10 November 2016
EMA/791522/2016
Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Xagrid

anagrelide

Procedure no: EMEA/H/C/000480/P46/055

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 26 August 2016, the MAH submitted a completed paediatric study for XAGRID, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the SPD422-404 study, "multicentre paediatric disease registry in essential thrombocythaemia (ET)", is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Xagrid is brand name for anagrelide hydrochloride presented as capsules in one dose strength of 0.5 mg.

In the SPD422-404 study, the drug was available as capsules at dosage strength of 0.5 mg.

2.3. Clinical aspects

2.3.1. Introduction

Anagrelide hydrochloride (XAGRID®) is the only selective inhibitor of megakaryocyte maturation and platelet production, and is indicated for the treatment of patients with essential thrombocythemia (ET). It is approved in a total of 47 countries globally including the United States (US) and European Union (EU) and is licensed as either AGRYLIN or XAGRID.

In 2007 the Paediatric Regulation came into force in the EU with the objective to improve the health of children in Europe by facilitating the development and availability of medicines for children. The Regulation introduced obligations and incentives for research into new and existing drugs and introduced the Paediatric Investigation Plan (PIP) which needs to be agreed with the EMA Paediatric Committee (PDCO). The need for such research for XAGRID was discussed extensively with the PDCO; a briefing document along with the study proposal was submitted and reviewed by the PDCO between August 2009 and April 2010.

In April 2010, the MAH agreed with the PDCO to conduct a disease registry study (study SPD422-404) to investigate disease progression, symptoms, and treatment effects on platelet count, to summarize drug utilization of cytoreductive therapies, to summarize long term assessment of disease progression, and to summarize safety of cytoreductive therapies in a population of paediatric subjects.

The Post Approval Measure is submitted under Article 46 and comprises of a final study report. The MAH confirms no changes to the approved Product Information have been requested as a consequence of this study report.

2.3.2. Clinical study

SPD422-404 study "Multicentre paediatric disease registry in essential thrombocythaemia (ET)"

Description

A noninterventional study to evaluate the conditions under which cytoreductive therapy is prescribed in paediatric population as well as the effect and duration of treatment.

This multicentre study was performed in Italy, UK, France, Germany, Spain, Greece, Swizerland and Czech Rep. This study aimed to enroll 60 subjects at approximately 29 sites. With an expected average of 2 subjects per site, analysis was not broken down by site.

Period of study: 28 September 2010 to 01 March 2016 (end of data collection)

Observation period will be at least 1 day and up to a maximum of 60 months.

A data cut will take place in March 2013.

Methods

Objectives

The objectives of this study were:

-To observe disease progression, symptoms and treatment effects on platelet count,

-To summarise drug utilisation of cytoreductive therapies,

-To summarise incidence and severity of adverse events (AEs),

-To summarise the long-term assessment of disease progression /safety.

Disease progression was defined for a patient if disease progression was reported as an AE or there were any reports of leukaemia or myelofibrosis. Patients who report the additional use of other cytoreductive therapy or any significant dose increases in cytoreductive drug therapy were investigated for possible disease progression.

Symptoms of the disease were captured through the reporting of AEs assessed by the investigator as being related to ET.

Details of drug utilisation of cytoreductive treatments included type of treatment, dose level, duration of exposure, and reasons for change or modification.

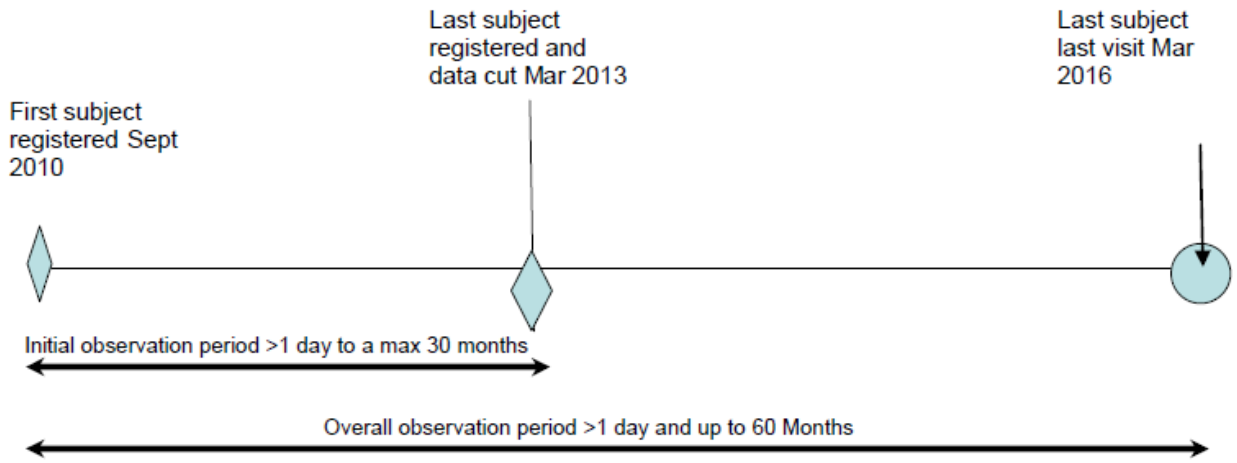
Percentages of patients taking each cytoreductive therapy (including patients who switch) were calculated.

Adverse events were collected throughout the duration of the study and were summarized by treatment and severity.

Frequency of drug related side effects observed were calculated over appropriate time periods for patients who were treated with cytoreductive therapy and for patients who were untreated (no treatment/ASA alone).

Study design

Figure 1:



Study population /Sample size

Planned

The study planned to recruit at least 60 subjects with ET (aged 6-17 years inclusive) during the enrollment period up to March 2013 who, according to the treating physician, had ET using the World Health Organization (WHO) criteria as guidance. Subjects could be enrolled regardless of cytoreductive therapy. To ensure 50% of subjects had at least 1 year observation at the time of data cut (March 2013), it was anticipated that 30 subjects would be enrolled by March 2012.

Analyzed

A total of 69 patients were enrolled and 64 had follow-up data.

Treatments

Commercially available ET treatments (hydroxycarbamide and interferon α-2A) were used; there was thus no specific paediatric formulation for anagrelide. The study followed the usual medicinal clinical practice of paediatrics haematologists and their decisions in treating children.

Outcomes/endpoints

The study outcomes will be assessed by measuring the following variables in accordance with routine clinical practice:

- Cytoreductive drug utilisation within this paediatric ET population (details will include duration of exposure and reasons for switching) for treatments recorded as taken prior to or during the study

- Platelet counts

- Adverse events

- Clinical laboratory evaluations

- Vital signs (weight, heart rate and blood pressure).

Efficacy endpoints:

The following efficacy information was collected:

- Platelet counts
- Number of thrombohemorrhagic events (collected as AEs)
- Information on disease progression
- Information on symptoms/side effects of ET
- Physician's Overall Assessment of Treatment Outcome

Safety endpoints:

The following safety information was collected:

- Adverse events (all AEs)
- Clinical laboratory evaluations
- Vital signs (including weight, heart rate, systolic and diastolic blood pressure [SBP and DBP])
- Electrocardiogram (ECG) and echocardiogram

Statistical Methods

All analyses and listings included all enrolled patients.

->Treatment cohorts

Data were summarized for subjects who were treated with cytoreductive therapy and for subjects who were not treated with cytoreductive therapy ("No treatment/anti-aggregatory [AA]) Alone") during the observation period only. Usage of cytoreductive therapy prior to date of assent was not considered for assignment to cohorts unless it was ongoing on the date of registration itself.

If no cytoreductive treatments were reported during the observation period it was assumed the subject did not take any cytoreductive therapy. It was anticipated that subjects may have changed their cytoreductive therapy during the observation period and therefore it was possible that a patient originating in the "No Treatment/AA Alone" group later qualified for the cytoreductive group. In these cases all data collected prior to the first dose of cytoreductive therapy was analyzed in the "No Treatment/AA Alone" group and all data collected at or after the first dose of cytoreductive therapy was analyzed in the Cytoreductive Therapy cohort. Once in the Cytoreductive Therapy cohort, subjects remained in the Cytoreductive Therapy cohort.

Subjects treated with XAGRID were of particular interest and therefore were summarized as a subset of the Cytoreductive Therapy cohort. Data collected at or after the first dose of XAGRID in the observation period were analyzed in the XAGRID cohort (as well as continuing to be analyzed in the Cytoreductive Therapy cohort). Once in the XAGRID cohort they remained in this cohort regardless of further treatment changes. Additional specific treatment groups could be analyzed separately depending on the frequency of use.

The first cohort date was the registration date and the end date of a cohort was the last visit date unless the subject switched cohorts and initiates cytoreductive therapies during the observation period. In this case, the first date of the Cytoreductive Therapy cohort was the date of start of cytoreductive therapy and the end date of the "No Treatment/AA Alone" cohort was the previous day.

These cohorts were not independent; however, no inferential analyses were planned for this study and the number of subjects included in multiple groups was reported.

->Definition of Baseline

Time of baseline and registration in the study were arbitrary times and could capture the subject at any time during the course of their disease. Some subjects could have been diagnosed many years before their data are captured and others diagnosed at or near the time of enrollment.

For subjects taking cytoreductive therapy at the time of the first visit, the registration visit was the baseline visit. In addition, for subjects not taking cytoreductive therapy at enrollment, the registration visit was baseline for the “No Treatment/AA Alone” cohort. If a subject initiated cytoreductive therapy during the observation period, the baseline for the Cytoreductive Therapy cohort was the date where therapy started.

Similarly for the XAGRID Group, if the subject was taking XAGRID at the time of registration, the registration visit was baseline. Otherwise, if the subject started treatment with XAGRID during the observation period, the visit where the subject started taking XAGRID was the baseline visit.

->Time intervals

The post baseline time intervals for analysis were driven by the frequency of visits to the investigator. If feasible, the data were summarized in 3-month intervals. This was reviewed prior to interim and final data cuts.

Depending on the frequency of visits, the time interval could be narrowed or expanded. Data collected less frequently could require longer time intervals to be used for analysis.

->Examination of subgroups

The subgroups of subjects with disease progression and symptoms at diagnosis were investigated.

Subject to the range of subjects enrolled, data could also be summarized according to age groups (6-11 years, 12-17 years).

->Interim analyses and data monitoring

Two sets of statistical analyses of all data were performed for this study, 1 at the completion of the study in 2016 and 1 at the time of the data cut in March 2013 (after completion of enrollment and after at least 30 subjects had been observed for at least 1 year).

All tables, figures, and listings planned for the final analysis were presented in 2013 after completion of enrollment. The long-term assessment of disease progression was made by including all the 3-year follow-up data collected up to the completion of the study in 2016.

There will not be a data monitoring committee for this study.

Results

Recruitment / Number analysed

Inclusion criteria:

To be eligible for the study, subjects had to fulfil each of the following criteria:

1. Subjects aged ≥6 and <18 years

2. Subjects who, in the opinion of the treating physician, had ET according to the WHO criteria as guidance

3. Subjects could be enrolled regardless of ET therapy (ie, they could be):

- Previously treated

- Currently being treated or

- Not receiving ET therapy/treatment naïve

4. Subjects with an understanding, ability, and willingness to participate in the study.

5. Subjects with an ability to provide written, signed, and dated (personally or via a legally authorized representative) informed consent/and assent, as applicable, to participate in the study.

Exclusion criteria:

Patients were excluded from the study if they are participating in a separate interventional clinical study where their ET treatment is defined by the study protocol.

Removal of subjects:

A subject could withdraw consent (ie, for data capture) from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. Subjects who discontinued were not replaced.

Any comments (spontaneous or elicited) or complaints made by the subject and the reason for withdrawal of consent had to be recorded in the electronic case report form (eCRF) and source documents.

Table 1: Subject Disposition (All Enrolled Patients)

	No Treatment AA alone N=53	Cytoreductive Therapy incl. XAGRID N=21	XAGRID N=15	Total N=69
Patients enrolled, n				69
Patients with follow-up data, n				64
Completed study, n (%)	40 (75.5)	19 (90.5)	13 (86.7)	54 (78.3)
Did not complete study, n (%)	13 (24.5)	2 (9.5)	2 (13.3)	15 (21.7)
Lost to follow-up	8 (15.1)	1 (4.8)	1 (6.7)	9 (13.0)
Other	4 (7.5)	1 (4.8)	1 (6.7)	5 (7.2)
Withdrawal by patient	1 (1.9)	0	0	1 (1.4)
Switched cohort, n (%)				
Switched to cytoreductive therapy	5 (9.4)[a]	0	0	5 (7.2)
Switched to XAGRID	2 (3.8)[b]	1 (4.8)[c]	0	3 (4.3)
Duration of observations (days)[d]				
Mean (SD)	1106.2 (489.02)	1277.1 (327.23)	1293.9 (332.36)	1249.1 (410.46)
Total patient years observed[e]	160.5	73.4	53.1	236.0

Source: Section 14, Table 1.1.1

Note: These cohorts are not independent; patients starting cytoreductive therapy during the study were included in the "No Treatment/AA Alone" cohort up until the time of first dose. After first dose of cytoreductive therapy, patients were included in the "Cytoreductive Therapy" cohort.

AA=anti-aggregatory; N=number of subjects in cohort; n=number of subjects who meet the criterion; SD=standard deviation; %=(n/N)*100

a. Number of and percent of patients in "No Treatment/AA Alone" and switch to Cytoreductive Therapy.

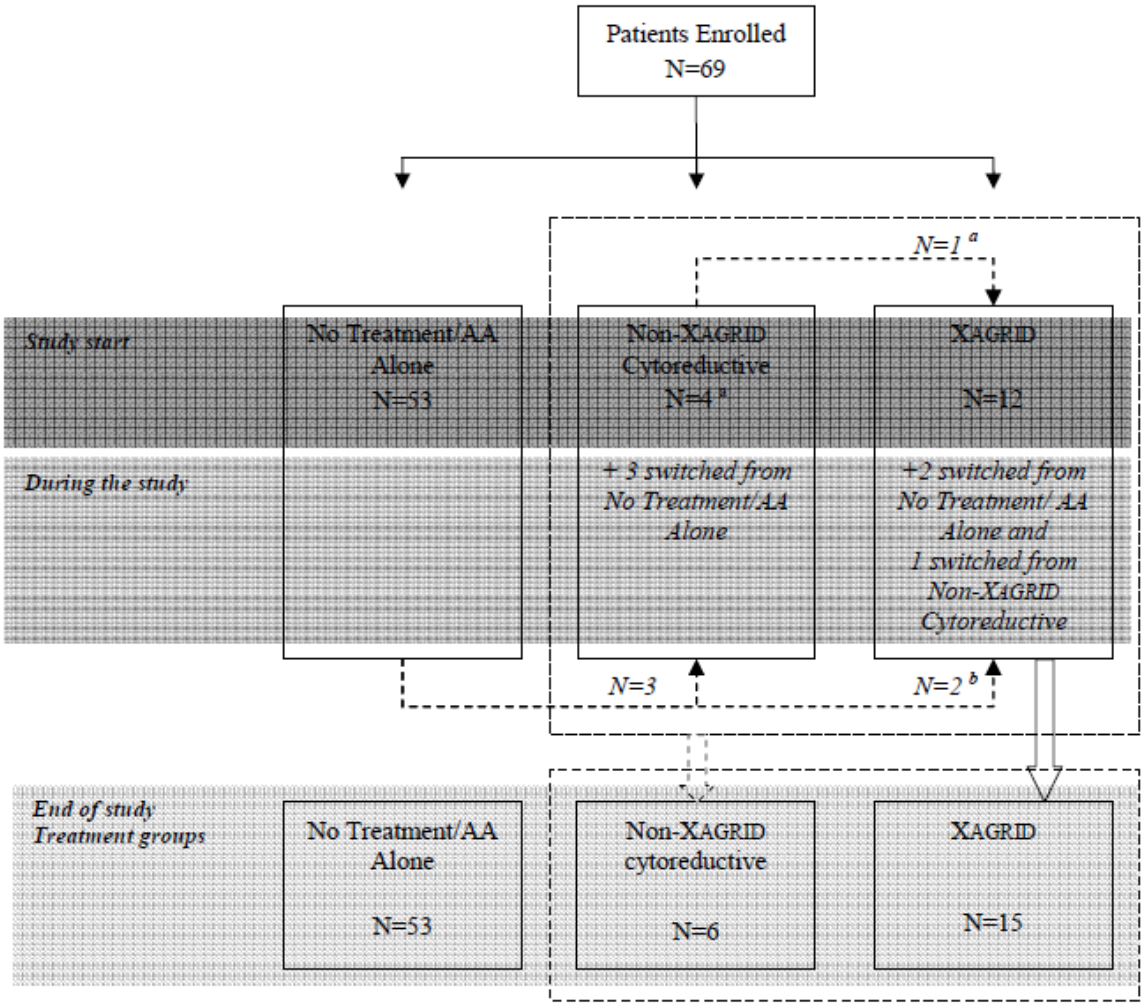
b. Number of and percent of patients taking "No Treatment/AA Alone" and switch to XAGRID.

c. Number of and percent of patients taking Cytoreductive Therapy (not XAGRID) and switch to XAGRID.

d. Duration of observation=last cohort date – first cohort date + 1.

e. Patient years observed=sum (duration of observation).

Figure 2 : Patient Disposition (All Enrolled Patients)



Source: Section 14, Table 1.1.1; Appendix 16.2, Listing 1.1

Note: A patient who switched from 1 cohort to another was counted in more than 1 cohort.

AA=anti-aggregatory; N=number of subjects per cohort/number of subjects who switched

[a] One patient (023-0004) started non-XAGRID cytoreductive therapy, then switched to XAGRID during the study, and switched back to non-XAGRID cytoreductive therapy at the end of the study. This subject has been counted in both the XAGRID and "Cytoreductive Therapy" cohorts.

[b] One patient (001-0007) started on "No treatment/AA Alone", then switched to XAGRID during the study and switched to non-XAGRID cytoreductive therapy at the end of study. This subject has been counted in the "No Treatment/AA Alone", XAGRID, and "Cytoreductive Therapy" cohorts.

Baseline data

Table 2: Demographics (All Enrolled Patients)

	No Treatment AA alone N=53	Cytoreductive Therapy incl. XAGRID N=21	XAGRID N=15	Total N=69
Age[a]				
Mean (SD)	12.0 (3.23)	14.0 (2.77)	13.3 (2.81)	12.4 (3.26)
Age category[a], n (%)				
6-11 years	20 (37.7)	4 (19.0)	4 (26.7)	24 (34.8)
12-17 years	33 (62.3)	17 (81.0)	11 (73.3)	45 (65.2)
Sex, n (%)				
Male	23 (43.4)	7 (33.3)	6 (40.0)	28 (40.6)
Female	30 (56.6)	14 (66.7)	9 (60.0)	41 (59.4)
Race, n (%)				
White	39 (73.6)	18 (85.7)	13 (86.7)	52 (75.4)
Black or African American	1 (1.9)	0	0	1 (1.4)
Asian	2 (3.8)	0	0	2 (2.9)
Other	10 (18.9)	3 (14.3)	2 (13.3)	13 (18.8)
Missing	1 (1.9)	0	0	1 (1.4)
Smoker, n (%)				
No	52 (98.1)	21 (100.0)	15 (100.0)	68 (98.6)
Missing	1 (1.9)	0	0	1 (1.4)

Source: Section 14, Table 1.2.1

Note: These cohorts are not independent; patients starting cytoreductive therapy during the study were included in the "No Treatment/AA Alone" cohort up until the time of first dose. After first dose of cytoreductive therapy, patients were included in the "Cytoreductive Therapy" cohort.

AA=anti-aggregatory; ET=essential thrombocythemia; N=number of subjects in cohort; n=number of subjects who meet the criterion; SD=standard deviation; %=(n/N)*100

[a] Age was calculated as the difference between date of birth and date of informed consent, in years. For patients starting ET therapy during the observation period, age was calculated as the difference between date of birth and baseline date, in years.

Overall, the majority of patients were female (59.4%) and White (75.4%). The mean (SD) age was 12.4 (3.26) years. Demographic data were well balanced between the different cohorts.

Overall, the mean (SD) time from diagnosis to cohort start was 58.2 (48.81) months. Patients who started cytoreductive therapy, did so after approximately 10 months: the time from diagnosis to cohort start was 66.7 (55.20) months in the "Cytoreductive Therapy" cohort and 66.1 (46.60) months and XAGRID cohort compared with 58.1 (50.04) months in the "No Treatment/AA Alone" cohort.

The majority of patients (64 patients [92.8%] overall) were diagnosed using the WHO criteria.

Symptoms of ET included headache (19 patients [27.5%] overall), dizziness and paraesthesia (5 patients [7.2%] overall), and symptoms listed as other (17 patients 24.6%] overall). Headache and dizziness were more commonly reported for patients in the "Cytoreductive therapy" and XAGRID cohorts. Symptoms listed as "other" were more commonly reported for patients in the "No treatment/AA Alone" cohort.

The majority of patients (65 patients [94.2%] overall) had no thrombohemorrhagic event at the time of diagnosis.

The majority of patients (61 patients [88.4%] overall) had no family history of MPN.

Efficacy results

All analyses were conducted on all enrolled patients.

Table 3: All Enrolled Patients per Cohort

	No Treatment AA Alone	Cytoreductive Therapy incl. XAGRID	XAGRID
All Enrolled Patients, N	53	21	15

Source: Section 14, Table 1.1.1

Note: These cohorts are not independent; patients starting cytoreductive therapy during the study were included in the "No Treatment/AA Alone" cohort up until the time of first dose. After first dose of cytoreductive therapy, patients were included in the "Cytoreductive Therapy" cohort.

AA=anti-aggregatory; N=number of subjects in cohort

Patients were treated with XAGRID in low doses (median dose of 0.028 mg/kg [based on the first weight measurement] or 0.019 mg/kg [based on the last weight measurement). Other cytoreductives taken during the study were hydroxycarbamide, taken at a median dose of 22.117 mg/kg (based on the first weight measurement) and 14.955 mg/kg (based on the last weight measurement), and interferon α-2A, taken at a median dose of 0.003 mg/kg (based on both the first and last weight measurement).

Salicylic acid was used by approximately 30% of patients at a median dose of 81.3 mg.

Platelet count

Mean (SD) platelet count at baseline was highest in the "No Treatment/AA Alone" cohort (980.4 [552.76 x 10^9/L) and lower in the "Cytoreductive Therapy" (766.8 [484.93] x10^9/L) and XAGRID (653.5 [338.34] x 10^9/L) cohorts. The majority of patients in all 3 cohorts had platelet count values ≤1500 x 10^9/L (ie, 85.7%, 87.5%, and 100% of patients, respectively).

Mean (SD) platelet count at Month 55-57 was higher compared with baseline in the "No Treatment/AA Alone" cohort (1067.3 [699.57] x 10^9/L) and lower compared with baseline in the "Cytoreductive Therapy" (364.0 [284.26] x 10^9/L) and XAGRID (364.0 [284.26] x 10^9/L). The majority of patients in all 3 cohorts had platelet count values ≤1500 x 10^9/L (ie, 75.0%, 100%, and 100% of patients, respectively). Note that at the Month 55-57 time point, platelet count data were available for a limited number of patients (N=4, 2, and 2, respectively).

Thrombohemorragic events

One patient in the "Cytoreductive Therapy" cohort experienced 2 thrombohemorrhagic events during the study (intracranial venous thrombosis and cerebral venous thrombosis).

None of the patients in the XAGRID cohort experienced a thrombohemorrhagic event during the study.

Disease progression

A total of 2 patients (3.8%) in the "No Treatment/AA Alone" cohort and 2 patients (9.5%) in the "Cytoreductive Therapy" cohort of which 1 patient (6.7%) on XAGRID, experienced disease progression during the study. Note that 2 of these patients (1 each the "No Treatment/AA Alone"and "Cytoreductive Therapy" [XAGRID] cohorts) experienced myelofibrosis.

Symptoms of essential thrombocythemia

Overall, 8 patients (15.1%) in the “No Treatment/AA Alone” cohort and 6 patients (28.6%) in the “Cytoreductive Therapy” cohort [of whom 4 patients (26.7%) on XAGRID], had ET symptoms during the study.

Physician’s overall assessment of treatment outcome

As per the investigator, 16 out of 24 patients who received cytoreductive therapy achieved their platelet targets and 14 out of these 24 patients had an improvement in ET symptoms. In addition, 12 out of 15 patients who received AA therapy experienced an improvement in ET symptoms and 28 out of 30 patients who did not receive AA therapy experienced no ET symptoms that required therapy.

CHMP comment

As a general comment, the SPD422-404 study “Multicentre paediatric disease registry in essential thrombocythaemia (ET)” is a noninterventional study assessing the conditions under which cytoreductive therapy is prescribed in paediatric population as well as the effect and duration of treatment. The results concerning the use of Xagrid specifically are limited. Indeed, the low number of patients in the Xagrid cohort (15 patients) limits the interpretation of the results. Consequently, the CHMP agrees with the MAH not to update the approved Product Information with these limited data.

Safety results

Overall, 49 patients (71.0%) experienced an AE during the observation period:

- 34 patients (64.2%) in the “No Treatment/AA Alone” cohort

- 16 patients (76.2%) in the “Cytoreductive Therapy of whom 11 patients (73.3%) on XAGRID.

The 100-patient-years exposure rate was 69.2, 74.9, and 69.6, respectively.

Fourteen patients (20.3%) experienced an AE related to ET disease during the observation period, with 8 patients (15.1%) in the “No Treatment/AA Alone” cohort and 6 patients (28.6%) in the “Cytoreductive Therapy of whom 4 patients (26.7%) on XAGRID. The 100-patient-years exposure rate was 10.6, 15.0, and 11.3, respectively.

TEAE

Globally, TEAEs were mainly reported in SOCs “Infections and infestations” (22 patients; 31.9%), “Nervous system disorders” (17 patients; 24.6%) and “Gastrointestinal disorders” (15 patients; 21.7%).

Most common TEAEs are summarized in the table hereafter.

Overall, 49 patients (71.0%) experienced an AE during the observation period. The most common AEs were gastroenteritis (5 patients [7.2%] overall), menorrhagia (4 patients [5.8%] overall), and

dizziness, abdominal pain, diarrhoea, epistaxis, dysmenorrhea, and joint dislocation (3 patients [4.3%] overall each). All other preferred terms occurred in at most 2 subjects overall.

In most of the SOCs, incidence was higher in the cytoreductive therapy cohort. Incidence was higher in the subcohort of Xagrid treatment in the following SOCs: "Reproductive system and breast disorders", "General disorders and administration site conditions" and "Musculoskeletal and connective tissue disorders". This was due to the higher incidence of asthenia, fatigue, and pyrexia (1 patient each on XAGRID and none on "No treatment/AA Alone") and muscular weakness and pain in extremity (1 patient each on XAGRID and none on "No treatment/AA Alone"), respectively. Moreover, regarding the "Reproductive system and breast disorders" SOC, menorrhagia (1) and dysmenorrhea (1) were reported with Xagrid.

Adverse events in the SOC "Injury, poisoning, and procedural complications" occurred solely in patients not receiving any treatment.

No medically significant differences between the treatment groups in incidence of preferred terms were observed.

Table 1: Most Common (>1 Patient Overall) Adverse Events (All Enrolled Patients)

System organ class Preferred term	No Treatment AA Alone N=53	Cytoreductive Therapy incl. XAGRID N=21	XAGRID N=15	Total N=69
Patients with ≥1 AE	34 (64.2)	16 (76.2)	11 (73.3)	49 (71.0)
Infections and infestations	14 (26.4)	8 (38.1)	5 (33.3)	22 (31.9)
Gastroenteritis	3 (5.7)	2 (9.5)	1 (6.7)	5 (7.2)
Nasopharyngitis	1 (1.9)	1 (4.8)	1 (6.7)	2 (2.9)
Tonsillitis	1 (1.9)	1 (4.8)	1 (6.7)	2 (2.9)
Urinary tract infection	1 (1.9)	1 (4.8)	1 (6.7)	2 (2.9)
Varicella	0	2 (9.5)	1 (6.7)	2 (2.9)
Nervous system disorders	11 (20.8)	6 (28.6)	4 (26.7)	17 (24.6)
Headache	8 (15.1)	2 (9.5)	1 (6.7)	10 (14.5)
Dizziness	2 (3.8)	1 (4.8)	1 (6.7)	3 (4.3)
Migraine	1 (1.9)	1 (4.8)	1 (6.7)	2 (2.9)
Paraesthesia	2 (3.8)	0	0	2 (2.9)
Gastrointestinal disorders	10 (18.9)	6 (28.6)	3 (20.0)	15 (21.7)
Abdominal pain	1 (1.9)	2 (9.5)	1 (6.7)	3 (4.3)
Diarrhoea	2 (3.8)	1 (4.8)	0	3 (4.3)
Haematemesis	1 (1.9)	1 (4.8)	0	2 (2.9)
Vomiting	1 (1.9)	1 (4.8)	1 (6.7)	2 (2.9)
Respiratory, thoracic, and mediastinal disorders	8 (15.1)	2 (9.5)	2 (13.3)	10 (14.5)
Epistaxis	2 (3.8)	1 (4.8)	1 (6.7)	3 (4.3)

Oropharyngeal pain	1 (1.9)	1 (4.8)	1 (6.7)	2 (2.9)
Reproductive system and breast disorders	5 (9.4)	4 (19.0)	3 (20.0)	8 (11.6)
Menorrhagia	3 (5.7)	1 (4.8)	1 (6.7)	4 (5.8)
Dysmenorrhoea	2 (3.8)	1 (4.8)	1 (6.7)	3 (4.3)
Injury, poisoning, and procedural complications	7 (13.2)	0	0	7 (10.1)
Joint dislocation	3 (5.7)	0	0	3 (4.3)
General disorders and administration site conditions	1 (1.9)	4 (19.0)	3 (20.0)	5 (7.2)
Chest pain	1 (1.9)	1 (4.8)	0	2 (2.9)
Musculoskeletal and connective tissue disorders	3 (5.7)	2 (9.5)	2 (13.3)	5 (7.2)
Metabolism and nutrition disorders	3 (5.7)	1 (4.8)	0	4 (5.8)
Iron deficiency	2 (3.8)	1 (4.8)	0	3 (4.3)
Neoplasm benign, malignant and unspecified (including cysts and polyps)	3 (5.7)	1 (4.8)	1 (6.7)	4 (5.8)
Myelofibrosis	1 (1.9)	1 (4.8)	1 (6.7)	2 (2.9)
Vascular disorders	4 (7.5)	0	0	4 (5.8)
Blood and lymphatic system disorders	1 (1.9)	2 (9.5)	1 (6.7)	3 (4.3)
Ear and labyrinth disorders	2 (3.8)	1 (4.8)	1 (6.7)	3 (4.3)
Tinnitus	1 (1.9)	1 (4.8)	1 (6.7)	2 (2.9)
Investigations	2 (3.8)	1 (4.8)	1 (6.7)	3 (4.3)
Psychiatric disorders	2 (3.8)	1 (4.8)	0	3 (4.3)
Skin and subcutaneous tissue disorders	1 (1.9)	2 (9.5)	1 (6.7)	3 (4.3)

Source: Section 14, Table 4.2.2

Note 1: Percentages were based on all enrolled patients.

Note 2: Adverse events were classified into preferred term using MedDRA version 18.0.

Note 3: Patients were counted once per system organ class and preferred term.

Note 4: These subgroups are not independent; patients starting cytoreductive therapy during the study were included in the "No Treatment/AA Alone" group up until the time of first dose. After first dose of cytoreductive therapy, patients were included in Cytoreductive Therapy.

AA=anti-aggregatory; AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects per treatment group; n=number of subjects with event

Overall, 1 patient in the "Cytoreductive Therapy" cohort experienced a thrombohemorrhagic event during the study. On 24 Nov 2011, a 17-year-old female, treated with hydroxycarbamide for ET disease from 01 Aug 2011, the patient experienced the serious AE of moderate cerebral venous thrombosis and the nonserious AE of severe intracranial venous sinus thrombosis. Both events were considered related to the underlying ET disease and not related to the ET treatment. The patient received heparin and fluindione. The SAE of cerebral venous thrombosis was considered resolved on 11 Jan 2012; the nonserious AE of intracranial venous sinus thrombosis was ongoing at the end of the observation period.

Related TEAE

Twelve patients (17.4%) experienced an AE related to ET therapy during the observation period:

- 6 patients (11.3%) in the "No Treatment/AA Alone" cohort

- 6 patients (28.6%) in the "Cytoreductive Therapy of whom 4 patient (26.7%) on XAGRID.

Apart from menorrhagia (experienced by 3 patients [4.3%] overall; 2 patients (3.8%) in the "No treatment/AA Alone" and 1 patient in the "Cytoreductive Therapy" cohort who was on XAGRID [4.8% and 6.7%, respectively]), none of the preferred terms occurred in more than 1 subject overall.

Related TEAE reported in the "Cytoreductive Therapy" were:

- Abdominal pain upper (1 patient, on XAGRID therapy)

- Menorrhagia (1 patient, on XAGRID therapy)

- Asthenia and Fatigue (1 patient each; each on XAGRID therapy)

- Anaemia (1 patient, on XAGRID therapy)

- Varicella (1 patient; none with Xagrid)

- Myelofibrosis (1 patient, on XAGRID therapy)

- Headache (1 patient; none with Xagrid)

Except for menorrhagia, none of these PTs were reported in the “no treatment/AA alone” cohort. However, except for menorrhagia, none of the PTs reported in the “no treatment/AA alone” cohort was reported in the “cytoreductive therapy” cohort; related TEAEs reported in the “no treatment/AA alone” cohort were:

- Menorrhagia (2 patients)

- Gingival disorder, Mouth haemorrhage, Nausea (1 each)

- Injury (1)

- Decreased appetite (1)

- Petechiae (1)

- Haematoma (1)

No significant safety finding was identified among the related TEAEs reported.

Severe TEAE

The majority of patients experienced AEs of mild or moderate intensity:

- mild intensity: 28 patients [40.6%] overall; 19 patients [35.8%] in the “No Treatment/AA Alone” cohort and 10 patients [47.6%] in the “Cytoreductive Therapy” cohort of whom 7 patients [46.7%] on XAGRID;

- moderate intensity: 16 patients [23.2%] overall; 13 patients [24.5%] in the “No Treatment/AA Alone” cohort and 3 patients [14.3%] in the “Cytoreductive Therapy” cohort of whom 2 patients [13.3%] on XAGRID).

A total of 5 patients (7.2%) experienced a TEAE of severe intensity (2 patients [3.8%] in the “No Treatment/AA Alone” cohort and 3 patients [14.3%] in the “Cytoreductive Therapy” cohort of whom 2 patients [13.3%] on XAGRID). The cases are further summarized below:

- Serious severe myelofibrosis in a 17-year-old female treated with Xagrid; The SAE was considered related to the ET disease and ET treatment and led to a dose reduction.

- Non-serious severe migraine in a 12-year-old female treated with Xagrid. The AE was considered not related to the ET disease or the ET treatment and resolved during the observation period.

- Non-serious severe intracranial venous sinus thrombosis and serious severe depression in a 17-year-old female treated with “cytoreductive therapy”. Both events were considered related to the ET disease.

- Serious severe atrial septal defect II in a 12-year-old female receiving “No treatment/AA Alone”. The SAE was considered not related to the ET disease and resolved during the observation period.

- Serious severe ascites, oesophageal varices haemorrhage, haematemesis, hepatic failure, and non-serious severe neutropenia in a 17-year-old female receiving “No treatment/AA Alone”. All 5 SAEs were considered related to the ET disease and resolved during the observation period.

No specific safety information was raised though these severe cases.

Of note, the case of severe depression was mistakenly associated by the MAH to the “no treatment/AA Alone” cohort, while it is associated to “cytoreductive treatment” as per the provided listings.

Serious TEAEs

Eleven patients (15.9%) experienced an SAE during the observation period:

- 7 patients (13.2%) in the “No Treatment/AA Alone” cohort

- 4 patients (19.0%) in the “Cytoreductive Therapy of whom 1 patient (6.7%) on XAGRID.

The 100-patient-years exposure rate was 8.1, 8.2, and 1.9, respectively.

There was no fatal AE.

No patient in any treatment group discontinued treatment due to an AE.

Apart from haematemesis (experienced by 2 patients [2.9%] overall; 1 patient (1.9%) in the “No Treatment/AA Alone” cohort and 1 patient [4.8%] in the “Cytoreductive Therapy” cohort who was not on XAGRID) and myelofibrosis (experienced by 2 patients [2.9%] overall; 1 patient (1.9%) on “No treatment/AA Alone” and 1 patient [6.7%] each XAGRID), none of the preferred terms occurred in more than 1 subject overall.

Clinical Laboratory Evaluation

A total of 16 patients (32.7%), 4 patients (25.0%), and 3 patients (25.0%) in the “No Treatment/AA Alone”, “Cytoreductive Therapy”, and XAGRID cohorts, respectively, had a platelet count >1500 x 109/L at the time of diagnosis. At baseline, this had already decreased to 7 patients (14.3%), 2 patients (12.5%), and 0 patients, respectively. After 22-24 months of observation, the proportion of patients with platelet count >1500 x 109/L was 2 patients (12.5%), 1 patient (10.0%), and 1 patient (14.3%), respectively. At the time of the last data collection (Months 55-57), only 1 patient (25.0%) in the “No Treatment/AA Alone” group had a platelet count >1500 x 109/L.

Hemoglobin levels showed a mild increase over time, which was generally most pronounced in patients in the “No Treatment/AA Alone” cohort:

- “No Treatment/AA Alone”: from 127.13 (11.178) g/L at diagnosis, to 134.33 (10.109) at baseline and 141.07 (13.398) after 22-24 months.

- “Cytoreductive Therapy”: from 121.87 (14.734) g/L at diagnosis, to 122.94 (14.808) at baseline and 128.42 (17.622) after 22-24 months.

- “Xagrid”: from 122.24 (16.714) g/L at diagnosis, to 125.42 (15.395) at baseline and 127.53 (15.619) after 22-24 months.

Hematocrit showed a mild increase over time, which was generally most pronounced in patients in the “No Treatment/AA Alone” cohort.

Mean corpuscular volume increased over time, especially in the “Cytoreductive Therapy” and XAGRID cohorts.

Mean platelet volume, at the time of diagnosis, was 7.922 (4.3573), 11.357(8.1808), and 8.125 (1.7251) fL in the “No Treatment/AA Alone”, “Cytoreductive Therapy”, and XAGRID cohorts, respectively. At baseline, mean (SD) platelet volume was 7.984 (1.1784), 8.760 (1.716), and 9.767 (1.4364) fL, respectively. Mean (SD) distribution width was 20.62 (13.652), 10.20 (NA; data for 1 patient only), and 10.20% (NA; data for 1 patient only). After 22-24 months of observation, mean (SD) platelet volume was 8.250 (1.6345), 9.320 (1.6208), and 9.700 (1.9519) fL, respectively. Mean (SD) distribution width was 15.40 (0.283), 14.90 (2.828), and 14.90 (2.828)%, respectively. In addition, mean platelet count showed a decrease over time in the “Cytoreductive Therapy” and XAGRID cohorts; see efficacy section for additional details.

Blasts were not present in the blood of any of the patients during the observation period. Apart from 1 patient on XAGRID (Month 52-54), the blast/leukocyte fraction was 0 for all patients throughout the observation period.

Bilirubin increased over time in both cohorts, including in the subgroup of Xagrid.
Alkaline phosphatase decreased over time in the “No Treatment/AA Alone” and XAGRID cohorts.

Aspartate aminotransferase also showed a decrease over time, which was most pronounced in patients on XAGRID.

Alanine aminotransferase showed a slight increase in the “No Treatment/AA Alone” cohort and remained fairly stable in the “Cytoreductive Therapy” and XAGRID cohorts.

Creatinine increased over time in both cohorts, including in the Xagrid sub-group. The increase was most pronounced in the “Cytoreductive Therapy” and XAGRID cohorts.

Gamma glutamyltransferase decreased over time in the “Cytoreductive Therapy” and XAGRID cohorts and increased in the “No Treatment/AA Alone” cohort.

Lactate dehydrogenase decreased over time in the “Cytoreductive Therapy” and XAGRID cohorts and remained fairly stable in the “No Treatment/AA Alone” cohort.

Mean changes from baseline in other laboratory parameters were generally small and none were considered clinically relevant.

CHMP assessment comment

According to the MAH, mean platelet volume and distribution width decreased over time in patients in the “Cytoreductive Therapy” and XAGRID cohorts. However, it should be noted that increase in mean

platelet volume was noted in the Xagrid group. Moreover, data on platelet distribution width were only available in 2 patients in "cytoreductive therapy" cohort (and 1 to 2 patients in Xagrid, depending on time of examination), making data very limited for further conclusion.

Similarly, PAL results should be considered limited in the "cytoreductive treatment" cohort, considering the low number of patients.

Bilirubine increased in both cohorts, including with Xagrid. No signal was raised regarding ASAT and ALAT. Increase in creatinine with observed in both cohorts, including with Xagrid. Of note, creatinine increase is listed in the SmPC for Xagrid.

Gamma-GT and LDH decreased in cytoreductive therapy cohort, including Xagrid, while gamma-GT increased in the "no treatment/AA alone" arm and LDH remained stable in this arm.

No specific safety signal was identified in the clinical laboratory results.

Vital Signs

The incidence of abnormalities for pulse, SBP, and DBP was limited throughout the observation period. One patient on "No Treatment/AA Alone" experienced the nonserious AE of mild hypertension, considered not related to ET disease or ET treatment and was ongoing at the end of the observation period. No other AEs related to vital signs abnormalities occurred.

BMI tended to increase over time, with a decrease in underweight patients tending to BMI normalization and increase in obese patients.

No clinically significant abnormalities in ECG and echocardiogram and no AEs related to ECG and echocardiogram occurred during the observation period.

2.3.3. Discussion on clinical aspects

In 2007 the Paediatric Regulation came into force in the EU with the objective to improve the health of children in Europe by facilitating the development and availability of medicines for children. The Regulation introduced obligations and incentives for research into new and existing drugs and introduced the Paediatric Investigation Plan (PIP) which needs to be agreed with the EMA Paediatric Committee (PDCO). The need for such research for XAGRID was discussed extensively with the PDCO;

a briefing document along with the study proposal was submitted and reviewed by the PDCO between August 2009 and April 2010.

In April 2010, the MAH agreed with the PDCO to conduct a disease registry study (study SPD422-404) to investigate disease progression, symptoms, and treatment effects on platelet count, to summarize drug utilization of cytoreductive therapies, to summarize long term assessment of disease progression, and to summarize safety of cytoreductive therapies in a population of paediatric subjects.

Efficacy discussion:

A total of 69 patients were enrolled and 64 had follow-up data. The majority of patients (N=53/64) who started the study were not taking any cytoreductive therapy. Five of these patients (9.4%) switched to cytoreductive therapy at some point during the observation period.

Two out of these 5 patients switched to XAGRID specifically. Twenty-one patients (including the aforementioned 5 switched patients who started the study on "No treatment/AA Alone") took cytoreductive therapy during the observation period. Fifteen out of these 21 patients took XAGRID. Note that patients starting cytoreductive therapy during the study were included in the "No Treatment/AA Alone" cohort up until the time of first dose. After first dose of cytoreductive therapy, patients were included in "Cytoreductive Therapy" cohort (and the XAGRID cohort when applicable).

A total of 15 patients (21.7%), of whom 13 (24.5%) in the "No Treatment/AA Alone" cohort, 2 (9.5%) in the "Cytoreductive Therapy" cohort, and 2 (13.3%) in the XAGRID cohort did not complete the study. The reasons for discontinuation included patients lost to follow-up (N=9 patients overall), reasons listed as other (N=5 patients overall), and withdrawal by patient (N=1 patient overall).

The mean (SD) duration of observation was 1106.2 (489.02) days in the "No Treatment/AA Alone" cohort, 1277.1 (327.23) days in the "Cytoreductive Therapy" cohort and 1293.9 (332.36) days in the XAGRID cohort (1249.1 [410.46] days overall).

Overall, the majority of patients were female (59.4%) and White (75.4%). The mean (SD) age was 12.4 (3.26) years. Demographic data were well balanced between the different cohorts.

A total of 21 patients (30.4%) took cytoreductive therapy during the study. Most of these patients (N=18) took 1 cytoreductive; 3 patients took 2 cytoreductives. Anagrelide (XAGRID) was used by 15 patients (21.7%) at a median dose of 1.0 mg for a median of 1253 days (20.5% of total patient years).

Patients were treated with XAGRID in low doses (median dose of 0.028 mg/kg [based on the first weight measurement] or 0.019 mg/kg [based on the last weight measurement).

Additional results indicate that cytoreductive therapy (and XAGRID more specifically) was effective in reducing platelet count. Mean (SD) platelet count at Month 55-57 was higher compared with baseline in the "No Treatment/AA Alone" cohort (1067.3 [699.57] x 10^9/L) and lower compared with baseline in the "Cytoreductive Therapy" (364.0 [284.26] x 10^9/L) and XAGRID (364.0 [284.26] x 10^9/L). Furthermore, no thrombohemorrhagic events or occurred in patients treated with XAGRID. One patient in the XAGRID cohort developed myelofibrosis.

Safety discussion:

Overall, 49 patients (71.0%) experienced an AE during the observation period.

Eleven patients (15.9%) experienced a serious AE, including 4 in the "cytoreductive therapy" cohort (19.0%) whom 1 on Xagrid. No SAE had a fatal outcome. No AE led to treatment discontinuation.

Apart from haematemesis (2 patients overall, none on Xagrid) and myelofibrosis (2 patients whom 1 on Xagrid), none of the PTs occurred in more than 1 subject overall.

One serious, severe and related case of MF was reported in a 17-years-odl female patient on Xagrid.

The most common AEs were gastroenteritis (5 patients [7.2%] overall), menorrhagia (4 patients [5.8%] overall), dizziness, abdominal pain, diarrhoea, epistaxis, dysmenorrhea, and joint dislocation (3 patients [4.3%] overall each). No medically significant differences between the treatment groups in incidence of PTs were observed.

The incidence of AEs in the SOCs "General disorders and administration site conditions" and "Musculoskeletal and connective tissue disorders was higher in the XAGRID cohort compared with the "No Treatment/AA Alone" cohort. This was due to the higher incidence of asthenia, fatigue, and pyrexia (1 patient each on XAGRID and none on "No treatment/AA alone") and muscular weakness and pain in extremity (1 patient each on XAGRID and none on "No treatment/AA alone"), respectively.

Twelve AEs were assessed as treatment related, including 6 in the "cytoreductive therapy" cohort whom 4 patients on Xagrid. Apart from menorrhagia (experienced by 3 patients [4.3%] overall; 2 patients (3.8%) in the "No treatment/AA Alone" and 1 patient each in the "Cytoreductive Therapy" cohort who was on XAGRID [4.8% and 6.7%, respectively]), none of the preferred terms occurred in more than 1 subject overall.

The majority of patients experienced AEs of mild (28 patients [40.6%] overall; 19 patients [35.8%] in the "No Treatment/AA Alone" cohort and 10 patients [47.6%] in the "Cytoreductive Therapy" cohort of whom 7 patients [46.7%] on XAGRID) or moderate intensity (16 patients [23.2%] overall; 13 patients [24.5%] in the "No Treatment/AA Alone" cohort and 3 patients [14.3%] in the "Cytoreductive Therapy" cohort of whom 2 patients [13.3%] on XAGRID). A total of 5 patients (7.2%) experienced a TEAE of severe intensity (2 patients [3.8%] in the "No Treatment/AA Alone" cohort and 3 patients [14.3%] in the "Cytoreductive Therapy" cohort of whom 2 patients [13.3%] on XAGRID).

Changes in clinical laboratory parameters in the different cohorts were consistent with what might be expected in pediatric patients with ET receiving "No Treatment/AA Alone" or cytoreductive treatment (XAGRID or other cytoreductive treatment). Lactate dehydrogenase decreased over time in the "Cytoreductive Therapy" and XAGRID cohorts and remained fairly stable in the "No Treatment/AA Alone" cohort.

No clinically relevant observations were made related to vital signs or ECG.

Based on these data, no new safety signal nor unexpected trend was identified with Xagrid in the paediatric population, from 6 to 17 years.

3. CHMP overall conclusion and recommendation

In April 2010, the MAH agreed with the PDCO to conduct a disease registry study (study SPD422-404) to investigate disease progression, symptoms, and treatment effects on platelet count, to summarize drug utilization of cytoreductive therapies, to summarize long term assessment of disease progression, and to summarize safety of cytoreductive therapies in a population of paediatric subjects.

Efficacy discussion:

A total of 69 patients were enrolled and 64 had follow-up data. The majority of patients (N=53/64) who started the study were not taking any cytoreductive therapy. Five of these patients (9.4%) switched to cytoreductive therapy at some point during the observation period.

A total of fifteen out of these 21 patients took XAGRID. Note that patients starting cytoreductive therapy during the study were included in the “No Treatment/AA Alone” cohort up until the time of first dose. After first dose of cytoreductive therapy, patients were included in “Cytoreductive Therapy” cohort (and the XAGRID cohort when applicable).

The mean (SD) duration of observation was 1106.2 (489.02) days in the “No Treatment/AA Alone” cohort, 1277.1 (327.23) days in the “Cytoreductive Therapy” cohort and 1293.9 (332.36) days in the XAGRID cohort (1249.1 [410.46] days overall).

Overall, the majority of patients were female (59.4%) and White (75.4%). The mean (SD) age was 12.4 (3.26) years. Demographic data were well balanced between the different cohorts.

A total of 21 patients (30.4%) took cytoreductive therapy during the study. Most of these patients (N=18) took 1 cytoreductive; 3 patients took 2 cytoreductives. Anagrelide (XAGRID) was used by 15 patients (21.7%) at a median dose of 1.0 mg for a median of 1253 days (20.5% of total patient years).

Additional results indicate that cytoreductive therapy (and XAGRID more specifically) was effective in reducing platelet count. Mean (SD) platelet count at Month 55-57 was higher compared with baseline in the “No Treatment/AA Alone” cohort (1067.3 [699.57] x 10^9/L) and lower compared with baseline in the “Cytoreductive Therapy” (364.0 [284.26] x 10^9/L) and XAGRID (364.0 [284.26] x 10^9/L).

One patient in the XAGRID cohort developed myelofibrosis.

Safety discussion:

Overall, 49 patients (71.0%) experienced an AE during the observation period, including 11 with SAE (15.9%). None had a fatal outcome and no AE led to treatment discontinuation.

One serious, severe and related case of MF was reported in a 17-years-old female patient on Xagrid.

The incidence of AEs in the SOCs “General disorders and administration site conditions” and “Musculoskeletal and connective tissue disorders” was higher in the XAGRID cohort, mainly due to cases of asthenia, fatigue, and pyrexia, and muscular weakness and pain in extremity only reported with Xagrid.

Twelve AEs were assessed as treatment related, including 6 in the “cytoreductive therapy” cohort whom 4 patients on Xagrid. No safety signal was raised.

Overall, the majority of patients experienced AEs of mild or moderate intensity. A total of 5 patients (7.2%) experienced a TEAE of severe intensity (2 patients [3.8%] in the “No Treatment/AA Alone” cohort and 3 patients [14.3%] in the “Cytoreductive Therapy” cohort of whom 2 patients [13.3%] on XAGRID).

Changes in clinical laboratory results did not raise safety signal. No clinically relevant observations were made related to vital signs or ECG.

Based on these data, no new safety signal or unexpected trend was identified with Xagrid in the paediatric population, from 6 to 17 years.

☒ Fulfilled:

No regulatory action required.

Annex. Line listing of all the studies included in the development program

Clinical studies

Product Name: Xagrid Active substance: Anagrelide Hydrochloride

Study title	Study number	Date of completion	Date of submission of final study report
Multicentre paediatric disease registry in essential thrombocythaemia (ET)	SPD422-404	01 March 2016	26 August 2016