Disorders, QT/QTc Prolongation, Hematological Toxicity, Thrombohemorrhagic Events, Interstitial Lung Disease, Headache)

TEAEs with an incidence 1.00% or more are defined as "Major TEAEs". "Major TEAEs" will be tabulated by PT.

11.2 Clinical Laboratory Variables

Except for platelet counts, laboratory tests are not mandatory for this survey and related data will be collected as available for the parameters relevant to AEs.

Laboratory test data will be listed only.

11.3 Vital Signs

Descriptive statistics for vital signs (e.g., systolic and diastolic blood pressure, pulse rate, and body weight) and their changes from baseline at each post-baseline visit (6 and 12 months visit) will be presented.

11.4 Electrocardiogram

Electrocardiogram is not mandatory test for this survey.

Electrocardiogram will be listed only if performed.

11.5 Other Safety Variables

Echocardiogram (ECHO):

An ECHO is not mandatory in this survey.

ECHO data will be listed only if performed.

12. ADVERSE EVENTS OF SPECIAL INTEREST (IMPORTANT ITEMS FOR INVESTIGATION)

The following CRF-specified categories of AEs are termed "important items for investigation" for this survey.

- Cardiac disorder
- QT/corrected QT interval (QTc) prolongation
- Thrombohemorrhagic events
- Interstitial lung disease
- Haematological toxicity
- Headache

These important items for investigation will be summarized using the number and proportion of subjects together with the 2-sided 95% CIs (exact binomial CI estimated by Clopper & Pearson method) per post-treatment visit (6 Months, 12 Months) and overall for the Pre-DLP Safety Analysis Set (Section 4.2.1) and Overall Safety Analysis Set (Section 4.2.2).

The number and percentage of subjects reporting TEAEs within each of these important items will be tabulated by SOC and PT.

13. INTERIM ANALYSIS

N/A

14. DATA MONITORING/REVIEW COMMITTEE

No analysis for data monitoring/review committee is planned for this survey.

15. COMPUTER METHODS

Statistical analyses will be performed using Version 9.4 (or higher) of SAS® on a suitably qualified environment.

16. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

None (TBD)

17. DATA HANDLING CONVENTIONS

17.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, SD, minimum, maximum. Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category. Percentages will be presented as whole numbers.

Refer to TFLs4Shire for rules on the number of decimal places to present data and p-values.

17.2 Derived Efficacy Endpoints

Not applicable for this survey.

17.3 Repeated or Unscheduled Assessments of Efficacy and Safety Parameters

The last observation within each reporting period (baseline, 6 month, 12 month) will be summarized. All assessments, including unscheduled, will be presented in the data listings.

17.4 Missing Date of Agrylin

Not applicable for this survey.

17.5 Missing Date Information for Concomitant Medications

For concomitant medication summaries, incomplete (i.e., partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

17.5.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing day and month

- If the year of the incomplete start date is the same as the year of the start date of Agrylin administration, then the day and month of the start date of Agrylin administration will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the start date of Agrylin administration, then December 31 will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the start date of Agrylin administration, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the start date of Agrylin administration, then the day of the start date of Agrylin administration will be assigned to the missing day

- If either the year is before the year of the start date of Agrylin administration or if both years are the same but the month is before the month of the start date of Agrylin administration, then the last day of the month will be assigned to the missing day

- If either the year is after the year of the start date of Agrylin administration or if both years are the same but the month is after the month of the start date of Agrylin administration, then the first day of the month will be assigned to the missing day.

17.5.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the same as the year as of the stop date of Agrylin administration, then the day and month of the date of the stop date of Agrylin administration will be assigned to the missing fields

- If the year of the incomplete stop date is before the year of the stop date of Agrylin administration, then 31 December will be assigned to the missing fields

- If the year of the incomplete stop date is after the year of the stop date of Agrylin administration, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the stop date of Agrylin administration, then the day of the stop date of Agrylin administration will be assigned to the missing day

- If either the year is before the year of the stop date of Agrylin administration or if both years are the same but the month is before the month of the stop date of Agrylin administration, then the last day of the month will be assigned to the missing day

- If either the year is after the year of the stop date of Agrylin administration or if both years are the same but the month is after the month of the stop date of Agrylin administration, then the first day of the month will be assigned to the missing day.

17.6 Missing Date Information for Adverse Events

For AEs, only incomplete (i.e., partially missing) start dates will be imputed.

17.6.1 Incomplete Start Date

The same rules as those provided in Section 17.5.1 will be followed.

17.6.2 Incomplete Stop Date

If required per the protocol, the same rules as those provided in Section 17.5.2 will be followed.

17.7 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the start date of Agrylin administration, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the start date of Agrylin administration, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

17.8 Missing Relationship to Agrylin for Adverse Events

If the relationship to Agrylin is missing for an AE starting on or after the start date of Agrylin administration, a causality of "Related" will be assigned. The imputed values for relationship to Agrylin will be used for incidence summaries, while the actual values will be presented in data listings.

17.9 Character Values of Clinical Laboratory Variables

Not applicable for this survey.

17.10 Baseline Values

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline, except for Adverse Events (AEs) and medications commencing on the reference start date, which will be considered post-baseline

18. REFERENCES

N/A