25 September 2014
EMA/CHMP/697040/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xagrid

International non-proprietary name: ANAGRELIDE

Procedure No. EMEA/H/C/000480/II/0059

Note

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

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List of abbreviations

AML	Acute myeloid leukemia
ET	essential thrombocythaemia
CSR	Case study report
MAH	marketing authorisation holder
MPD	myeloproliferative disorders
PD	pharmacodynamics
PDE	phosphodiesterase
PIP	paediatric investigation plan
PK	pharmacokinetics
Bid	twice a day
A-A	anti-aggregatory
AE	adverse event
AUC	area under the curve
AUC_{τ}	a standardized measurement of AUC over 1 dosing interval
CHMP	Committee for Medicinal Products for Human Use
Cmax	maximum concentration occurring at tmax
ET	essential thrombocythemia
EU	European Union
IC50	50% inhibitory concentration
MPD	myeloproliferative disorder
MPN	myeloproliferative neoplasm
PDE	phosphodiesterase
PIP	Pediatric Investigational Plan
SAE	serious adverse event
SmPC	Summary of Product Characteristics
tmax	time of maximum observed concentration sampled during a dosing interval

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Shire Pharmaceutical Contracts Ltd. submitted to the European Medicines Agency on 7 February 2014 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Xagrid	ANAGRELIDE	See Annex A

The following variation was requested:

Variation requested		**Type**
C.1.6 a	Addition of a new therapeutic indication or modification of an approved one	II

The MAH proposed a variation to update the indication for use in paediatric patients aged 6 to 17 years. The proposed updates to the SmPC include sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2. The PL is proposed to be updated accordingly. The MAH also took the opportunity to update the list of local representatives.

Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.0.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0325/2013 of 19 December 2013 on the agreement of a paediatric investigation plan (PIP) and on the granting of a waiver for paediatric patients under 6 years of age.

At the time of submission of the application, the EMA Decision P/0325/2013 of 19 December 2013 for the PIP EMEA-000720-PIP01-09-M02 was completed.

Information relating to orphan market exclusivity

Xagrid was designated as an orphan medicinal product EU/3/00/010 on 29 December 2000. Xagrid was designated as an orphan medicinal product in the following indication: Treatment of essential thrombocythaemia.

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Derogation(s) of market exclusivity

Not applicable.

Protocol assistance

The applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Pierre Demolis Co-Rapporteur: Daniel Brasseur

Submission date:	7 February 2014
Start of procedure:	21 February 2014
Rapporteur's preliminary assessment report circulated on:	17 April 2014
CoRapporteur's preliminary assessment report circulated on:	16 April 2014
Joint Rapporteur's updated assessment report circulated on:	21 May 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	22 May 2014
MAH's responses submitted to the CHMP on:	23 June 2014
Joint Rapporteur's assessment report on the MAH's responses circulated on:	11 July 2014
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	18 July 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 July 2014
MAH's responses submitted to the CHMP on:	22 August 2014
Joint Rapporteur's assessment report on the MAH's responses circulated on:	8 September 2014
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	19 September 2014
CHMP opinion:	25 September 2014

2. Scientific discussion

• *Introduction*

Anagrelide hydrochloride (Xagrid) is an inhibitor of cyclic AMP phosphidiesterase III and is indicated for the reduction of elevated platelet counts in at risk essential thrombocythaemia (ET) patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy.

An at risk patient

An at risk essential thrombocythaemia patient is defined by one or more of the following features:

- > 60 years of age or
- a platelet count > 1000 x 10^9/l or
- a history of thrombo-haemorrhagic events.

The specific mechanism of action by which anagrelide reduces platelet count is not yet fully understood although it has been confirmed that anagrelide is platelet selective from in vitro and in vivo study information. In vitro studies of human megakaryocytopoiesis established that anagrelide's inhibitory actions on platelet formation in man are mediated via retardation of maturation of megakaryocytes, and reducing their size and ploidy. Following oral administration, anagrelide is rapidly absorbed and extensively metabolized to form a pharmacologically active metabolite, BCH24426 (3-hydroxy-anagrelide), which is further metabolized to the major pharmacologically inactive metabolite, RL603. In healthy subjects, less than 1% of the anagrelide dose is recovered in urine as unchanged anagrelide and approximately 3% and 16–20% is recovered in urine as BCH24426 and RL603, respectively.

Xagrid was designated as an orphan medicinal product EU/3/00/010 on 29 December 2000. The Marketing Authorisation for Xagrid remains under exceptional circumstances.

The MAH applied for a variation to the Xagrid (anagrelide hydrochloride) marketing authorisation (EU/1/04/295/001) to change the indication and include the use in paediatric patients aged 6 to 17 years. The proposed indication was as follows:

Xagrid is indicated for the reduction of elevated platelet counts in:

- adult at-risk essential thrombocythaemia (ET) patients

- children and adolescents aged 6-17 years with ET who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy.

This application was made following the completion of Paediatric Investigation Plan in March 2013 (EMEA-000720-PIP01-09-M02). A waiver was granted for paediatric patients under 6 years of age.

Shire submitted a Paediatric Investigation Plan (PIP) on a voluntary basis under Article 8 of the Paediatric Regulation (EC) No. 1901/2006 with a view to obtaining a 2-year extension to the marketing exclusivity of Xagrid in the EU. The PIP was agreed with the EMA on 4 June 2010. The indication targeted by the PIP was as follows:

> Treatment of essential thrombocythaemia (ET) in paediatric patients aged 6 to less than 18 years who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy.

Three clinical measures were agreed for the completion of the PIP:

- Retrospective analysis of pooled data from studies SPD422-202 and SPD422-203 to compare PK/PD parameters across the age groups 6-11 years, 12-17 years, 18-64 years and ≥ 65 years SPD-422-405a
- A retrospective analysis of pooled safety data from patients aged <18 years of age from studies available in the Shire anagrelide clinical database – Study SPD422-405b.
- Multicentre paediatric observational study in Essential Thrombocythaemia (ET), evaluating drug utilisation and effects of cytoreductive agents treatment in children 6 to less than 18 years of age - Study SPD422-404

Study SPD422-202 was submitted in April 2005 with the Type II variation application EMEA/H/C/480/II/01 and resulted in an update to the XAGRID SmPC Sections 5.1 and 5.2 but not a paediatric indication. The CHMP concluded that the data were insufficient to support a dosage recommendation in paediatrics and the efficacy below the age of 16 years was not yet established. Study could provide safety information and provide guidance on the identification of an appropriate dose for the paediatric indication.

As agreed, a data cut was performed at the completion date of the PIP and core part of the SPD422-404 study in March 2013 and the results from this interim data cut were submitted for this variation.

Long-term safety and efficacy are being collected from subjects enrolled in the SPD422-404 registry study during an additional one year follow-up. This long-term follow-up is outside of the PIP.

Study SPD422-404 (a multi-centre, paediatric, observational study in essential thrombocythaemia (ET), to assess drug utilisation and effects of cytoreductive treatment) that was specifically focused on paediatric population was initiated and additional pooled analyses on the existing clinical database (SPD422-405a & 405b) was undertaken in accordance with a Paediatric Investigation Plan (PIP) agreed on 4 June 2010 with the Paediatric Committee of the European Medicines Agency (EMEA-000720-PIP01-09).

The study SPD422-404 was not completed by March 2013 (the agreed date of completion of the PIP). The modification allowed the applicant to complete the core part of the study within the PIP when at least 30 patients had one-year follow-up. The second part of the registry study is outside of the PIP and part of the specific measures for long-term follow-up. The PDCO opinion on the modified PIP was adopted on the 6th December 2013 and the decision included a waiver for children aged less than 6 years.

A data cut was performed at the completion date of the PIP and core part of the SPD422-404 study in March 2013 and the results from this data cut were submitted in support for the variation.

In addition, as per opinion of the Paediatric committee on the agreement of the PIP, the applicant was requested to perform a retrospective analysis of pool studies SPD422-202 and SPD422-203 in order to compare pharmacokinetics / pharmacodynamics parameters across the age groups 6-11 years, 12-17 years, 18-64 years and ≥65 years. Therefore, Shire proposed a reanalysis of existing PK and safety data using a reclassification into ICH age groups.

The Marketing authorisation holder (MAH) proposed updates to the following sections of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) : 4.1 Therapeutic indications, 4.2 Posology and method of administration, Section 4.4 Special warnings and precautions for use, 4.8 Undesirable effects, 5.1 Pharmacodynamic properties, and 5.2 Pharmacokinetic properties.

2.1. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2. Clinical aspects

2.2.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1 presents an overview of clinical studies providing data on the pharmacokinetics, efficacy and/or safety of anagrelide for the treatment of ET in the paediatric population.

Table 1: Overview of clinical studies providing data on the pharmacokinetics, efficacy and/or Safety of anagrelide for the treatment of essential thrombocythemia in the paediatric population

Study ID M5 location	Short Description	Phase	Study Design	Subjects Dosed	Dosage Regimen	Duration of Dosage/ Observation
SPD422-202 5.3.3.3	Safety, PK, and PD study in pediatric/ adolescent and adolescent/adult subjects	2	MC, O	17 M/F aged 7-14 years (17 ET) 18 M/F aged	Start dose 0.5-2mg/day, titrated up to a maximum of 10mg/day	3 months

Study ID M5 location	Short Description	Phase	Study Design	Subjects Dosed	Dosage Regimen	Duration of Dosage/ Observation
				16-86 years (12 ET)		
SPD422-203 5.3.3.3	Safety, PK, and PD in young and elderly ET subjects	2	MC, O	12 M/F aged 22-50 years 12 M/F aged ≥65 years	Subjects received their usual daily anagrelide dose, divided as evenly as possible into a twice daily regimen (8am/8pm)	1 day (PK sampling day)
13970-301 5.3.5.2	Compassionate use, long-term safety and efficacy in patients with MPD	3	MC, O, SC	3660 M/F (2251 ET)	2–12mg/day (maximum dose later reduced to 10mg/day), titrated to maintain platelet count of <$60x10^4$/µL and ideally 13-$45x10^4$/µL	Up to 5 years
700-014 5.3.5.2	Platelet reduction and safety in subjects with MPD	2	MC, O, SC	498 M/F (274 ET)	Start dose 2–4mg/day. Permitted dose: 2-12mg/day, titrated weekly to maintain platelet count within 13-$40x10^4$/µL	Up to 4 years
700-999 5.3.5.2	Compassionate use, platelet reduction, and safety in patients with MPD	3	MC, O, SC	406 M/F (242 ET)	Start dose 2–4mg/day for 1 week, titrated weekly (dose range: 0.5-13mg/day) to maintain platelet count within 15-$60x10^4$/µL	Over 4 years
SPD422-404 5.3.5.2	Pediatric disease registry in ET	4	MC, O	69 M/F (6-17 years)	Non-interventional	Up to 5 years[a]

[a] Interim data cut. Study SPD422-404 is ongoing.

ET=essential thrombocythemia; F=female; M=male; MC=multicenter, MPD=myeloproliferative disorder; O=open-label; PD=pharmacodynamic; PK=pharmacokinetic; SC=self-controlled.

Supportive analyses are also provided by the following 2 pooled analyses:

- SPD422-405a: A pooled analysis of Studies SPD422-202 and SPD422-203. The pooled analysis includes all age groups; paediatric (6-11 years), adolescent (12-17 years), adult (18-64 years) and elderly (≥65 years)
- SPD422-405b: A re-analysis of the integrated clinical summary developed in 2002. The re-analysis includes paediatric (6-11 years) and adolescent (12-17 years) subjects only.

2.2.2. Pharmacokinetics

The two Phase 2, open-label studies SPD422-202 and SPD422-203 studies have investigated the effects of age on the PK / PD of anagrelide and its active metabolite BCH24426 (3-hydroxyanagrelide).

Study SPD422-202

Study SPD422-202 was an open-label, single-arm, multicentre, safety, pharmacokinetic and pharmacodynamic, Phase 2 study in pediatric and adult subjects with thrombocythaemia secondary to MPDs. used the licensed 0.5 mg capsules (and previously US-licensed 1 mg capsules) of anagrelide in

paediatric/adolescent subjects (aged ≤15 years) and adolescent/adult subjects (aged ≥16 years) with thrombocythaemia secondary to myeloproliferative disorders (MPD).

The main inclusion criteria were as per the original study protocol:

- Paediatric (≤11 years old), adolescent (12-15 years old, inclusive) or adolescent/adult (≥16 years old) patients of either sex, with a diagnosis of ET, polycythemia vera, chronic myelogenous leukemia or other MPDs, and a history of thrombocythemia secondary to MPDs treated with or without anagrelide therapy.
- Anagrelide-naïve patients, patients receiving a stable maintenance dose of anagrelide or patients currently undergoing anagrelide titration were enrolled into the study.

The main exclusion criteria were as follows:

- Current or recurrent disease that could affect, the action, absorption or disposition of the study medication, or clinical or laboratory assessments.
- Current or relevant previous history of serious, severe or unstable (acute or progressive) physical or psychiatric illness, any medical disorder that may have required treatment or made the subject unlikely to fully complete the study, or any condition that presented undue risk from the study medication or procedures.
- Any history of bleeding disorders including haemophilia, history of intra-cranial bleed or gastro-intestinal bleeding.
- History of severe head injury or history of keloid scarring (inability for cuts/incisions to heal properly).
- Use of any medication including Over-The-Counter (OTC) medication, vitamins and herbal treatments considered likely to affect subject safety within one week of dosing.
- Use of aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) or other known antiaggregant agents or compounds known to contain these agents within 4 weeks prior to or during the study.
- Treatment with any known enzyme altering agents e.g. barbiturates, phenothiazines, cimetidine, within 4 weeks prior to or during the study.
- Known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
- Subjects contraindicated for aspirin administration (e.g. subjects with gastric and duodenal mucosal lesions, history of bronchospasm, aspirin-induced allergies, dyspepsia).

This multicentre study was conducted in the EU, South Korea, and USA.

Dosage, treatment regimen, route: As per study protocol, dose titration was permitted on a weekly basis as required, however the daily dose was not increased by more than 0.5mg/day in any one week and the total daily dose was not to exceed 10mg/day.

There were no controls.

Duration of treatment: Eligible subjects received study drug for a period of 3 months.

Study SPD422-203

Study SPD422-203 was a Phase 2, open-label, multicentre, pharmacokinetic, pharmacodynamic, and safety study of anagrelide hydrochloride in young adults (18–50 years) and elderly (≥65 years) patients with essential thrombocythaemia.

The main inclusion criteria were as per the original study protocol:

- (platelet count ≥60x104/µL)
- young adults (aged 18–50 years) or elderly (≥65 years) patients with a diagnosis of ET and receiving a stable dose of anagrelide (≤5 mg/day) for at least 4 weeks.

The exclusion criteria were as follows:

- Diagnosis of any other MPD.
- Current or recurrent disease that could have affected the action, absorption or disposition of the investigational product, or clinical or laboratory assessments.
- Any significant disease or condition that was judged by the Investigator to pose unacceptable risk to the patient or prevent the patient from completing the study or impact on the validity of the results.
- A resting ejection fraction below the limit of normal.
- Haemoglobin <15% below laboratory lower limit of normal.
- Treatment with any known enzyme-altering agents (barbiturates, phenothiazines, cimetidine etc.) within 30 days prior to or during the study.
- Current (within 1 week of the start of the study) or regular use of any other medication (including over-the-counter, herbal or homeopathic preparations) that could have affected the action, absorption or disposition of the investigational product, or clinical or laboratory assessment.
- Concomitant therapy that had been altered within 1 week of the start of the study or was likely to require alteration during the course of the study.
- Treatment with any other cytoreductive agent either during or within 4 weeks of the start of the study.
- Known or suspected intolerance or hypersensitivity to the investigational product (or closely related compounds) or any of the stated ingredients.
- Patients with a history of alcohol or other substance abuse within the last year.
- Patients who had used another investigational product or taken part in a clinical trial within the last 30 days prior to enrolment (patients from study SPD422-403 may have been included).
- Pregnant or lactating females, including females with a positive pregnancy test at screening or on the PK day.
- Patients enrolled and subsequently withdrawn from this study.

This multicentre study was conducted in the EU.

Dosage, treatment regimen, route: As per study protocol. During a 3-day run-in period, subjects divided their usual daily anagrelide dose as equally as possible into 2 daily doses.

Study SPD422-203 also used the licensed 0.5 mg capsules of anagrelide in young adult (18-50 years) versus elderly (≥65 years) ET patients.

Study SPD422-405a

Study SPD422-405a is a retrospective analysis of pooled data from studies SPD422-202 and SPD422-203. It examined PK/PD data across defined age groups from age 6 years to the elderly after 30 days of treatment.

The objectives of the study were to compare PK, PD, and safety outcomes across defined age groups from age 6 years to the elderly.

The efficacy primary endpoints were:

- Treatment history
- Platelet count
    - At screening and after 4 weeks of treatment (i.e. Day 30 for study 202 and 10-12 hours post-dose on Day 1 for study 203).
- Dose of anagrelide
    - Change from first to last dose
    - Average dose during the 4-week study/evaluation window
- Duration of exposure to anagrelide

The secondary endpoint was Safety

- Adverse events (based on the 4-week evaluation window)

Pharmacokinetics (anagrelide and BCH24426 metabolite)

- Dose-normalised AUC_T (AUC over the dosing interval)
- Dose-normalised Cmax
- Clearance (dose/AUC)
- Weight-normalised clearance

Secondary endpoints were adverse events.

The statistical plan included the summaries of demography, treatment history, anagrelide dosing, pharmacokinetics parameters (AUC_T, clearance, weight-normalised clearance, Cmax), platelet count (at the start and end of 4 weeks treatment), exposure, and adverse events were presented.

A total of 8 children (6-11 years), 10 adolescents (12-17 years), 17 adults (18-64 years), and 24 elderly (≥ 65 years) were entered in this retrospective analysis.

The majority of subjects had previously been treated with cytoreductives, of which anagrelide was the most frequently administered.

In the paediatric children and adolescents, only 1 subject had previously been treated with antiaggregants and none with anti-coagulants.

Results

Baseline characteristics

The baseline characteristics for the pooled study 405a are presented below.

Table 2: Treatment history – Pooled 202 and 203 studies (safety population)

Table 1: Treatment History - Pooled Studies 202 & 203 (Safety Population)				
	Child (N=8) n (%)	Adolescent (N=10) n (%)	Adult (N=17) n (%)	Elderly (N=24) n (%)
Treatment-naïve subjects[a]	1 (12.5)	0	0	1 (4.2)
Subjects Previously Treated with Cytoreductives	7 (87.5)	10 (100.0)	16 (94.1)	21 (87.5)
Anagrelide	7 (87.5)	10 (100.0)	16 (94.1)	20 (83.3)
Hydroxycarbamide	0	0	1 (5.9)	2 (8.3)
Interferon	0	0	0	1 (4.2)
Subjects Previously Treated with Anti-Aggregants	1 (12.5)	0	8 (47.1)	13 (54.2)
Subjects Previously Treated with Anti-Coagulants	0	0	3 (17.6)	1 (4.2)

[a] Subjects who were completely treatment naïve. Table 2 presents subjects who were anagrelide naïve.
Note: Percentages are based on the number of subjects in the safety population for each age group.

Table 3: Summary of demographic characteristics – Pooled 202 and 203 studies (safety population)

Table 2: Summary of Demographic Characteristics - Pooled Studies 202 & 203 (Safety Population)				
Statistic	Child (N=8)	Adolescent (N=10)	Adult (N=17)	Elderly (N=24)
Age				
N	8	10	17	24
Mean (SD)	9.50 (1.690)	13.40 (1.174)	40.24 (11.183)	72.58 (6.494)
Median	10.00	13.00	42.00	70.00
Min, max	7.0, 11.0	12.0, 16.0	19.0, 57.0	65.0, 86.0
Sex				
Female	4 (50.0%)	6 (60.0%)	10 (58.8%)	15 (62.5%)
Male	4 (50.0%)	4 (40.0%)	7 (41.2%)	9 (37.5%)
Race				
Caucasian	7 (87.5%)	5 (50.0%)	16 (94.1%)	23 (95.8%)
Black	1 (12.5%)	2 (20.0%)	0	1 (4.2%)
Hispanic	0	0	1 (5.9%)	0
Asian/Pacific Islander	0	3 (30.0%)	0	0
Anagrelide naïve?				
No	7 (87.5%)	10 (100.0%)	16 (94.1%)	20 (83.3%)
Yes	1 (12.5%)	0	1 (5.9%)	4 (16.7%)

Note: Percentages are based on the number of subjects in the safety population for each age group.

The pooled analysis for Studies SPD422-202 and SPD422-203 (Study SPD422-405a) examined for pharmacokinetics and pharmacodynamics data for 8 children, 10 adolescents, 17 adults, and 24 elderly subjects of anagrelide and its active metabolite BCH24426 (3-hydroxy-anagrelide). The ET subjects in this pooled analysis were receiving individualised dosing regimens of anagrelide administered at different doses and different dosing intervals (potentially 2, 3, or 4 times daily). The results are presented in Table 1 and Figure 1 and 2. The dosage regimen for study SPD422-202 was a start dose of 0.5-2mg/day, titrated up to a maximum of 10mg/day and for study SPD422-203 the Subjects received their usual daily anagrelide dose, divided as evenly as possible into a twice daily regimen. The

duration of the dosage/observation was 3 months and 1 day (PK sampling day), respectively. The median anagrelide total daily dose was 1.06mg in children, 2.25mg in adolescents, 2.00mg in adults and 1.00mg in elderly subjects.

Table 4: Summary of Normalised Pharmacokinetic Parameters for Anagrelide and BCH24426 Metabolite after 4 Weeks Treatment - Pooled Studies 202 & 203 (Safety Population)

Statistic	Anagrelide				BCH24426 (3-hydroxy-anagrelide)			
	Child (N=8)	Adolescent (N=10)	Adult (N=17)	Elderly (N=24)	Child (N=8)	Adolescent (N=10)	Adult (N=17)	Elderly (N=24)
AUC_τ (ng•h/mL, dose-normalised)								
N	7	10	17	24	7	10	17	24
Mean (SD)	15.96 (6.326)	16.60 (6.121)	10.49 (10.919)	15.68 (11.975)	53.04 (19.395)	54.00 (21.103)	31.08 (10.426)	34.28 (27.923)
Median	14.30	16.22	7.53	13.25	47.33	47.01	32.05	26.84
Min, max	8.8, 27.4	7.0, 26.4	3.0, 51.2	3.2, 65.3	29.5, 79.0	31.7, 96.1	13.3, 50.3	10.0, 135.6
Clearance (L/h)								
N	7	10	17	24	7	10	17	24
Mean (SD)	70.95 (26.070)	69.79 (31.408)	141.49 (76.161)	88.10 (56.878)	21.28 (7.970)	20.71 (6.574)	36.39 (14.543)	45.36 (28.093)
Median	69.95	61.68	132.81	75.47	21.13	21.28	31.20	37.26
Min, max	36.5, 114.1	37.9, 142.8	19.5, 331.9	15.3, 313.0	12.7, 33.9	10.4, 31.6	19.9, 75.4	7.4, 99.8
Clearance (L/h/kg, weight-normalised)								
N	7	10	17	24	7	10	17	24
Mean (SD)	1.89 (0.463)	1.26 (0.592)	1.95 (1.014)	1.24 (0.629)	0.60 (0.258)	0.38 (0.163)	0.50 (0.213)	0.66 (0.449)
Median	1.79	1.10	1.93	1.15	0.50	0.34	0.41	0.53
Min, max	1.2, 2.6	0.6, 2.4	0.2, 4.2	0.3, 3.2	0.3, 1.0	0.2, 0.7	0.3, 1.0	0.2, 1.9
C_{max} (ng/mL, dose-normalised)								
N	7	10	17	24	7	10	17	24
Mean (SD)	5.01 (1.527)	4.04 (1.454)	3.79 (2.599)	5.00 (2.736)	13.80 (4.181)	9.31 (2.421)	8.13 (3.587)	6.96 (3.837)
Median	4.72	3.71	3.13	4.39	14.40	9.40	7.08	6.26
Min, max	3.3, 7.7	1.8, 6.4	1.4, 12.7	1.0, 11.3	6.8, 18.2	5.3, 13.2	3.0, 14.7	1.4, 14.3

Note: Timepoints derived as follows:
Week 4: Study 202 - data used from Day 30
Week 4: Study 203 - data used from 12-hour measurements on Day 1

The dose-normalised Cmax and AUCτ for anagrelide and its active metabolite, BCH24426 are plotted against age in Figure 1, and the clearance and weight normalised clearance of anagrelide and BCH24426 after 4 weeks treatment are plotted against age in Figure 2.

Figure 1: Scatterplot of Cmax and AUCτ of Anagrelide and BCH24426 vs. Age – Pooled Studies 202 & 203 (Safety Population)

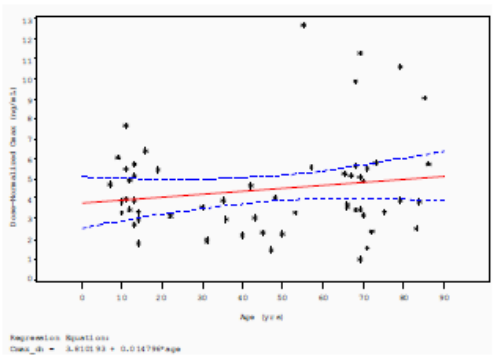
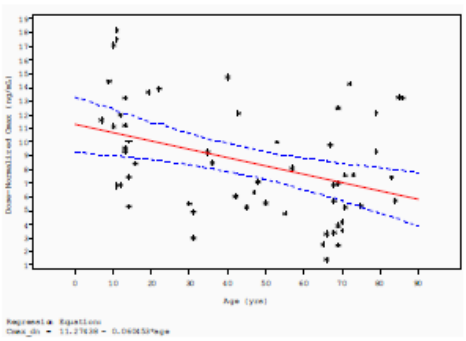
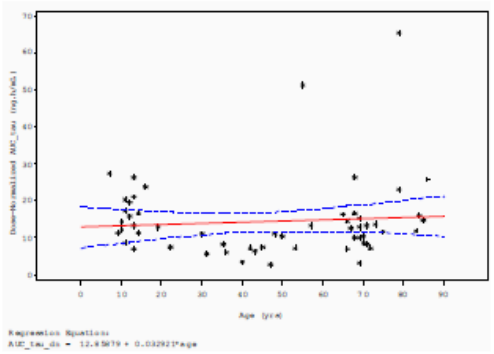
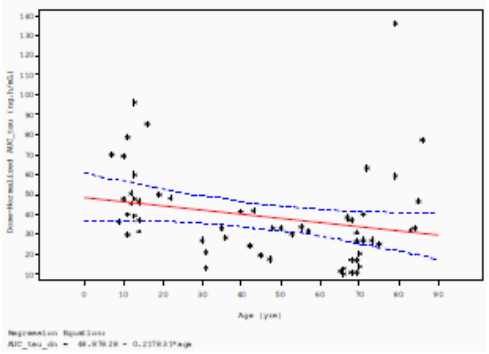
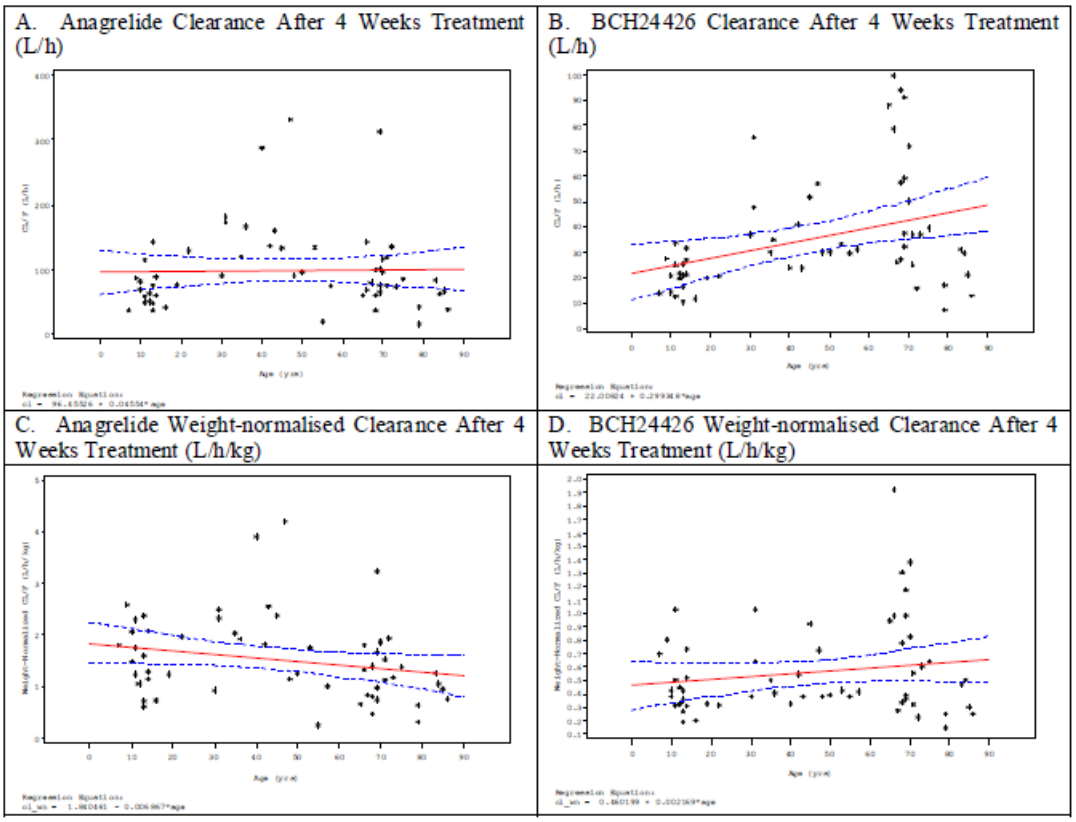
A. Anagrelide Dose-normalised C_{max} (ng/mL)	B. BCH24426 Dose-normalised C_{max} (ng/mL)
	
C. Anagrelide Dose-normalised AUC_{τ} (ng•h/mL)	D. BCH24426 Dose-normalised AUC_{τ} (ng•h/mL)
	

Figure 2: Scatterplot of Clearance and Weight-normalised Clearance of Anagrelide and BCH24426 vs. Age After 4 Weeks Treatment - Pooled Studies 202 & 203 (Safety Population)



2.2.3. Pharmacodynamics

Primary and secondary pharmacology

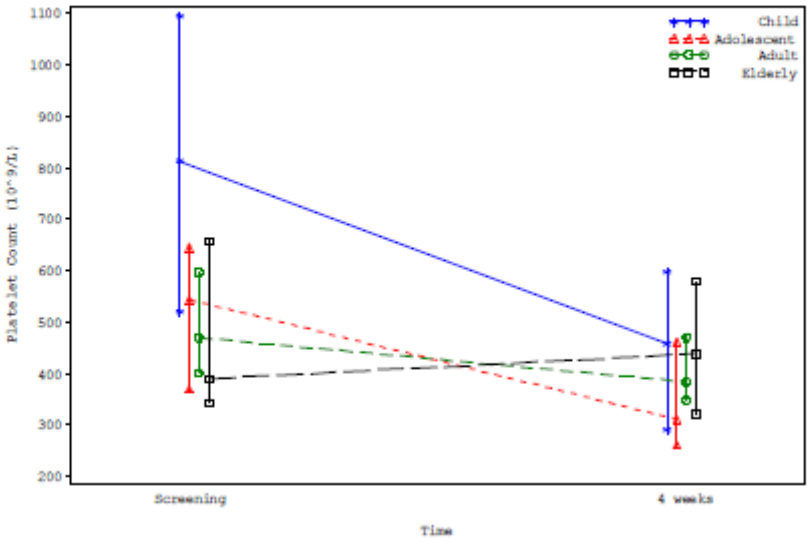
A summary of platelet count at screening and after 4 weeks treatment is presented in Table 4 and Figure 3

Table 5: Summary of Platelet Count at Screening and After 4 Weeks Treatment -Pooled Studies 202 & 203 (Safety population)

Statistic	Child (N=8)	Adolescent (N=10)	Adult (N=17)	Elderly (N=24)
Platelet count (10^9/L) at Screening				
Mean (SD)	779.9 (357.91)	525.1 (195.77)	539.5 (208.82)	512.8 (258.62)
Median	813.5	544.0	470.0	390.0
Min, max	173, 1208	225, 894	262, 1061	208, 1220
Platelet count (10^9/L) at Week 4				
Mean (SD)	475.0 (237.05)	380.7 (161.42)	424.9 (154.29)	470.7 (223.30)
Median	458.0	311.5	384.0	439.0
Min, max	186, 921	238, 738	161, 730	125, 1183

Note: Timepoints derived as follows:
Screening: Studies 202 and 203 - data used from Screening visit
Week 4: Study 202 - data used from Day 30
Week 4: Study 203 - data used from 12-hour measurements on Day 1

Figure 3: Summary of median platelet count (with interquartile range) at screening and after 4 weeks treatment – pooled studies 202 and 203 (safety population)



2.2.4. Discussion on clinical pharmacology

The data for platelet counts were pooled from the two phase II clinical SPD422-202 and SPD422-203 studies in order to compare them across different age groups. However, pediatric patients were only enrolled in Study SPD422-202 and methodological differences in PD assessments in the two studies do not allow appropriate comparisons. In particular, patients in Study SPD422-202 received the treatment for 4 weeks were at an anagrelide PK steady-state at the time of sampling whereas patients in study SPD422-203 received the treatment for 1 day. Therefore the 'baseline' measure was taken within 5 minutes prior to dosing on PK sampling day and shows the effects of regular anagrelide administration in patients receiving a stable anagrelide dose. The 'week 4' timepoint for patients from Study SPD422-203 corresponds to 12 hours post-dose on the PK sampling day. Therefore, neither 'baseline' nor 'week 4' platelet counts could be compared between different age groups.

In addition to assessments of baseline platelet count and platelet count changes following anagrelide dose adjustments, the relationship of anagrelide and its active metabolite BCH24426 plasma levels with the vasodilatory and positive inotropic effects observed with the drug were explored in the Study SPD422-202 and assessed in 2005. In the Study SPD422-202, significant positive correlations were identified between maximal increases in heart rate and corresponding maximum plasma concentrations of anagrelide and the metabolite BCH24426. However, these relationships were no longer statistically significant when the data were analyzed by subject age group.

2.2.5. Conclusions on clinical pharmacology

The paediatric patients enrolled in the studies had a prior exposure to Xagrid and therefore the relevance of 'baseline' data in assessing the effect of Xagrid on platelet count is of concern. Therefore, the pooled analysis of the data from studies SPD422-202 and SPD422-203 was not considered robust and does not allow for an accurate and reliable assessment of PK and PD data in children. Nevertheless, the CHMP agreed to include the following wording in section 5.2 of the SmPC on the exposure of anagrelide in children:

Pharmacokinetic data from exposed fasting children and adolescents (age range 7 - 16 years) with essential thrombocythaemia indicate that dose normalised exposure, Cmax and AUC, of anagrelide tended to be higher in children/adolescents compared with adults. There was also a trend to higher dose-normalised exposure to the active metabolite.

2.3. Clinical efficacy

2.3.1. Main studies

Study SPD422-404

Multicentre paediatric observational study in Essential Thrombocythaemia (ET), evaluating drug utilisation and effects of cytoreductive agents treatment in children 6 to less than 18 years of age

SPD422-405a Pooled Analysis

SPD422-405a was a retrospective analysis of pooled data to evaluate the PK, PD, and safety of anagrelide across Studies SPD422-202 and SPD422-203 for the following age groups; paediatric (6-11 years), adolescent (12-17 years), adult (18-64 years), and elderly (≥ 65 years). Summaries of demography, treatment history, anagrelide dosing, PK parameters (AUC_t, clearance, weight-normalized clearance, C_{max}), platelet count (at the start and end of 4 weeks treatment), exposure, and AEs were presented.

Clinical Study Report **SPD422-202** entitled 'A Phase 2, Open Label, Singlearm, Multi-center Safety, Pharmacokinetic and Pharmacodynamic Study of Anagrelide Hydrochloride in Paediatric and Adult subjects with Thrombocythemia Secondary to Myeloproliferative Disorders' (included in variation EMEA/H/C/480/II/01).

Clinical Study Report **SPD422-203** entitled 'A Phase 2, Open-Label, Multicentre, Pharmacokinetic, Pharmacoydnamic and Safety Study of Anagrelide Hydrocloride in Young (18-50 years) and Elderly (≥ 65 years) Patients with Essential Thrombocythaemia' (included in variation EMEA/H/C/480/II/26).

SPD422-405b Pooled Analysis

Study SPD422-405b was a retrospective pooled analysis which evaluated safety data from subjects with a diagnosis of ET <18 years of age who were treated with anagrelide from completed global studies available in the Shire anagrelide clinical database, excluding Studies SPD422-202 and SPD422-203.

Study 700-014 was an open-label, self-controlled, efficacy and safety study of anagrelide in the treatment of subjects with thombocythaemia who were on anagrelide maintenance therapy (recruited from other studies) or treatment-naïve subjects.

Study 13,970-301 was a long-term, open-label, efficacy and safety study of anagrelide in the treatment of subjects with thombocythaemia who had switched from another therapy or treatment-naïve subjects.

Study 700-999 was an open-label, self-controlled, efficacy and safety study of anagrelide in the treatment of subjects with thombocythaemia who had failed other therapy.

Study 700-012 was included in the 2002 safety assessment but did not include paediatric subjects and does not, therefore, contribute to this analysis.

Methods

Study SPD422-404 Interim Analysis at PIP Completion

SPD422-404 is a multicentre, open-label, non-interventional, observational registry study, conducted to observe disease progression, symptoms and treatment effects on platelet count in children aged 6 to less than 18 years of age with a diagnosis of ET. It is currently ongoing to collect long-term safety and efficacy data. In addition, drug utilization data for anagrelide and other treatments for ET, and the incidence and severity of AEs were described. Treatment was administered according to the usual medical clinical practice of paediatric hematologists and their decisions in treating children. Due to its non-interventional design, this study did not employ any form of randomization, stratification, blinding or control cohorts. Further, there was no established schedule of assessments, and data were only provided if an assessment had occurred as part of routine clinical practice, and at the discretion of the treating physician. This study therefore provides data describing standard treatment of ET in children across Europe.

The clinical study report provided in this application presents a planned interim analysis with a data cut date of 13 Mar 2013 which is the agreed completion date of the PIP.

This study planned to recruit at least 60 ET subjects during the enrolment period up to March 2013 who, according to the treating physician, had ET using the WHO criteria.

Subjects could be enrolled regardless of ET therapy, i.e., they could be:

- Previously treated

- Currently being treated or

- Not receiving ET therapy / treatment-naive.

The primary efficacy endpoint is platelet count (pre-treated, titration and treatment targets). A summary of the platelet count included n, mean, SD, median, minimum, and maximum at each visit. It was anticipated that platelet count data would be collected at frequent intervals to monitor the disease.

SPD422-405a Pooled Analysis

SPD422-405a was a retrospective analysis of pooled data to evaluate the PK, PD, and safety of anagrelide across Studies SPD422-202 and SPD422-203 for the following age groups; paediatric (6-11 years), adolescent (12-17 years), adult (18-64 years), and elderly (≥ 65 years). Summaries of demography, treatment history, anagrelide dosing, PK parameters (AUC_t, clearance, weight-normalized clearance, C_{max}), platelet count (at the start and end of 4 weeks treatment), exposure, and AEs were presented.

SPD422-405b Pooled Analysis

Study SPD422-405b was a retrospective pooled analysis which evaluated safety data from subjects with a diagnosis of ET <18 years of age who were treated with anagrelide from completed global studies available in the Shire anagrelide clinical database, excluding Studies SPD422-202 and SPD422-203.

Study 700-014 was an open-label, self-controlled, efficacy and safety study of anagrelide in the treatment of subjects with thombocythaemia who were on anagrelide maintenance therapy (recruited from other studies) or treatment-naïve subjects.

Study 13,970-301 was a long-term, open-label, efficacy and safety study of anagrelide in the treatment of subjects with thombocythaemia who had switched from another therapy or treatment-naïve subjects.

Study 700-999 was an open-label, self-controlled, efficacy and safety study of anagrelide in the treatment of subjects with thombocythaemia who had failed other therapy.

Study 700-012 was included in the 2002 safety assessment but did not include paediatric subjects and does not, therefore, contribute to this analysis.

Results

Study SPD422-404 Interim Analysis at PIP Completion

Within the planned recruitment target, at least 30 subjects were required to have at least one year's data by the PIP completion date. This interim analysis includes 69 subjects who had been enrolled at the time of the data cut and PIP completion date of March 2013.

Of the 69 subjects included in the study at the time of data cut, approximately one-third of subjects were aged 6-11 years, with the remainder aged 12-17 years. Mean (SD) age was 12.4 (3.26) years. Just over half of subjects (59.4%) were female and the majority (75.4%) was white.

At the time of the data cut for this interim analysis, of the 69 subjects included in the study, 56 subjects (81%) had been observed for more than 1 year. Mean (SD) subject duration in the study was 506.2 (178.01) days. The median duration of observation was 492 days (range: 58, 898 days).

Participant flow

Table 6 shows patient disposition for study SPD422-404.

During the observation period, out of 69 patients,

- 53 were under no treatment or anti-agregant alone of whom 3 switched to cytoreductive therapy (2 to Xagrid, 1 to hydroxycarbamide);

- 14 were under cytoreductive therapy Xagrid® either in combination (3) or as monotherapy (11);

- 5 were under cytoreductive therapy, excluding Xagrid®, either in combination with other treatment of ET or as monotherapy; of these 4 were treated with hydroxycarbamide and 1 with interferon alpha 2A.

Table 6: Subject disposition – Study SPD422-404 (all enrolled subjects)

		No Treatment/ A-A Alone (N=53)	Cytoreductive Therapy (N=19)	XAGRID (N=14)	Total (N=69)
Subjects enrolled	n				69
Subjects with follow-up data	n				56
Ongoing	n (%)	53 (100)	19 (100)	14 (100)	69 (100)
Did not complete study	n (%)	0	0	0	0
Switched cohort					
Switched to cytoreductive therapy	n (%)	3 (5.7)[a]			3 (4.3)
Switched to XAGRID	n (%)	2 (3.8)[b]	0[c]		2 (2.9)
Duration of observation (days)[d]	n	53	19	14	69
	Mean (SD)	487.0 (202.77)	479.8 (128.68)	473.7 (145.92)	506.2 (178.01)
	Median	463.0	465.0	438.0	492.0
	Min, Max	58, 898	164, 682	164, 682	58, 898
Total subject-years observed[e]	Sum	70.7	25.0	18.2	95.6

[a] Number of and percent of subjects in No Treatment/A-A Alone cohort who switched to cytoreductive therapy.
[b] Number of and percent of subjects in No Treatment/A-A Alone cohort who switched to XAGRID.
[c] Number of and percent of subjects taking cytoreductive therapy (not XAGRID) who switched to XAGRID.
[d] Duration of observation = last cohort date – first cohort date + 1. For subjects ongoing in study, the date of the data cut, 13 Mar 2013, is used as the end date for duration of observation.
[e] Subject-years observed=mean duration of observation (in years) x number of subjects.
Note: Subgroups are not independent; subjects starting cytoreductive therapy during the study are included in the No Treatment/A-A Alone cohort up until the time of first dose of cytoreductive therapy. After first dose of cytoreductive therapy, subjects are included in the Cytoreductive Therapy cohort.
A-A=anti-aggregatory; SD=standard deviation.

Conduct of the study

Treatment switching was relatively infrequent during the study. During the observation period, 3 of the 53 subjects (5.7%) in the No Treatment/A-A Alone cohort switched to other cytoreductive therapy of whom 2 subjects (3.8%) switched to anagrelide and 1 subject (1.9%) switched to hydroxycarbamide. No subjects switched from other cytoreductive therapy to anagrelide. Notably, 17 subjects were identified as having taken anagrelide as first-line therapy since diagnosis.

Baseline data

Table 7: Cytoreductive therapies during observation period: frequency and duration (all enrolled subjects)

	Total[a] (N=69) n (%)	Median Dose[b]	Duration (days)[c] Median (min, max)	% of Total Subject-years[d]
None since diagnosis	35 (50.7)			
Any cytoreductive therapy[e] since diagnosis but none during observation period	15 (21.7)			
Any cytoreductive therapy[e] during observation period	19 (27.5)			
1	17 (24.6)			
2	2 (2.9)			
3	0			
4 or more	0			
Anagrelide	14 (20.3)	1.0mg	438 (139, 682)	18.3
Hydroxycarbamide	6 (8.7)	975.0mg	478 (10, 588)	6.7
Interferon alfa	1 (1.4)	7.0mIU	405	1.2

[a] Subjects were counted once per category per treatment group.

[b] The dose most frequently taken is identified for each subject and each therapy.

[c] Duration of medication in days, overlapping periods are counted once, disjoint periods are summed. If the medication was ongoing then the end date was imputed with the last visit date.

[d] % of total subject-years = (Number of subject-years treated / total subject-years observed)*100.

[e] Medications coded using World Health Organisation Drug Dictionary of March 2012 and grouped by a blinded medic review of preferred terms;
Cytoreductive therapies include anagrelide, anagrelide hydrochloride, busulfan, hydroxycarbamide, interferon alfa and interferon alfa-2A;
A-A=anti-aggregatory..

Within the planned recruitment target, at least 30 subjects were required to have at least one year's data by the PIP completion date. This interim analysis included 69 subjects who had been enrolled at the time of the data cut and PIP completion date of March 2013.

Of the 69 subjects included in the study at the time of data cut, approximately one-third of subjects were aged 6-11 years, with the remainder aged 12-17 years. Mean (SD) age was 12.4 (3.26) years. Just over half of subjects (59.4%) were female and the majority (75.4%) was white.

At the time of the data cut for this interim analysis, of the 69 subjects included in the study, 56 subjects (81%) had been observed for more than 1 year. Mean (SD) subject duration in the study was 506.2 (178.01) days. The median duration of observation was 492 days (range: 58, 898 days).

Numbers analysed

Between diagnosis and start of observation, patients received cytoreductive treatment mostly anagrelide and/or hydroxycarbamide. Of 18 patients identified as having taken anagrelide, 14 received it as first cytoreductive treatment. As well, of 18 patients identified as having taken hydroxycarbamide, 16 received it as first cytoreductive treatment. During the observation period, 19 subjects (27.5%) received cytoreductive therapy, of whom 14 subjects were treated with anagrelide at a median dose of 1 mg, and 6 subjects were treated with hydroxycarbamide at a median dose of 975 mg. Note that individual subjects may be counted in more than 1 treatment cohort due to treatment switching.

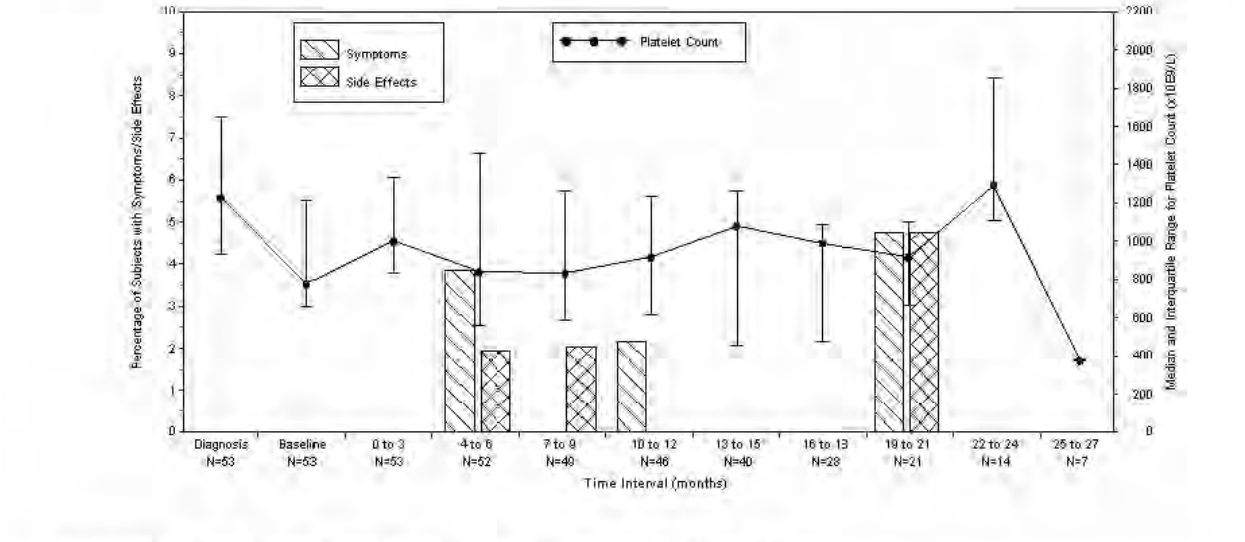
Of the 19 subjects who did not receive cytoreductive ET therapy, 18 subjects received salicylic acid at a median dose of 81.3 mg.

Outcomes and estimation

Platelet counts

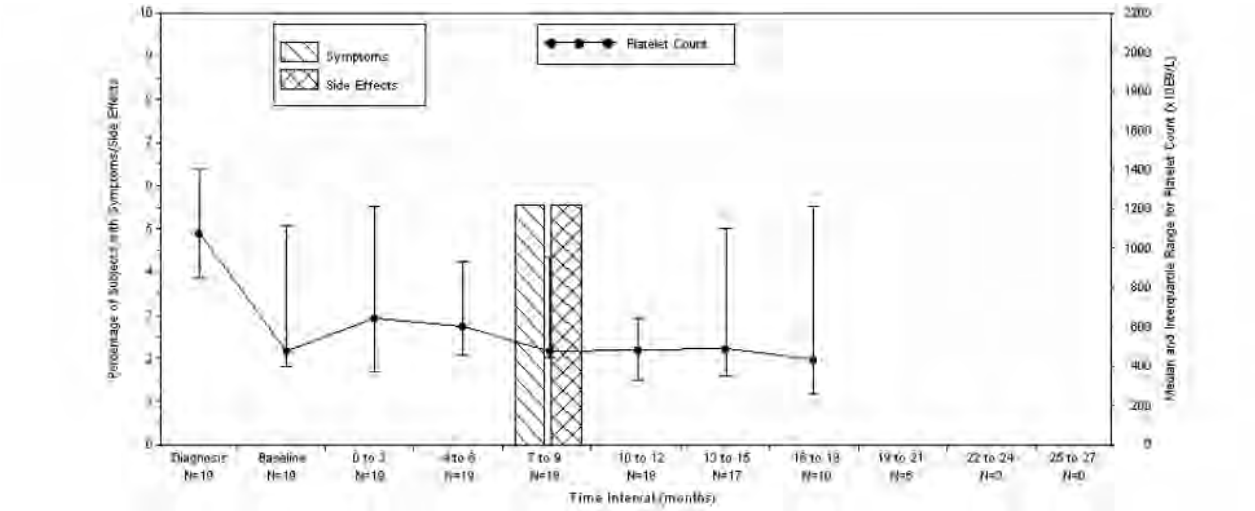
Essential thrombocythaemia symptoms and side effects are plotted against median platelet count for subjects receiving no treatment/A-A alone in Figure 4, cytoreductive therapy in Figure 5, and anagrelide in Figure 6. The overall incidence of symptoms and side effects was low.

Figure 4: Symptoms and side effects versus platelet count (no treatment/A-A Alone[a]) – SPD422-404 Interim results



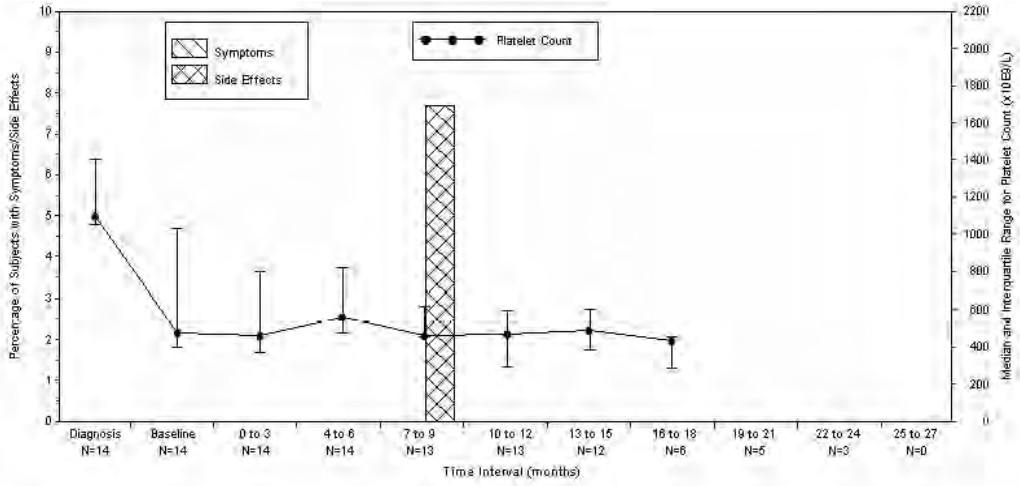
[a]Includes all data whilst subjects are in the No Treatment/A-A Alone cohort.
Proportion of subjects with symptoms or side effects are calculated out of the number of subjects ongoing in the time interval.
The error bars for platelet count represent the first and third quartiles.

Figure 5: Symptoms and side effects versus platelet count (cytoreductive therapy[a]) – SPD422-404 Interim results



[a] Includes all data whilst subjects are in the Cytoreductive Therapy cohort.
Proportion of subjects with symptoms or side effects are calculated out of the number of subjects ongoing in the time interval.
The error bars for platelet count represent the first and third quartiles.

Figure 6: Symptoms and side effects versus platelet count (anagrelide[a]) – SPD422-404 Interim results



[a] Includes all data whilst subjects are in the anagrelide cohort.
Proportion of subjects with symptoms or side effects are calculated out of the number of subjects ongoing in the time interval.
The error bars for platelet count represent the first and third quartiles.

As would be expected, median platelet counts at diagnosis were elevated in all treatment cohorts (1227. 10^9/L in the no treatment/A-A alone cohort, 1077. 10^9/L in the cytoreductive therapy cohort, and 1097. 10^9/L in the anagrelide cohort).

By baseline, median platelet counts had substantially decreased (778. 10^9/L in the no treatment/A-A alone cohort, 477. 10^9/L in the cytoreductive therapy cohort, and 476. 10^9/L in the anagrelide cohort).

Thereafter, platelet counts were maintained for both the cytoreductive therapy and anagrelide cohorts, whereas platelet counts in the no treatment/A-A alone cohort generally remained at elevated levels of around 1000. 10^9/L.

During observation period, reasons for change or dose modification of medication were failure to reach platelet objective.

Analysis performed across trials (pooled analyses and meta-analysis)

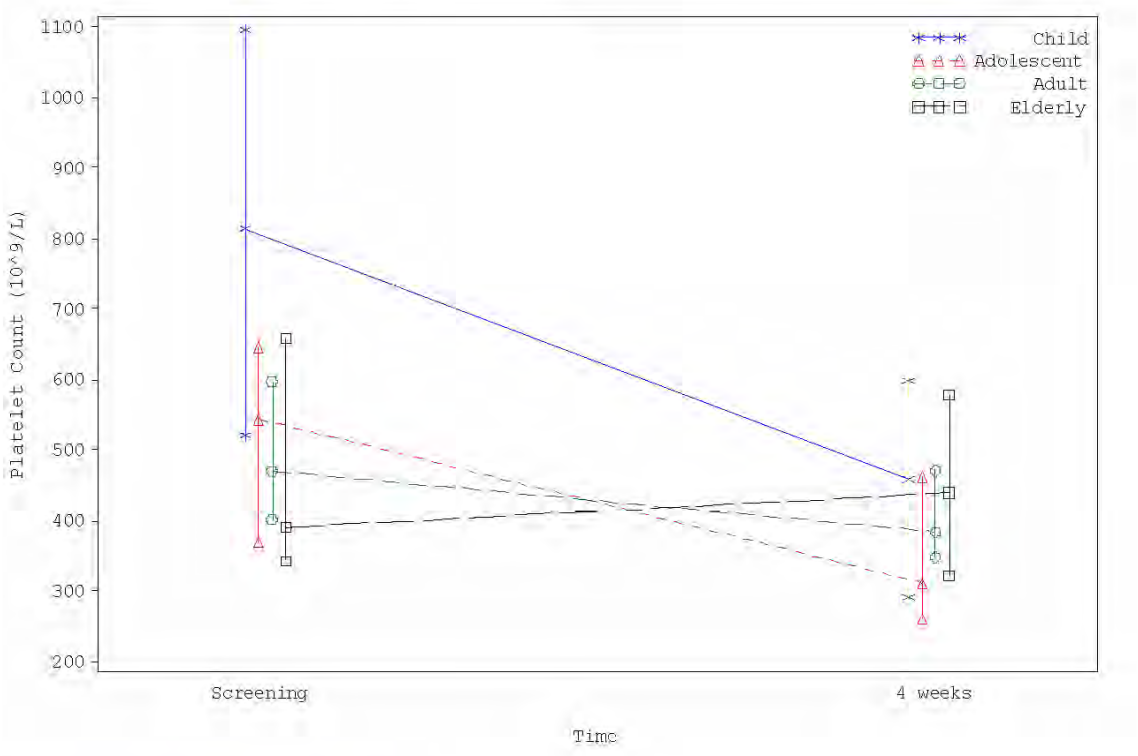
SPD422-405a Pooled Analysis

A total of 59 subjects were included in this pooled analysis from 2 studies: Study SPD422-202 and Study SPD422-203. A summary of platelet count at screening and after 4 weeks treatment is presented Figure 7.

Median platelet count at screening was substantially higher for children (813,5. 10^9/L) than any other age group, ranging from median values of 390. 10^9/L for elderly subjects to 544. 10^9/L for adolescents.

Marked reductions were seen in children and adolescents after 4 weeks of treatment, and median values were below 500. 10^9/L by Week 4 for all age groups.

Figure 7: Summary of median platelet count (with interquartile range) at screening and after 4 weeks treatment – pooled studies SPD422-202 and SPD422-203



SPD422-405b Pooled Analysis

In total, 16 subjects were included in this pooled analysis from 3 studies: Study 700-014, Study13970-301, and Study 700-999. Of these 16, 7 subjects were children (aged 6-11 years) and 9 subjects were

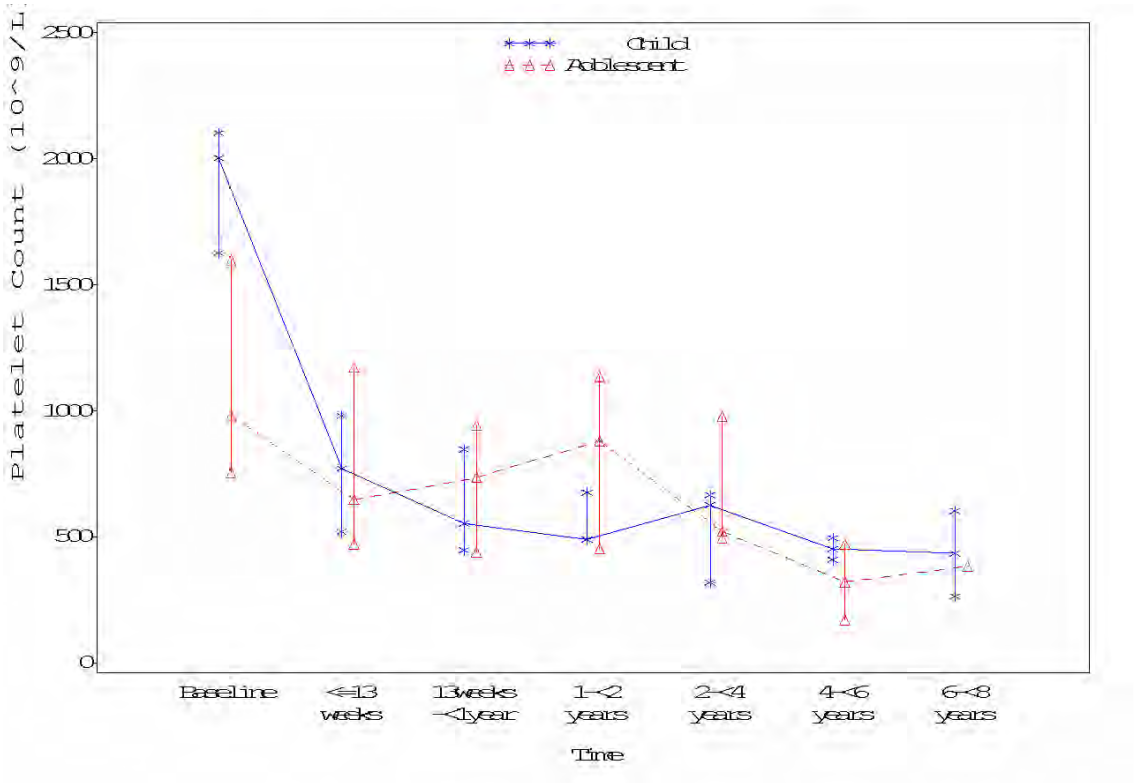
adolescents (aged 12-17 years). There was a slightly greater proportion of females amongst adolescents (6 subjects, 66.7%) compared to children (3 subjects, 42.9%).

The majority of subjects in both groups were White. The majority of subjects were treatment naïve, with just 2 children (28.6%) and 1 adolescent (11.1%) having undergone previous treatment for ET.

The median average total daily dose was 0.87 mg (range; 0.6 to 3.5mg) for children and 3.01 mg (range; 1.1 to 5.6 mg) for adolescents. Anagrelide dosing information was unavailable for 1 child and 1 adolescent.

A summary of platelet count at baseline, ≤13 weeks, 13 weeks to <1 year, 1 to <2 years, 2 to <4 years, 4 to <6 years, and 6 to <8 years for children and adolescents included in the integrated analysis developed in 2002 is presented in Figure 8.

Figure 8: Summary of median platelet count with interquartile range (integrated summary of safety studies) – Study SPD422-405b



Apart from the pharmacodynamic results, this study informs on overall exposure to anagrelide. Five children and 7 adolescents were exposed to anagrelide for more than 6 months (duration of exposure was missing for 2 subjects). Median exposure was higher for children (2.33 years) as compared to adolescents (1.57 years).

2.3.2. Discussion on clinical efficacy

Design and conduct of clinical studies

SPD422-405a study, which pools SPD422-202 and SPD422-203 studies, was designed to extend Pk/PD

information for paediatric patients (demography, treatment history), anagrelide dosing, PK parameters, exposure, and adverse events. As study SPD422-203 did not enrol any child or adolescent, the pooling of both studies did not increase the sample size of the paediatric population. Efficacy data i.e., reduction of platelet count in paediatric patients come exclusively from SPD422-202 study.

The CHMP had major concerns over some methodological issues from the pivotal study SPD422-404. The majority of paediatric patients were already on anagrelide treatment at study entry (an average of 2 years) which limited the clinical data on the starting dose recommendation for paediatric patients. In the retrospective review of patients' records in the study, the total daily starting dose appeared to be lower (0.75 mg to 1.5 mg per day) in paediatric patients, as well as in adult patients (0.5 mg to 2.0 mg per day), than the currently recommended starting dose (2 mg per day as given by 0.5 mg qid or 1 mg bid) for adult patients. However, the study was limited by the number of patients available and a retrospective review of data for starting doses. Median platelet counts were substantially reduced from diagnosis for the duration of the observation period in subjects receiving cytoreductive therapy but remained elevated for subjects who received no treatment or A-A alone, as expected.

Efficacy data and additional analyses

Reductions in platelet counts were seen in children and adolescents after 4 weeks of treatment but it should be noted that previous exposure to anagrelide in all age groups confounds the interpretation of these results. Consequently, SPD422-405a study is unlikely to bring new efficacy information (compared to isolated SPD422-202) related to anagrelide in paediatric patients.

SPD422-405b study, a study designed to evaluate safety, provides confirmatory data on the pharmacodynamic activity of anagrelide in reducing platelet counts in children and adolescents. It was observed that median average total daily dose was lower for children as compared to adolescents.

The reporting of the paediatric data was not satisfactory, giving rise to outstanding issues that were not completely resolved. Response to anagrelide was defined in adults as a decrease in platelet count to ≤600. 10^9/l or a ≥ 50% reduction from baseline and maintenance of the reduction for at least 4 weeks. For paediatric patients, titration to maintain platelet count was performed according to standard adult recommendations. However, a platelet count target or an optimal duration for anagrelide treatment was not predefined and there were no stopping rules based on efficacy concerns. Another issue raised was the concern over compliance to treatment. The CHMP had concerns over the pharmaceutical form (hard capsule) as the capsules cannot be crushed or diluted in a liquid and might not be adapted to children who cannot swallow capsules.

The paediatric population in the observational study enrolled only 14 Xagrid-treated patients which is a very limited size of population. There were a minority of patients that were treatment naive before registration but most had received prior medication i.e. administered between diagnosis and baseline which can confound the data. Most of those who were treated with cytoreductive therapy were given Xagrid or hydroxycarbamide as their initial cytoreductive therapy. Notably, 34 out of 69 (49.3%) patients did receive a cytoreductive therapy including Xagrid from diagnosis to start of observation. 18 subjects were identified as having taken Xagrid as first-line therapy since diagnosis.

Only15 subjects (21.7%) reported any concomitant medication, with most medications reported for 1 subject only; there was no discernible pattern of clinical relevance with regard to the administration of concomitant medications.

2.3.3. Conclusions on the clinical efficacy

The results from the pivotal observational study SPD422-404 supported by the results of the pooled studies SPD422-202 and SPD 422-203 (SPD422-405a) did not provide satisfactory evidence on the benefit of anagrelide treatment in the paediatric population of 6-18 years with ET. Moreover, the threshold for platelet count for starting anagrelide treatment as well as a recommended posology could not be clearly defined from the analyses submitted. There were several methodological issues that raised major concerns which could not be resolved during the procedure. Therefore, the CHMP is of the opinion that the indication for "the reduction of elevated platelet counts in children and adolescents aged 6-17 years with ET who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy" is not supported by the clinical data submitted. However, the CHMP agreed that the information from the paediatric population was relevant to healthcare professionals specialised in treating ET patients and agreed to include the results of the studies in section 4.2 and section 5.1 of the SmPC

2.4. Clinical safety

Introduction

The safety database providing data on the paediatric population on anagrelide comprises of the patients in the clinical studies SPD422-202, SPD422-203, 13970-301, 700-014, 700-999, SPD422-404.

Patient exposure

SPD422-405a

First 30 days of treatment from both original studies were used for the pooled analysis.

Table 8: Overall exposure to anagrelide – pooled studies 202 and 203 (safety population)

	Child (N=8)	Adolescent (N=10)	Adult (N=17)	Elderly (N=24)
<3 months	1 (12.5%)	0	1 (5.9%)	4 (16.7%)
3-6 months	0	0	3 (17.6%)	1 (4.2%)
6-12 months	3 (37.5%)	0	1 (5.9%)	1 (4.2%)
1-2 years	1 (12.5%)	3 (30.0%)	2 (11.8%)	5 (20.8%)
2-5 years	3 (37.5%)	6 (60.0%)	5 (29.4%)	8 (33.3%)
>5 years	0	1 (10.0%)	5 (29.4%)	5 (20.8%)
Exposure (years)				
Mean (SD)	2.00 (1.741)	2.97 (1.403)	3.85 (3.514)	2.80 (2.243)
Median	1.32	2.77	2.98	2.11
Min, max	0.2, 4.9	1.3, 5.1	0.2, 12.0	0.2, 7.0

Note: Percentages are based on the number of subjects in the safety population for each age group.
Duration of exposure based on length of time since first dose of Anagrelide (pre-study if subject not treatment-naïve) to last dose in study.

SPD422-405b

Paediatric subjects available for analysis were treated up to a maximum of 6.7 years.

A summary of overall exposure to anagrelide for children and adolescents included in the integrated analysis developed in 2002 is presented in Table 9, based on length of time since first dose of anagrelide (pre-study if the subject was not treatment-naïve) to last dose in study.

Table 9: Overall exposure to anagrelide (ISS studies) – Study SPD422-405b (safety population)

	Child (N=7)	Adolescent (N=9)
3-6 months	1 (14.3%)	1 (11.1%)
6-12 months	1 (14.3%)	1 (11.1%)
1-2 years	1 (14.3%)	3 (33.3%)
2-5 years	1 (14.3%)	2 (22.2%)
>5 years	2 (28.6%)	1 (11.1%)
Missing	1 (14.3%)	1 (11.1%)
N	6	8
Mean (SD)	3.11 (2.910)	2.28 (1.936)
Median	2.33	1.57
Min, max	0.4, 6.7	0.3, 6.0

Note: Percentages are based on the number of subjects in the safety population for each age group.
Duration of exposure based on length of time since first dose of anagrelide (pre-study if subject not treatment-naïve) to last dose in study.

SPD422-404 Interim Analysis at PIP Completion

Approximately one-third of subjects were aged 6-11 years, with the remainder aged 12-17 years. Mean (SD) age was 12.4 (3.26) years. Just over half of subjects (59.4%) were female and the majority (75.4%) was White.

SPD422-405a

Of the 59 subjects included in the analysis, 8 (13.6%) were children, 10 (16.9%) were adolescents, 17 (28.8%) were adults and 24 (40.7%) were elderly. Subject age ranged from 7 to 86 years.

SPD422-405b

Of the 16 subjects included in the analysis, 7 (43.8%) were children and 9 (56.3%) were adolescents. Subject age ranged from 5 to 17 years. It should be noted that 1 subject aged 5 years was included. Although this subject fell outside the age category for children (6-11 years), the subject was retained in the pooled analysis in order to include all available paediatric data.

There was a slightly greater proportion of females amongst adolescents (6 subjects, 66.7%) as compared to children (3 subjects, 42.9%). The majority of subjects in both groups were White. The majority of subjects were treatment-naïve, with just 2 children (28.6%) and 1 adolescent (11.1%) had undergone previous treatment for ET.

Adverse events

SPD422-404 Interim Analysis at PIP Completion

All AEs reported during the observation period are presented in Table 10 by system organ class and preferred term.

Table 10: Adverse events by system organ class and preferred term (interim CSR) – Study SPD422-404 (all enrolled subjects)

	No Treatment/ A-A Alone (N=53) n (%)	Cytoreductive Therapy (N=19) n (%)	XAGRID (N=14) n (%)	Total (N=69) n (%)
Subjects experiencing any adverse event	12 (22.6)	5 (26.3)	2 (14.3)	16 (23.2)
Blood and lymphatic system disorders	0	1 (5.3)	0	1 (1.4)
Splenomegaly	0	1 (5.3)	0	1 (1.4)
Gastrointestinal disorders	5 (9.4)	1 (5.3)	0	5 (7.2)
Abdominal pain	1 (1.9)	0	0	1 (1.4)
Diarrhoea	1 (1.9)	1 (5.3)	0	2 (2.9)
Gingival disorder	1 (1.9)	0	0	1 (1.4)
Lip blister	1 (1.9)	0	0	1 (1.4)
Nausea	1 (1.9)	0	0	1 (1.4)
Vomiting	1 (1.9)	0	0	1 (1.4)
Infections and infestations	3 (5.7)	2 (10.5)	1 (7.1)	5 (7.2)
Folliculitis	0	1 (5.3)	0	1 (1.4)
Gastroenteritis	1 (1.9)	0	0	1 (1.4)
Laryngitis	1 (1.9)	0	0	1 (1.4)
Oral candidiasis	0	1 (5.3)	1 (7.1)	1 (1.4)
Parasitic gastroenteritis	1 (1.9)	0	0	1 (1.4)
Rash pustular	1 (1.9)	0	0	1 (1.4)

	No Treatment/ A-A Alone (N=53) n (%)	Cytoreductive Therapy (N=19) n (%)	XAGRID (N=14) n (%)	Total (N=69) n (%)
Injury, poisoning and procedural complications	3 (5.7)	0	0	3 (4.3)
Buttock crushing	1 (1.9)	0	0	1 (1.4)
Contusion	1 (1.9)	0	0	1 (1.4)
Joint dislocation	1 (1.9)	0	0	1 (1.4)
Investigations	1 (1.9)	0	0	1 (1.4)
Blood fibrinogen decreased	1 (1.9)	0	0	1 (1.4)
Metabolism and nutrition disorders	2 (3.8)	0	0	2 (2.9)
Decreased appetite	1 (1.9)	0	0	1 (1.4)
Iron deficiency	1 (1.9)	0	0	1 (1.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.9)	0	0	1 (1.4)
Myelofibrosis	1 (1.9)	0	0	1 (1.4)
Nervous system disorders	4 (7.5)	2 (10.5)	1 (7.1)	6 (8.7)
Cerebral venous thrombosis	0	1 (5.3)	0	1 (1.4)
Headache	3 (5.7)	0	0	3 (4.3)
Migraine	0	1 (5.3)	1 (7.1)	1 (1.4)
Paraesthesia	1 (1.9)	0	0	1 (1.4)
Reproductive system and breast disorders	1 (1.9)	3 (15.8)	2 (14.3)	3 (4.3)
Dysmenorrhoea	1 (1.9)	0	0	1 (1.4)
Menorrhagia	0	1 (5.3)	1 (7.1)	1 (1.4)
Menstrual discomfort	0	1 (5.3)	0	1 (1.4)
Ovarian cyst	0	1 (5.3)	1 (7.1)	1 (1.4)
Respiratory, thoracic and mediastinal disorders	1 (1.9)	0	0	1 (1.4)
Oropharyngeal pain	1 (1.9)	0	0	1 (1.4)
Skin and subcutaneous tissue disorders	0	1 (5.3)	0	1 (1.4)
Skin striae	0	1 (5.3)	0	1 (1.4)
Vascular disorders	1 (1.9)	0	0	1 (1.4)
Hypotension	1 (1.9)	0	0	1 (1.4)

Percentages are based on all enrolled subjects.

Adverse events were classified into preferred term using MedDRA version 15.0.

Subjects were counted once per system organ class and preferred term.

These subgroups are not independent; subjects starting cytoreductive therapy during the study were included in the No Treatment/ A-A Alone cohort up until the time of first dose. After first dose of cytoreductive therapy, subjects were included in the Cytoreductive Therapy cohort.

A-A=anti-aggregatory.

Four subjects (5.8%) reported a total of 5 AEs that were assessed by the investigator to be related to ET treatment. One subject reported menorrhagia in the Xagrid (and Cytoreductive Therapy) cohort.

All other ET treatment-related AEs (gingival disorder, nausea, buttock crushing, and decreased appetite) were reported in the No Treatment/A-A Alone cohort.

SPD422-405a

Since SPD422-203 did not include paediatric patients, SPD422-405a safety findings come down to results of SPD422-202. Based on SPD422-202 safety findings, the MAH states that the type of events reported as related to study drug were similar between the paediatric/adolescent (palpitations, headache, nausea, vomiting, abdominal pain, back pain, anorexia, fatigue and muscle cramps) and adolescent/adult (tachycardia, palpitations, headache, dizziness, dyspnoea, nausea, abdominal pain, diarrhoea, oedema peripheral and vascular skin condition) groups.

For SPD422-405 study, adverse events reported within the 30-day window are presented by MedDRA system organ class and preferred term for the pooled studies in Table 11.

Table 11: Adverse events within 30-day window by MedDRA system organ class and preferred term, pooled studies 202 & 203 – Study SPD422-405a (safety population)

	Child (N=8) n (%)	Adolescent (N=10) n (%)	Adult (N=17) n (%)	Elderly (N=24) n (%)
Subjects With at Least One Adverse Event	4 (50.0)	2 (20.0)	4 (23.5)	6 (25.0)
Cardiac Disorders	0	0	0	2 (8.3)
Palpitations	0	0	0	2 (8.3)
Ear and Labyrinth Disorders	0	0	0	1 (4.2)
Tinnitus	0	0	0	1 (4.2)
Gastrointestinal Disorders	1 (12.5)	0	0	0
Toothache	1 (12.5)	0	0	0

	Child (N=8) n (%)	Adolescent (N=10) n (%)	Adult (N=17) n (%)	Elderly (N=24) n (%)
General Disorders and Administration Site Conditions	1 (12.5)	1 (10.0)	0	2 (8.3)
Fatigue	0	1 (10.0)	0	1 (4.2)
Injection site haemorrhage	0	0	0	1 (4.2)
Oedema peripheral	0	1 (10.0)	0	0
Pyrexia	1 (12.5)	0	0	0
Infections and Infestations	2 (25.0)	0	1 (5.9)	1 (4.2)
Cellulitis	0	0	0	1 (4.2)
Nasopharyngitis	0	0	1 (5.9)	0
Pharyngitis viral NOS	1 (12.5)	0	0	0
Viral infection NOS	1 (12.5)	0	0	0
Injury, Poisoning and Procedural Complications	1 (12.5)	0	0	0
Poisoning deliberate	1 (12.5)	0	0	0
Investigations	0	1 (10.0)	0	1 (4.2)
Blood cholesterol increased	0	1 (10.0)	0	0
Heart rate increased	0	0	0	1 (4.2)
Nervous System Disorders	1 (12.5)	1 (10.0)	3 (17.6)	1 (4.2)
Dizziness	0	0	1 (5.9)	0
Headache	1 (12.5)	1 (10.0)	2 (11.8)	0
Memory impairment	0	0	0	1 (4.2)
Psychiatric disorders	0	0	0	1 (4.2)
Anxiety	0	0	0	1 (4.2)
Renal and Urinary Disorders	0	0	0	1 (4.2)
Micturition urgency	0	0	0	1 (4.2)
Urinary incontinence	0	0	0	1 (4.2)
Respiratory, Thoracic and Mediastinal Disorders	2 (25.0)	1 (10.0)	1 (5.9)	0
Epistaxis	1 (12.5)	1 (10.0)	1 (5.9)	0
Rhinorrhoea	1 (12.5)	0	0	0
Skin and Subcutaneous Tissue Disorders	0	0	0	1 (4.2)
Pruritus	0	0	0	1 (4.2)

Note: Percentages are based on the number of subjects in the safety population for each age group.
Adverse events reported from Study 202 are summarised using MedDRA V6.
Adverse events reported from Study 203 are summarised using MedDRA V9.
Windows taken as up to Day 30 for Study 202 and Days -30 to Day 1 for Study 203.

The most common AE reported for the pooled studies was headache, reported by 1 child, 1 adolescent and 2 adults; there were no reports of headache in elderly subjects.

Epistaxis was reported by 3 subjects; 1 child, 1 adolescent, and 1 adult. Epistaxis is an uncommon adverse drug reaction associated with anagrelide.

Palpitations were reported in 2 elderly subjects and fatigue was reported in 1 adolescent and 1 elderly subject.

Palpitations and fatigue are common adverse drug reactions associated with anagrelide. No other AE was reported by more than 1 subject during the 30-day window.

The overall incidence of AEs was higher in children (50%) than with any other age group (20-25%). The events reported in children were toothache, pyrexia, viral pharyngitis, viral infection, deliberate poisoning (inhalation of lighter gases), headache, epistaxis, and rhinorrhoea.

SPD422-405b

Adverse events reported in children and adolescents included in the integrated analysis developed in 2002 are presented by MedDRA system organ class and preferred term for the pooled studies in Table 12.

Table 12: Adverse events by MedDRA system organ class and preferred term, ISS studies – Study SPD422-405b (safety population)

	Child (N=7) n (%)	Adolescent (N=9) n (%)
Subjects With at Least One Adverse Event	4 (57.1)	8 (88.9)
Blood and Lymphatic System Disorders	1 (14.3)	1 (11.1)
Anaemia NOS	1 (14.3)	0
Thalassaemia NOS	0	1 (11.1)
Cardiac Disorders	0	3 (33.3)
Myocardial infarction	0	1 (11.1)
Palpitations	0	2 (22.2)

	Child (N=7) n (%)	Adolescent (N=9) n (%)
Eye Disorders	0	1 (11.1)
Diplopia	0	1 (11.1)
Gastrointestinal Disorders	1 (14.3)	4 (44.4)
Abdominal pain upper	0	1 (11.1)
Diarrhoea NOS	1 (14.3)	0
Nausea	0	2 (22.2)
Vomiting NOS	0	1 (11.1)
General Disorders and Administration Site Conditions	2 (28.6)	4 (44.4)
Chest pain NEC	0	1 (11.1)
Fatigue	2 (28.6)	1 (11.1)
Lethargy	0	1 (11.1)
Mass NOS	0	1 (11.1)
Pyrexia	0	2 (22.2)
Hepato-biliary disorders	0	1 (11.1)
Jaundice NOS	0	1 (11.1)
Infections and Infestations	0	3 (33.3)
Cholangitis NOS	0	1 (11.1)
Sepsis NOS	0	1 (11.1)
Tinea NOS	0	1 (11.1)
Upper respiratory tract infection NOS	0	1 (11.1)
Investigations	1 (14.3)	0
Weight decreased	1 (14.3)	0
Musculoskeletal, connective tissue and bone disorders	0	1 (11.1)
Muscle cramps	0	1 (11.1)
Nervous System Disorders	1 (14.3)	5 (55.6)
Dizziness (exc vertigo)	0	1 (11.1)
Headache NOS	1 (14.3)	4 (44.4)
Insomnia NEC	0	1 (11.1)
Syncope	0	2 (22.2)
Psychiatric disorders	1 (14.3)	1 (11.1)
Depression NEC	1 (14.3)	1 (11.1)

	Child (N=7) n (%)	Adolescent (N=9) n (%)
Respiratory, Thoracic and Mediastinal Disorders	0	2 (22.2)
Bronchitis acute NOS	0	1 (11.1)
Sore throat NOS	0	1 (11.1)
Skin and Subcutaneous Tissue Disorders	1 (14.3)	1 (11.1)
Acne NOS	1 (14.3)	0
Skin hyperpigmentation	0	1 (11.1)
Skin nodule	0	1 (11.1)
Sweating increased	0	1 (11.1)
Vascular Disorders	1 (14.3)	2 (22.2)
Epistaxis	1 (14.3)	1 (11.1)
Haematoma NOS	0	1 (11.1)
Hypertension NOS	0	1 (11.1)

Note: Percentages are based on the number of subjects in the safety population for each age group.
Adverse events are summarized using MedDRA.

The overall incidence of AEs was lower in children (57%) than with adolescents (89%).

The most common AE reported in paediatric subjects included in the integrated analysis were headache (1/7 children, 4/9 adolescents), fatigue (2/7 children, 1/9 adolescent). Palpitations, nausea, pyrexia, syncope, depression NEC, and epistaxis were all reported in 2 subjects. Palpitations and nausea are common adverse drug reactions and are expected, based on the pharmacology of anagrelide. Syncope, depression and epistaxis are listed as uncommon adverse drug reactions. All other AEs were reported in no more than 1 subject.

Serious adverse event / deaths / other significant events

Deaths

There were no deaths in Study SPD422-404 or in the pooled analysis SPD422-405a.

Two subjects of <18 years in the long-term Study 13,970-301, which was included in the pooled analysis SPD422-405b, developed serious AEs (SAEs) leading to death.

Subject 0003 was a 17-year-old white female, weighing 43 kg, with essential thrombocythemia. The date of diagnosis was unknown, but the subject started hydroxyurea therapy in Feb 1992. She had numerous medical conditions including diabetes mellitus, recurrent pulmonary embolism, drug-related seizures and chronic pancreatitis. She had also undergone a splenectomy and was immunosuppressed following liver transplant, secondary to Budd Chiari syndrome. The subject received anagrelide between 18 Mar 1992 and 10 Jun 1996. During this period, she was also taking procardia, cyclosporine, pen V, prednisolone, heparin, insulin and pancrease. The subject died in ICU on 10 Jun 1996 from sepsis, due to enteroccocus faecium, found to be positive in ascitic aspirate. She had multi-organ failure and acute respiratory distress syndrome. The investigator assessed the event to be unrelated to anagrelide treatment.

Subject 3326 was a 17-year-old white male, weighing 43 kg, with essential thrombocythemia. The date of diagnosis was Feb 1996. The subject was treated with hydroxyurea for 3 months, but this failed

to reduce his platelet levels. He presented with recurrent pulmonary emboli and was receiving coumadin. In May 1997 the subject died due to myocardial infarction. It is not known whether the investigator attributed this to anagrelide, but compliance with the drug was apparently very poor. The last platelet level available was in Mar 1997 of 466. 10^9/L. Further information for this subject was unavailable.

Other serious adverse events

There were no other significant AEs reported in either SPD422-405a or SPD422-405b studies.

As for SPD422-404 Interim Analysis at PIP Completion, one subject in the cytoreductive therapy cohort developed a thrombohaemorrhagic event of cerebral venous thrombosis during the observation period. No other thrombohaemorrhagic events were reported during this study. The investigator considered this SAE unrelated to cytoreductive therapy.

Two subjects were determined to have experienced disease progression, of whom 1 was in the No Treatment/A-A Alone cohort (Subject 041-0002, myelofibrosis) and 1 had switched from No Treatment /A-A Alone cohort to the cytoreductive therapy cohort (Subject 031-0001). The latter subject was reported as having iron deficiency while in the No Treatment/A-A Alone cohort and splenomegaly while in cytoreductive therapy cohort. No subjects in the Xagrid cohort experienced disease progression. Neither subject exhibited symptoms at diagnosis, and only 1 exhibited symptoms during the study. Of these subjects, 041-0002 had a platelet count at diagnosis of 1378. 10^9/L.

Four subjects reported any symptom of ET during the observation period. Single subject incidences of splenomegaly, gingival disorder, contusion, paraesthesia, and headache were reported. Events for 3 subjects were reported under the No Treatment/A-A Alone cohort and for 1 subject under the Cytoreductive Therapy cohort.

Laboratory findings

Laboratory parameters abnormalities

There was no report of laboratory parameters abnormalities in SPD422-405a or SPD422-405a studies since laboratory parameters were not collected in these analyses.

As for SPD422-404 Interim Analysis at PIP Completion, no AEs were associated with clinical laboratory abnormalities except 1 non-serious event of blood fibrinogen decreased.

2.4.1. Discussion on clinical safety

In total, the paediatric safety population was very limited with only14 paediatric patients in study SPD422-404 study (4 children/10 adolescents), 18 paediatric patients in study SPD422-405a (8 children/10 adolescents) and 14 paediatric patients in study in SPD422-405b (7 children/9 adolescents). The median overall exposure was shorter in SPD422-404 than SPD422-405a or SPD422-405b studies.

In SPD422-404, 16 out of 59 patients experienced any adverse event related or not to ET treatment. The majority of AEs occurred in the no treatment/A-A alone cohort. Some AEs, which were not cited in the adult population, were reported in paediatric population in system organ class such as injury poisoning, infections and infestations or reproductive system and breast disorders. Drug related adverse reactions like headache, nausea, diarrhoea, which are described in the adult population were also reported in the paediatric population. Palpitations and hypotension were reported in paediatric

patients. Other cardiovascular events like tachycardia, prolonged QT interval, torsades de pointes were not reported. As SPD422-404 results come from an interim analysis, final CSR is expected to gather long term safety data. A warning on the need to monitor and assess cardiac, hepatic and renal functions is included in the SmPC in section 4.4.

The transformation of ET to myelofibrosis or acute myeloid leukemia (AML) was not investigated and no cases were identified in the study population. However, this is a concern especially in children and adolescents if they are treated with anagrelide for a prolonged period of time. Therefore, the SmPC recommends regular monitoring for early signs of progression to AML and myelofibrosis in section 4.4 of the SmPC. Children should be monitored regularly for disease progression according to standard clinical practices, such as physical examination, assessment of relevant disease markers, and bone marrow biopsy. Any abnormalities should be evaluated promptly and appropriate measures taken, which may also include dose reduction, interruption or discontinuation.

The incidence of headache was slightly lower for the pooled studies (6.8% overall) than seen across the programme (approximately 14%). This is likely due to the relatively short observation period encompassed by this analysis.

The results in study SPD422-405a indicated that similar safety profiles were observed between children and adolescents compared to adults and elderly subjects. However, the results are based on an arbitrary cut off in ages in SPD422-202 study (≤15 years versus ≥16 years) and the pooled analysis is based on the the first 30 days of treatment. Therefore, it is not possible to determine conclusively if there are any particular safety concern associated with the administration of anagrelide to children. The SmPC has been updated to reflect the uncertainty in the safety data with the following paragraph in section 4.8:

Paediatric population
48 patients aged 6-17 years (19 children and 29 adolescents) have received anagrelide for up to 6.5 years either in clinical studies or as part of a disease registry (see section 5.1).
The majority of adverse events observed were among those listed in the SmPC. However, safety data are limited and do not allow a meaningful comparison between adult and paediatric patients to be made (see section 4.4).

2.4.2. Conclusions on clinical safety

The estimation of the anagrelide safety in paediatric population is limited by the short duration of treatment, the restricted number of paediatric patients enrolled in the studies and that the safety of anagrelide compared to other cytoreductive therapies may be confounded by prior anagrelide exposure. Therefore, the CHMP is of the opinion that it is not possible to conclude that the safety of anagrelide treatment in children is similar as in adults.

2.4.3. PSUR cycle

The PSUR cycle remains unchanged.

2.5. Risk management plan

The product was approved in 2004, before the implementation of the pharmacovigilance legislation. Thus, the product does not have a risk management plan.

2.6. Update of the Product information

The indication in section 4.1 of the SmPC was not agreed by the CHMP. However, other changes to the SmPC have been revised and sections 4.2, 4.4, 4.8, 5.1 and 5.2 and section 2 and 3 of PL were amended with information on the study results of anagelide in children. Section 4.8 of the SmPC and section 4 of the PL has been reformatted and adverse reactions are presented in order of decreasing seriousness.

The SmPC was updated with information on the paediatric clinical data from the studies submitted. The main relevant changes to the information in relation to the paediatric population are as follows:

Section 4.2 of the SmPC:

[…]

Paediatric population

The safety and efficacy of anagrelide in children has not been established. The experience in children and adolescents is very limited; anagrelide should be used in this patient group with caution. In the absence of specific paediatric guidelines, WHO diagnostic criteria for adult diagnosis of ET are considered to be of relevance to the paediatric population. Diagnostic guidelines for essential thrombocythemia should be followed carefully and diagnosis reassessed periodically in cases of uncertainty, with effort made to distinguish from hereditary or secondary thrombocytosis, which may include genetic analysis and bone marrow biopsy.

Typically cytoreductive therapy is considered in high risk paediatric patients.

Anagrelide treatment should only be initiated when the patient shows signs of disease progression or suffers from thrombosis. If treatment is initiated, the benefits and risks of treatment with anagrelide must be monitored regularly and the need for ongoing treatment evaluated periodically.

Platelet targets are assigned on an individual patient basis by the treating physician.

Discontinuation of treatment should be considered in paediatric patients who do not have a satisfactory treatment response after approximately 3 months.

Currently available data are described in sections 4.4, 4.8, 5.1 and 5.2, but no recommendation on a posology can be made.

Method of Administration

For oral use. The capsules must be swallowed whole. Do not crush or dilute the contents in a liquid.

[…]

Section 5.1 of the SmPC:

[…]

Paediatric population

In an open-label clinical study in 8 children and 10 adolescents (including patients who were anagrelide treatment naïve or who had been receiving anagrelide for up to 5 years pre-study), platelet counts were decreased to controlled levels after 12 weeks of treatment. The average daily dose tended to be higher in adolescents.

In a paediatric registry study, median platelet counts were reduced from diagnosis and maintained for up to 18 months in 14 paediatric ET patients (4 children, 10 adolescents) with anagrelide treatment. In earlier, open-label studies, median platelet count reductions were observed in 7 children and 9 adolescents treated for between 3 months and 6.5 years.

The average total daily dose of anagrelide across all studies in paediatric ET patients was highly variable, but overall the data suggest that adolescents could follow similar starting and maintenance doses to adults and that a lower starting dose of 0.5 mg/day would be more appropriate for children over 6 years (see sections 4.2, 4.4, 4.8, 5.2). In all paediatric patients, careful titration to a patient-specific daily dose is needed. . ~~An open-label clinical study with a 3-month treatment period did not raise any safety concerns for anagrelide in 17 children/adolescent patients with ET (age range 7 - 14 years) compared to 18 adult patients. Earlier during clinical development a limited number (12) of children (age range 5 - 17 years) with essential thrombocythaemia were treated with anagrelide.~~

[…]

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed by QRD and accepted by the CHMP.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Anagrelide has been shown to reduce and maintain platelet counts close to or within the physiological range in paediatric patients with ET. In study SPD422-404 study, median platelet counts had substantially decreased between diagnosis and baseline ($778x10^9$/L in the no treatment/A-A alone cohort, $477x10^9$/L in the cytoreductive therapy cohort, and $476x10^9$/L in the anagrelide cohort). Thereafter, platelet counts were maintained for both the cytoreductive therapy and anagrelide cohorts, whereas platelet counts in the no treatment/A-A alone cohort generally remained at elevated levels of around $1000x10^9$/L.

Uncertainty in the knowledge about the beneficial effects

There are several uncertainties in relation to efficacy. There is uncertainty in the knowledge on the absolute or relative reduction of platelet count that is expected and whether there is a set interval of time that the platelet count should have reduced. For adult patients, anagrelide treatment is titrated to a patient-specific dosing regimen in order to optimise platelet reduction while limiting adverse events. However, no such recommendation that can be made for paediatric patients based on the adult data since there is insufficient evidence to extrapolate the data to paediatric patients. The PK/PD data from Studies SPD422-202 and SPD422-203 are not robust enough determine a starting dose for paediatric patients because of the deficiencies in the methodology employed.

The minimal threshold or range for platelets count in paediatric population has not been defined. Using the same platelet level target for paediatric as for adult patients has not been robustly justified. In addition, there is no optimal regimen of treatment proposed.

The pivotal efficacy study, SPD422-404, is limited to a retrospective non interventional registry with only 14 paediatric patients treated, although the demographic data, medical and ET history and clinical laboratory data were captured retrospectively in the case report form. Many patients had previously received treatment with anagrelide, which could confound the treatment effect of anagrelide and the interpretation of the results.

The SPD422-405b pooled analysis was not designed to measure efficacy and therefore is only informative in terms of exposure and confirmation of pharmacodynamic activity in children and adolescents.

There is also uncertainty on the compliance of treatment for paediatric patients who cannot swallow capsules. There is concern that the pharmaceutical form is not appropriate for young children as it cannot be crushed or diluted in a liquid.

Risks

Unfavourable effects

The paediatric safety study population was representative of the expected ET population where the adult ET population are predominantly women. Across all studies, there was a slightly greater proportion of females among adolescents (60% in SPD422-405a, 67% in SPD422-405b and 70% in SPD422-404) and in the subgroup of children, proportion of females was 50%, 43% and 60% respectively.

A minority of patients (16 / 59) experienced any adverse event related or not to ET treatment in the pivotal SPD-422-404. The majority of AEs occurred in the no treatment/A-A alone cohort.

Treatment switching was relatively infrequent during SPD422-404 study. Of the subjects who were currently receiving cytoreductive therapy, only 1 subject switched from Xagrid to hydroxycarbamide.

There were no unexpected safety concerns raised in the safety population and most ADRs were consistent with the safety adult population described in the SmPC. The ADRs such as headache, tachycardia, palpitations, hypotension and diarrhoea have already been described in the SmPC and they were found to be mild to moderate in severity in the paediatric population. Some AEs, which were not cited in the adult population, were reported in paediatric population in system organ class such as injury poisoning, infections and infestations or reproductive system and breast disorders.

Uncertainty in the knowledge about the unfavourable effects

There is uncertainty in the knowledge of the estimation of anagrelide safety in paediatric population since the number of paediatric patients available in the studies was low, the duration of treatment was short and there was prior anagrelide exposure in patients that entered the study. In addition, there was no comparative safety with other cytoreductive agents and reporting of ADRs was part of routine clinical practice and at the discretion of the treating physician with no scheduled safety assessments.

The transformation of ET to myelofibrosis or acute myeloid leukemia (AML) was not investigated. PSUR 11 (covering the period 14-Sep-2012 to 13-Sep-2013) and the 9th Annual Reassessment Report (submitted on 2-Dec-2013) concluded that the clinical trial experience to date does not suggest that transformation to these disorders is enhanced by treatment with anagrelide, and rates at which these conditions are being reported as adverse events has remained stable. Nonetheless, the risk is appropriately managed with warnings in section 4.4 of the SmPC.

Benefit-Risk Balance

Based on the results of the pivotal trial SPD422-404, the pooled study SPD422-405 and the supportive paediatric data submitted, the benefits of anagrelide in the paediatric population have not been robustly demonstrated. There are remaining uncertainties concerning the safety of anagrelide in the paediatric population which were not sufficiently addressed. Therefore, the CHMP was of the opinion that there was not enough robust clinical data in the studies submitted to support the indication and that the benefit-risk balance for the indication: “children and adolescents aged 6-17 years with ET who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy ” was negative. However, it was agreed that the information on the paediatric clinical results of the studies could be included in the SmPC.

4. Recommendations

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change(s):

Variation accepted		**Type**
C.1.6 a	Addition of a new therapeutic indication or modification of an approved one	II

Update of the SmPC in order to add information on the study results from study SPD422-405 and SPD422-404. As a consequence, update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to update the efficacy and safety information of anagrelide in the paediatric population. A warning on the risk of progression to AML and myelofibrosis and monitoring of signs and symptoms of disease progression have also been highlighted. The Package Leaflet is updated accordingly.

Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.0.

The requested variation proposed amendments to the SmPC and the Package Leaflet.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0325/2013 of 19 December 2013 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Update of the SmPC in order to add information on the study results from study SPD422-405 and SPD422-404. As a consequence, update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to update the efficacy and safety information of anagrelide in the paediatric population. A warning on the risk of progression to AML and myelofibrosis and monitoring of signs and symptoms of disease progression have also been highlighted. The Package Leaflet is updated accordingly.

Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.0.

The requested variation proposed amendments to the SmPC and the Package Leaflet.

Summary

Please refer to the Scientific Discussion Xagrid-H-C-480-II-59.