19 December 2018
EMA/47444/2019
Committee for Orphan Medicinal Products

Withdrawal Assessment Report – Orphan Maintenance

Besremi (pegylated proline-interferon alpha-2b)
Treatment of polycythaemia vera
EU/3/11/932 (EMA/OD/055/11)
Sponsor: AOP Orphan Pharmaceuticals AG

Note

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

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Table of contents

1. Product and administrative information

Product	
Active substance	Pegylated proline-interferon alpha-2b
International Non-Proprietary Name	Ropeginterferon alfa-2b
Orphan indication	Treatment of polycythaemia vera
Pharmaceutical form	Solution for injection in pre-filled pen
Route of administration	Subcutaneous use
Pharmaco-therapeutic group (ATC Code)	L03AB15
Sponsor's details:	AOP Orphan Pharmaceuticals AG Wilheminenstrasse 91/ II f 1160 Wien Austria
Orphan medicinal product designation procedural history	
Sponsor/applicant	AOP Orphan Pharmaceuticals AG
COMP opinion date	7 October 2011
EC decision date	9 December 2011
EC registration number	EU/3/11/932
Marketing authorisation	
Rapporteur / co-Rapporteur	H. Enzmann, A. Moreau
Applicant	AOP Orphan Pharmaceuticals AG
Application submission date	2 February 2017
Procedure start date	23 February 2017
Procedure number	EMA/H/C/004128
Invented name	Besremi
Therapeutic indication	Besremi is indicated in adults for the treatment of polycythaemia vera without symptomatic splenomegaly. Further information on Besremi can be found in the European public assessment report (EPAR) on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/besremi
CHMP opinion date	13 December 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	F. Naumann-Winter, K. Penttila
Sponsor's report submission date	25 May 2018
COMP discussion and adoption of list of questions	6-8 November 2018
Oral explanation	5 December 2018
Sponsor's removal request	18 December 2018

Following communication of the outcome of the discussion, the sponsor fomally requested the withdrawal of the orphan designation on 18 December 2018, prior to final opinion.

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2011 was based on the following grounds:

- polycythaemia vera (hereinafter referred to as "the condition") was estimated to be affecting approximately 3 in 10,000 persons in the European Union, at the time the application was made;
- the condition is life-threatening and seriously debilitating due to thromboembolic and haemorrhagic events, progression to myelofibrosis and leukaemogenic transformation;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that pegylated proline-interferon alpha-2b may be of significant benefit to those affected by the condition. This appears justified with regards to a clinically relevant advantage based on the potential to reduce pathological JAK2 positive clones which was supported by preliminary clinical data. Moreover, the product has potential to improve safety aspects compared to the current treatments, based on the expected lack of neoplastic potential vis a vis the existing authorised treatments.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Polycythemia vera (PV) is currently classified by the WHO classification system under myeloproliferative neoplasms. Diagnosis requires the presence of a *JAK2* mutation, in addition to documentation of increased hemoglobin/hematocrit (>16.5 g/dl 49% for males and >16 g/dl 48% for females) (Arber et al. Blood. 2016 May 19;127(20):2391-405). Bone marrow morphologic assessment is encouraged. Clinical features in PV include mild-to-moderate degree of splenomegaly, mild-to-moderate degree of constitutional symptoms, including fatigue and pruritus, symptoms of hyperviscosity, leukocytosis, thrombocytosis, microvascular symptoms (e.g., headaches, lightheadedness, visual disturbances, atypical chest pain, erythromelalgia, paresthesia), thrombotic and bleeding complications, and risk of leukemic transformation or fibrotic progression (Tefferi et al, Blood Cancer J. 2018 Jan; 8(1): 3.).

The proposed therapeutic indication in the MAA is "Treatment of polycythaemia vera in adults without symptomatic splenomegaly". The proposed therapeutic indication falls entirely within the designated orphan condition which is broadly worded as "treatment of polycythemia vera".

Intention to diagnose, prevent or treat

Based on the positive CHMP assessment, the intention to treat the condition is justified.

Chronically debilitating and/or life-threatening nature

The applicant has not identified any change in the seriousness of the proposed condition. Polycythemia vera is still considered a severely debilitating and life-threatening condition due to thromboembolic and haemorrhagic events, progression to myelofibrosis and leukaemic transformation as well as a significantly reduced relative survival compared to the general population.

It can be acknowledged that the condition is chronically debilitating and life-threatening due to splenomegaly, constitutional symptoms such as fatigue and pruritus, symptoms of hyperviscosity, leukocytosis, thrombocytosis, microvascular symptoms (e.g. headaches, lightheadedness, visual disturbances, atypical chest pain, erythromelalgia, paresthesia), thrombotic and bleeding complications, and risk of leukemic transformation or fibrotic progression (Tefferi et al, Blood Cancer J. 2018 Jan; 8(1): 3.).

Number of people affected or at risk

The sponsor has not identified a change in the prevalence of the proposed condition and proposes, after a review of relevant literature, a 3 per 10,000 estimate.

This is based on literature (e.g. Brochnann et al, Clin Epidemiol 9: 141–150 and the orphanet report of June 2017) and cancer registries from the Nordic countries. The sponsor argues that the incidence of the disease has remained stable over long period of times in Sweden, (between 1970 and 2015).

The conclusion can be considered acceptable. Indeed, NORDCAN (accessed 30/10/2018) gives a combined full-point prevalence figure for all myeloproliferative disorders – thereby also including ET and PMF - of approximately 4.5/10,000 in 2015 (4.1 for males, 4.8 for females). This is in line with the conclusion of the applicant which was considered acceptable.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

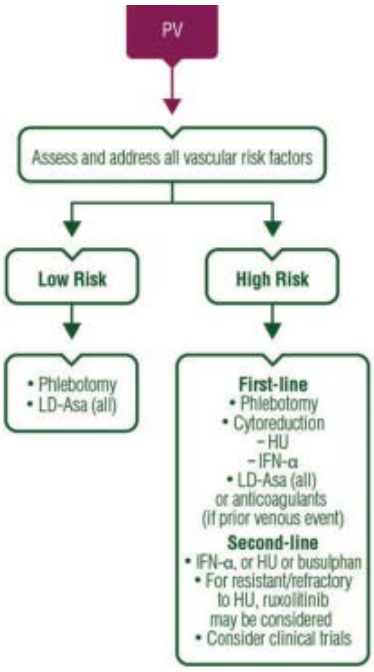
Existing methods

At the time of granting of the orphan designation in 2011, hydroxyurea and busulfan (and pipobroman) had been approved as first line treatment of PV. Since then, Jakavi (ruxolitinib) was authorised as second line treatment of PV in 2015.

The European Society for Medical Oncology (ESMO) has published guidelines on Philadelphia Chromosome-Negative Chronic Myeloproliferative Neoplasms (Vannucchi et al. Ann Oncol (2015) 26 (suppl 5): v85-v99). As per these guidelines, the therapeutic algorithm for high risk patients (>60 years and/or with a history of a vascular event) includes IFN-α (off label) or hydroxyurea as cytoreductive treatment as well as anticoagulation therapy. For second line, IFN-α, HU, ruxolitinib, or participation in trials are discussed.

Moreover, with reference to the revised management recommendations from European Leukemia Net (Barbui et al, 2018 Leukaemia 32, 1057-1069), cytoreduction is strongly recommended in high-risk cases, i.e., older than 60 years, or those with a previous thrombotic event. Treatment with either hydroxyurea or rIFNα is the first-line cytoreductive therapy at any age, the former with a cautious approach in young patients.

Figure 1. adopted from the 2015 ESMO guidelines



Significant benefit

The applicant argues a clinically relevant advantage versus hydroxyurea based on improved efficacy and improved safety claims.

Improved efficacy is argued on the basis of the extension study at 24 months. The following points are reiterated:

- Complete haematological response: 70.5% vs 49.3% (RR 1.42 [1.09 to 1.87]; p=0.0101)
- Complete haematological response & improvement in disease burden: 49.5% vs 36.6% (RR 1.34 [0.93 to 1.92]; p=0.1183)
- Maintenance of haematological response: 43.2% vs 18.4% (RR 2.33, 95% CI 1.38 to 3.93; p=0.0015)
- Trend analysis for the haematological response: ropegIFN alfa-2b showed an improvement in the slopes (positive slope using log-binomial regression: Mean, 0.013; 95% CI, 0.000 to 0.025) and response rate ratio estimates (calculation of response ratios (RR): Mean, 1.039; 95% CI, 1.000 to 1.078, p=0.0015) while control treated patients showed a statistical significant decrease in haematological response rate (negative slope and a RR of 1.017 (0.991 to 1.044), p=0.2079)
- Molecular Response: 69.2% vs 28.6% (RR 2.13 [1.26 to 3.59]; p=0.0046)
- Decrease in mean JAK2V617F allelic burden: 18.2% vs 34.3% (p<0.01)
- JAK2V617 change from baseline: -24.4% vs -10.4% (p<0.01)

The sponsor also includes an argument of improved safety, but this is not quantified nor examined in the context of the broader safety profile. It is argued that the overall safety profile was consistent with class effects of other interferons used (interferon alfa-2a and 2b), and that during AOP's clinical development, no leukaemogenic transformations have been observed in ropegIFN alfa-2b treated patients, whereas two acute leukaemia were observed in the control arm (i.e. HU-treated patients). The Committee considered that an improved safety argument would require further elaboration.

Moreover, the other arguments discussed above have to be interpreted with caution taking into consideration that to establish non-inferiority, post-hoc modifications were introduced in the primary endpoint and non-inferiority margin. It was also pointed out that a non-inferiority conclusion by itself would not suffice to justify significant benefit.

A list of issues was raised to the applicant.

4. COMP list of issues

Significant benefit

Significant benefit is argued on the basis of improved efficacy and safety versus hydroxyurea. The sponsor is requested to further elaborate on the issue taking into consideration the following points:

- Provide a discussion versus all authorised counterparts, indicated for the updated indication as discussed with the CHMP;
- Further elaborate on the issue of improved efficacy versus hydroxyurea, taking into consideration that to establish non-inferiority, post-hoc modifications were introduced in the primary endpoint and non-inferiority margin;
- Further elaborate on the argument of improved safety, in the context of the broader safety profile of the proposed product and the comparator(s);