Innovation Observatory

NHS National Institute for Health Research

HEALTH TECHNOLOGY BRIEFING FEBRUARY 2019

Ropeginterferon alfa-2b for polycythaemia vera without symptomatic splenomegaly

NIHRIO ID	7399	**NICE ID**	10140
Developer/Company	AOP Orphan Pharmaceuticals AG	**UKPS ID**	N/A

Licensing and market availability plans	A positive CHMP opinion was received in December 2018.

SUMMARY

Ropeginterferon alfa-2b for injection is under development for the treatment of polycythaemia vera (PV), a rare blood disease in which the body makes too many red blood cells. The extra red blood cells make the blood thicker than normal and as a result, blood clots can form more easily. These clots may block blood flow through arteries and veins, which can cause a heart attack or stroke. Thicker blood also does not flow as quickly and may prevent organs from getting enough oxygen. A mutation, or change, in a gene called *JAK2* is the major cause of PV. This gene makes a protein that helps the body produce blood cells. PV develops slowly and may not cause symptoms for years. PV has no cure, but treatments can help control the disease and its complications.

Ropeginterferon alfa-2b belongs to the group 'interferons'. Interferons are natural substances produced by the body to help it fight against attacks. The exact way alpha interferons work is not fully understood, but are thought to modify how the immune system works by targeting blood cells produced by the *JAK2 gene*. Ropeginterferon alfa-2b is expected to work in PV by blocking the production of blood cells in the bone marrow. If licensed, ropeginterferon alfa-2b may offer an additional treatment option for patients with PV who currently have few effective therapies available.

PROPOSED INDICATION

Polycythaemia vera (PV) in adults without symptomatic splenomegaly[a]

TECHNOLOGY

DESCRIPTION

Ropeginterferon alfa-2b (Besremi) is a next-generation, mono-pegylated interferon (IFN) α-2b isoform. Polycythemia vera (PV) is characterised by the acquisition of the *JAK2*^{V617F} mutation. Ropeginterferon has a potent targeted activity against *JAK2*-mutant cells and is able to drastically reduce the proportion of malignant progenitors. [1, 2] The mechanism of action of IFNα in myeloproliferative neoplasms is not clearly elucidated, but several studies confirmed a targeted effect against *JAK2*^{V617F} mutant clones in both patient and animal models. [3,4] Ropeginterferon alfa-2b inhibits the proliferation of hematopoietic and bone marrow fibroblast progenitor cells and antagonises the action of growth factors and other cytokines involved in the development of myelofibrosis. [5]

Ropeginterferon alfa-2b intended for the treatment of polycythaemia vera (PV) without symptomatic splenomegaly will be available as a solution for injection (250 microgram/0.5 ml and 500 microgram /0.5 ml).[5] Ropeginterferon alfa-2b is administered once every 2 weeks or until the patient status allows a dose reduction and/or monthly dosing. Dosing will be dependent on patient factors, haematologic and molecular response.[a]

INNOVATION AND/OR ADVANTAGES

IFNs have been shown to yield high rates of haematologic and molecular response in PV with limited toxicity, and could even eliminate the JAK2 mutated clone in selected cases.[6] Ropeginterferon alfa-2b has been shown to induce complete haematologic and high clinical response rates with good tolerability, as well as high molecular response rates and disease modifying capabilities, which may result in a delay of disease progression.[7]

A unique feature of ropeginterferon alfa-2b is a prolonged half-life in human serum, allowing the dosing interval to be significantly extended, i.e. dosing once every two–four weeks.[1, 2] Available as a pen for patient self-administration, this treatment schedule is expected to lead to overall better safety, tolerability and adherence compared to conventional pegylated IFNs. If licensed, ropeginterferon alfa-2b will be the first INF indicated for the treatment of a myeloproliferative neoplasm.[7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Ropeginterferon alfa-2b does not currently have Marketing Authorisation in the EU/UK for any indication.

Ropeginterferon alfa-2b is in phase II clinical development for Chronic Myeloid Leukaemia.[8]

[a] Information provided by AOP Orphan Pharmaceuticals AG

PATIENT GROUP

DISEASE BACKGROUND

Polycythaemia vera (PV) is currently classified by the World Health Organization classification system under the major category of myeloproliferative neoplasms (MPN).[9] Although the WHO MPN category includes seven subcategories, the term 'MPN' usually refers to the three *JAK2* mutation-enriched clinicopathologic entities: PV, essential thrombocythemia (ET) and primary myelofibrosis (PMF).[10] PV and its sister diseases constitute stem cell-derived clonal myeloproliferation that are characterised by three mutually-exclusive 'driver' mutations: *JAK2*, *CALR*, and *MPL*. The most frequent MPN-associated *JAK2* mutation is the exon 14 *JAK2*^{V617F}, which is responsible for almost all the *JAK2* mutations in ET and PMF, and 97% of those seen in PV.[11,12,13,20]

The disease is characterised by bone marrow that produces too many red blood cells. Patients may also have elevated levels of white blood cells and platelets. The key clinical consequence of PV is the risk of blood clots or bleeding. Other significant disease-related symptoms include headaches, microvascular complications, and pruritus. Patients with PV have the potential to develop more advanced chronic blood diseases, such as myelofibrosis or even acute leukaemia. PV can lead to fatal complications in some cases.[14] PV typically develops in adulthood, around age 60 years, although in rare cases it occurs in children and young adults.[15] Patients with PV can have a pronounced symptom burden that negatively impacts their quality of life.[16]

CLINICAL NEED AND BURDEN OF DISEASE

PV is a rare condition, with registry-based studies from the EU suggesting an incidence of between 0.6 and 2.8 per 100,000 per year, while The Health Improvement Network (THIN) database estimates a UK prevalence of 6.05 per 100,000.[17] If these prevalence figures are applied to the mid-year 2017 population estimate of 66 million, there are approximately 3,993 individuals with PV in the UK.[18]

According to HES data for England, there were 11,571 admissions in 2017-18 for 'polycythaemia vera' (ICD-10 D45) resulting in 11,627 finished consultant episodes (FCEs) and 592 FCE bed days.[19] Recently reported mature survival data have confirmed favorable prognosis in PV, with an estimated median survival of 24 years in patients younger than age 60 years old.[20]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Community-based oncologists often take a leading role in managing patients with PV, and optimal care requires up-to-date knowledge of management strategies, treatment guidelines, and approved therapies.[21]

The aims of treatment of PV as noted by The British Society for Haematology are to:[22]

- Reduce the risk of thrombosis and haemorrhage;
- Minimise the risk of transformation to acute leukaemia and myelofibrosis;
- Manage complications which may occur including thrombosis, haemorrhage and pruritus; and
- Manage pregnancy (if applicable)

CURRENT TREATMENT OPTIONS

- The recommended management of all people with PV in secondary care by NICE includes:[23]
  - Venesection to maintain the haematocrit at less than 0.45.
  - Prescription of aspirin 75 mg daily (unless this is contraindicated).

- In addition, pharmacological cytoreductive therapy is recommended for people at high risk of thrombosis (people over the age of 60 years, or those with any history of thrombosis). The first-line drug is usually hydroxycarbamide, with interferon alfa or ruxolitinib as possible alternatives where hydroxycarbamide is contraindicated, not tolerated, or ineffective.

- Pharmacological cytoreductive therapy may also be considered if:
  - The platelet count is abnormally high.
  - There is evidence of disease progression, such as weight loss or night sweats.
  - Splenomegaly progresses or becomes symptomatic.
  - The person is poorly tolerant of venesection.

PLACE OF TECHNOLOGY

If licensed, ropeginterferon alfa-2b may offer an additional first line treatment option for patients with PV without symptomatic splenomegaly requiring cytoreductive treatment who currently have few effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	PROUD-PV, NCT01949805, EudraCT 2012-005259-18; ropeginterferon alfa-2b vs hydroxyurea (HU); phase III	CONTI-PV, NCT02218047, EudraCT 2014-001357-17; ropeginterferon alfa-2b vs best available therapy (BAT); phase IIIb extension
Sponsor	AOP Orphan Pharmaceuticals AG	AOP Orphan Pharmaceuticals AG
Status	Published	Ongoing
Source of Information	Publication[24], trial registry[25], manufacturer	Trial registry[26], manufacturer
Location	EU (not UK), Russia	EU (not UK), Russia
Design	Randomised, open-label, active-controlled, parallel arm	Randomised, open-label
Participants	n=257; 18 yrs or older, diagnosed with PV according to WHO2008 criteria; either naïve to cytoreduction or HU pre-treated	n=171; 18 yrs and older, who completed the 12 mos ropeginterferon alfa-2b treatment or control treatment in the PROUD-PV study
Schedule	Pts randomised to active comparator (HU) or experimental (ropeginterferon alfa-2b) arms: • **Active comparator**: HU, administered orally at the starting dose of 500 mg daily dose, titration allows doses up 3,000 mg to for up to 12 months of treatment	Pts allocated to active comparator (BAT) or experimental (ropeginterferon alfa-2b) arms: • **Active comparator**: The BAT arm received standard first line treatment for treatment of PV disease, as per investigator's discretion

	• **Experimental**: ropeginterferon alfa-2b: administered, subcutaneously (s.c.) at the starting dose of 100 µg (up to 500 µg) every 2 weeks for up to 12 months of treatment	• **Experimental**: Dosing scheme achieving optimal disease response in the individual patients, as determined in the PROUD-PV study- administered every two, three or four weeks until the end of the study Subjects were to continue to receive the individualized dosage delivering the optimal disease response (haematocrit [Hct] <45%, platelets [PLTs] <400 x 10^9/L and leukocytes [WBCs] <10 x 10^9/L), as determined in the PROUD-PV study, preferably at the level of target blood values
Follow-up	Active treatment 12 mos; safety follow-up: 28 days after the end of treatment (EOT)	Active treatment: interim analysis for 3 year data available; study planned to be ongoing for up to 5 yrs
Primary Outcomes	*Primary efficacy endpoint:* Disease response rate at 12 months: • Composite endpoint (complete haematological response + normal spleen size) was defined as the rate of patients with a complete haematological response (haematocrit < 45% without phlebotomy [at least 3 months since last phlebotomy], platelets < 400 x 10^9/L and leukocytes < 10 x 10^9/L) and a spleen normality (longitudinal spleen length ≤12 cm for females and ≤13 cm for males).	*Primary efficacy endpoint:* The main efficacy evaluation criterion was to be disease response defined as (1): • Hct<45% without phlebotomy (at least 3 months since the last phlebotomy), • PLTs<400 x 10^9/L, • WBCs<10 x 10^9/L, and • normal spleen size. and (2) as: • Hct<45% without phlebotomy, • PLTs < 400 x 10^9/L, • WBCs < 10 x 10^9/L, • resolution and/or clinically improvement of disease-related signs (clinically significant splenomegaly) and disease-related symptoms (microvascular disturbances, pruritus, headache).
Secondary Outcomes	*Key secondary endpoint:* Disease response rate at 12 months (=complete haematological response only, without normal spleen size). *Other prespecified secondary endpoints were:* • Disease response rates at 3 months and 9 months. • time to first disease response. • disease response duration. • number of phlebotomies performed (per protocol, a	*Secondary efficacy endpoints:* • Change in haematological parameters, Hct, WBCs, PLTs and red blood cells (RBCs), from baseline over time up to last patient visit. • Change in spleen size from baseline over time up to last patient visit, including change in clinical assessment of asymptomatic to symptomatic /progressive splenomegaly.

	phlebotomy was performed any time the patient's Hct was higher than 45%) • Hct-, leukocytes-, platelet- and spleen size-change from baseline to last patient visit. • disease-related symptoms (microvascular disturbances. pruritus, headache). • molecular response as measured with change of JAK2V617F allelic burden over time. • Quality of Life (EQ-5D).	• Maintenance rate of disease response at assessment visits. • Duration of response maintenance. • Time to disease response. • Progression free time. • Phlebotomy need. • Change of disease related signs and disease-related symptoms (microvascular disturbances, pruritus, headache) • Change in QoL (EQ-5D-3L) from baseline over time up to last patient visit. • Change in JAK2V617F allelic burden and other molecular and genetic abnormalities from baseline over time up to last patient visit. • Molecular response *Safety endpoints (safety evaluation):* • Incidence, causality and intensity of adverse events (AEs) according to common terminology criteria for adverse events (CTCAE 4.0). • Events leading to dose reduction or permanent treatment discontinuation. Adverse events of special interest (AESI).
Key Results	*Primary endpoint* • The disease response at 12 months of treatment was 21.3% for ropeginterferon alfa-2b and 27.6% for HU, with a difference in responder rates of -6.6 (95% CI: -17.2 to 4.1; p=0.2233). *Secondary endpoints* • The disease response (complete haematological response without spleen size) at 12 months of treatment was 43.1% for ropeginterferon alfa-2b and 45.6% for HU, with a difference in responder rates of -3.0 (95% CI: -15.6 to 9.5; p=0.0028) • At 12 months, the JAK2V671F allele burden was 30.7% and 25.9% for ropeginterferon alfa-2b or HU treated patients, respectively.	*Key efficacy results for ropeginterferon alfa-2b and control treatment arm were:* • Complete haematological response and spleen size normality at Month 36: 42.2% vs 30.4% • Complete haematological response at Month 36: 70.5% vs 51.4% • Complete haematological response & improvement in clinical symptoms and signs at Month 36: 52.6% vs 37.8% • Maintenance of complete haematological response in the third year of treatment (Month 24 to Month 36): 70.5% vs 46.1% • Molecular Response at Month 36: 66.0% vs 27.0%

		• Median absolute levels of JAK2V617F allele burden at Month 36: 9.5% vs 42.3% Median JAK2V617F change from baseline at Month 36: -24.3% vs 2.5%
Adverse effects (AEs)	*Adverse events reported in the study:* • A total of 813 treatment-emergent adverse events (TEAEs) in 104/127 patients (81.9%) occurred in the ropeginterferon alfa-2b arm, a total of 747 TEAEs in 111/127 (87.4%) patients occurred in the HU arm. • 369 TEAEs in 76 /127 (59.8%) patients were classified as related to study drug in the ropeginterferon alfa-2b arm; 343 TEAEs in 96 /127 (75.6%) patients were classified as related to study drug in the HU arm.	*Summary of the safety profile from PROUD-PV and CONTI-PV study (according to SmPC):* The most common adverse drug reactions reported for ropeginterferon alfa-2b are leukopenia (19.1%), thrombocytopenia (18.5%), arthralgia (12.9%), fatigue (12.4%), increased gamma-glutamyltransferase (11.2%), influenza like illness (10.7%), myalgia (10.7%), pyrexia (8.4%), pruritus (8.4%), increased alanine aminotransferase (8.4%), anaemia (7.9%), pain in extremity (6.7%), alopecia (6.7%), neutropenia (6.7%), increased aspartate aminotransferase (6.2%), headache (6.2%), diarrhoea (5.6%), chills (5.1%), dizziness (5.1%) and injection site reaction (5.1%). Serious adverse reactions are depression (1.1%), atrial fibrillation (1.1%) and acute stress disorder (0.6%).
Expected reporting date	-	Estimated primary completion date reported as June 2020.

ESTIMATED COST

The cost of ropeginterferon alfa-2b is not yet know.

ADDITIONAL INFORMATION

AOP Orphan Pharmaceuticals AG did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

RELEVANT GUIDANCE

NICE GUIDANCE

- No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance identified.

OTHER GUIDANCE

- NICE Clinical Knowledge Summary. Polycythaemia/erythrocytosis. January 2018.[23]
- British Society for Haematology. A guideline for the diagnosis and management of polycythaemia vera. 2018[27]

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