NATIONAL PHARMACEUTICAL REGULATORY AGENCY MINISTRY OF HEALTH MALAYSIA

TECHNICAL EVALUATION SUMMARY

PRODUCT NAME:
BESREMi 500mcg/mL solution for injection in prefilled syringe (MAL24066032AZ)

ACTIVE INGREDIENT:
Ropeginterferon alfa-2b 0.5 mg/mL

PRODUCT REGISTRATION HOLDER:
IDB Resources Sdn Bhd

PRODUCT MANUFACTURER:
PharmaEssentia Corporation, Taichung Plant, Taiwan

APPROVAL DATE:
10 June 2024 (DCA 397)

1.0 BACKGROUND INFORMATION

- Besremi contains ropeginterferon alfa-2b as active ingredient, which is a PEGylated, recombinant human interferon alpha-2b modified by an additional proline residue at the N-terminus.
- The proposed indication for ropeginterferon alfa-2b is the treatment of polycythaemia vera (PV) in adults without symptomatic splenomegaly.
- PV is a chronic, rarely-occurring proliferative stem cell disorder responsible for elevated absolute red blood cell mass (i.e. haematocrit) caused by uncontrolled red blood cell production. It is frequently associated with uncontrolled white blood cell (i.e. leukocytes) and platelet production, and if left untreated can lead to impaired blood circulation, an increased risk of bleeding and thrombotic complications, as well as increased mortality. The key clinical features of PV are highly variable and may include increased red blood cell mass (hematocrit), increased white blood cell (leucocyte) and platelet counts in the peripheral blood, and splenomegaly in advanced disease stages, or any combination of these.
- Compared to other peg-IFN-α drug substances, which have a relative short half-life, ropeginterferon alfa-2b formulation allows for a twice-monthly (i.e., once every two weeks) s.c. injection for use in PV. Optionally, patients with adequate disease control can, at the discretion of the physician, be switched to monthly treatments.
- There is no first line treatment option approved by the DCA for patients with PV. Hydroxyurea and conventional interferons have been used off-label for the treatment of PV. Priority review is granted for this application.

1.1 Approved Indication

Besremi is indicated as monotherapy in adults for the treatment of polycythaemia vera without symptomatic splenomegaly.

1.2 Approved Posology

Treatment should be initiated under supervision of a physician experienced in the management of the disease.

<u>Posology</u>

Titration phase

The dose is titrated individually with a recommended starting dose of 100 micrograms (or 50 micrograms in patients under another cytoreductive therapy). The dose should be gradually increased by 50 micrograms every two weeks (in parallel, other cytoreductive therapy should be decreased gradually, as appropriate) until stabilisation of the haematological parameters is achieved (haematocrit <45%, platelets <400 x $10^{9/}$L and leukocytes <10 x 10^{9}/L). The maximum recommended single dose is 500 micrograms injected every two weeks. Phlebotomy as rescue treatment to normalise blood hyperviscosity may be necessary.

Maintenance phase

The dose at which stabilisation of the haematological parameters is achieved should be maintained in a two-week administration interval for at least 1.5 years. After that, the dose may be adapted and/or the administration interval prolonged up to every four weeks, as appropriate for the patient.

If adverse events develop during therapy, the administered dose should be reduced or treatment discontinued temporarily until adverse events abate; further, treatment should be re-initiated with a lower dose than the dose that caused adverse events.

If an increase of haematological parameters (haematocrit, platelets, leukocytes) is observed, the dose and/or dosing interval needs to be adapted individually.

Special populations

Hepatic impairment

In patients with compensated cirrhosis (i.e. Child-Pugh A), another pegylated interferon alfa medicinal product (pegylated interferon alfa-2a) has been shown to be safe. No ropeginterferon alfa-2b dose adjustment is required for adult patients with mild liver impairment.

The use of interferon alfa has not been evaluated in patients with decompensated cirrhosis (i.e. Child-Pugh B or C) and is contraindicated in these patients (see section 4.3).

Increased liver enzyme levels have been observed in patients treated with ropeginterferon alfa-2b. When the increase in liver enzyme levels is progressive and persistent, the dose should be reduced. If the increase in liver enzymes is progressive and clinically significant despite dose reduction, or if there is evidence of hepatic decompensation, therapy should be discontinued (see section 4.4).

Renal impairment

The pharmacokinetic profile of other interferon alfa medicinal products (pegylated interferon alfa-2a and pegylated interferon alfa-2b) was evaluated in renal impaired patients (see section 5.2).

No dose adjustment for ropeginterferon alfa-2b is required for adult patients with mild (GFR 60-89 mL/min) or moderate (GFR 30-59 mL/min) renal impairment. A reduced starting dose for ropeginterferon alfa-2b of 50 micrograms is recommended for patients with severe (GFR 15-29 mL/min) renal impairment. Ropeginterferon alfa-2b is contraindicated in patients with end stage renal disease (GFR <15 mL/min) (see section 4.3).

Elderly

Adjustments in the recommended dose for ropeginterferon alfa-2b are not necessary when starting therapy in elderly patients (see section 5.2).

Obese or underweighted patients

The pharmacokinetic profile of ropeginterferon alfa-2b has not been determined in obese and underweighted patients. No recommendation on dose adjustment for ropeginterferon alfa-2b can be given for these patients.

Paediatric population

The safety and efficacy of BESREMi in children and adolescents has not been established. No data are available (see section 4.4).

Method of administration

For subcutaneous use. The medicinal product is intended for long-term treatment and can be administered by a physician, nurse, family member or patient when trained in the administration of subcutaneous injections with the prefilled syringe. The instructions for use in the package leaflet should be followed.

The recommended injection site is the abdominal skin around but not within 5 cm of the navel or the thigh. Rotate (change) the injection site for each injection. Do not inject into an area where the skin is irritated, reddened, bruised, infected or scarred.

1.3 Method of administration

Subcutaneous

1.4 Pharmacological Aspects

Pharmacodynamic Properties:

Pharmacotherapeutic group: Immunostimulants, interferons, ATC code: L03AB15

Ropeginterferon alfa-2b is a recombinant interferon alfa-2b protein conjugated with polyethylene glycol derivative at a degree of substitution of 1 mole of polymer per mole of protein. The average molecular mass is approximately 60 kDa, of which the PEG moiety constitutes approximately 40 kDa.

Mechanism of action

Interferon alfa belongs to the class of type I interferons which exhibit their cellular effects by binding to a transmembrane receptor termed interferon alfa receptor (IFNAR). Binding to IFNAR initiates a downstream signalling cascade through the activation of kinases, particularly Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2) and signal transducer and activator of transcription (STAT) proteins. Nuclear translocation of STAT proteins controls distinct gene-expression programs and exhibits various cellular effects. Interferon alfa was shown to have an inhibitory effect on the proliferation of hematopoietic and bone marrow fibroblast progenitor cells and antagonised the action of growth factors and other cytokines that have a role in the development of myelofibrosis. These actions may be involved in the therapeutic effects of interferon alfa in polycythaemia vera.

Further, it was demonstrated that interferon alfa is able to decrease the mutated JAK2V617F allele burden in patients with polycythaemia vera (a V617F point mutation in the JAK2 kinase is a hallmark of polycythaemia vera and is present in approximately 95% of patients).

Absorption

The absorption of ropeginterferon alfa-2b is sustained in patients with peak serum concentrations reached after 3 to 6 days.

The absolute bioavailability of subcutaneous administered ropeginterferon alfa-2b was not investigated in humans. Thus, no valid estimation of the absolute bioavailability could be done. Based on data in monkeys, it is approx. 80%, similar to that seen for pegylated interferon alfa-2a.

Distribution

Ropeginterferon alfa-2b is found mainly in the bloodstream and extracellular fluid as seen by the volume of distribution at steady-state (V_d) of 6.6 to 17 litres in patients after subcutaneous administration (dose range 50 – 450 micrograms). Mean C_{max} was 2.4 ng/mL (with a dose of 50 – 80 micrograms) to 49 ng/mL (with a dose of 450 micrograms) and AUC_{0-t} ranged from 28.5 ng.h/mL (with a dose of 50 – 80 micrograms) to 552.6 ng.h/mL (with a dose of 450 micrograms) in patients after subcutaneous multiple dose administration. Inter-subject variability was observed with 25% and 35% for AUC and C_{max}, respectively, in healthy volunteers.

In patients who received ropeginteferon alfa-2b at 2-weeks interval (400-500 micrograms, PK Group 1) or at 4-weeks interval (100-500 [mean 350] micrograms, PK Group 2) at steady-state, mean Vd_{ss} was 10.7 L in PK Group 1 and 18.3 L in PK Group 2. In PK Group 1 mean C_{max} ss was 28.26ng/mL, $AUC_{tau\ ss}$ was 7504.0ng*h/mL and C_{min} was 14.52 ng/mL. In PK Group 2 mean $C_{max\ ss}$ was 18.82 ng/mL, $AUC_{tau\ ss}$ was 6021.3 ng*h/mL and C_{min} was 2.10 ng/mL.

From mass balance, tissue distribution and whole body autoradioluminography studies performed in rats, it was shown that a similar interferon alfa medicinal product (pegylated interferon alfa-2a) was distributed to the liver, kidney and bone marrow in addition to being highly concentrated in the blood.

Biotransformation

The metabolism of ropeginterferon alfa-2b is not fully characterised. The attachment of interferon alfa-2b to a high molecular weight (40 kDa) branched polyethylene glycol moiety is considered as the main reason for the differences in the elimination compared to unpegylated interferons. Studies in rats with a similar interferon alfa medicinal product (pegylated interferon alfa-2a) showed a primarily elimination via hepatic metabolism. The same elimination route is considered for ropeginterferon alfa-2b.

Pharmacokinetic interaction studies in humans with pegylated interferon alfa-2a indicated a moderate inhibitory effect on substrates metabolised by CYP1A2 and CYP2D6 (see section 4.5).

Elimination

The elimination of ropeginterferon alfa-2b is not fully characterised. Studies with a similar interferon alfa medicinal product (pegylated interferon alfa-2a) indicated that the kidney is a major organ for excretion of radiolabelled metabolic products (study in rats) and that the systemic clearance of pegylated interferon alfa-2a in humans is about 100-fold lower compared to the native, unpegylated interferon alfa-2a.

After subcutaneous multiple dose administration (dose range 50 – 450 micrograms), the terminal half-life of ropeginterferon alfa-2b in patients is approximately 6 to 10 days and the clearance of ropeginterferon alfa-2b is 0.023 to 0.061 L/h.

The involvement of transport proteins in absorption, distribution and elimination of ropeginterferon alfa-2b is not known.

Linearity/non-linearity

Over a dose range of 24 to 270 micrograms, ropeginterferon alfa-2b C_{max} increased proportionally with dose in a pharmacokinetic study with healthy subjects. A higher than proportional increase in exposure was observed. Inter-subject variability for ropeginterferon alfa-2b was 35% (C_{max}) and 25% (AUC).

Hepatic impairment

Comparable exposure and pharmacokinetic profile were reported for another interferon alfa medicinal product (pegylated interferon alfa-2a) in cirrhotic (Child-Pugh A) and non-cirrhotic patients. Pharmacokinetics were not evaluated in patients with increased severity of hepatic impairment.

Renal impairment

The pharmacokinetic profile in patients with moderate or severe renal impairment and in patients with end stage renal disease (ESRD) has been evaluated only for other pegylated interferon alfa medicinal products.

Patients with moderate or severe renal impairment receiving 180 micrograms of pegylated interferon alfa-2a once weekly showed a comparable or 60% higher drug plasma exposure, respectively, compared to subjects with normal renal function.

In 13 patients with ESRD requiring chronic haemodialysis, administration of 135 micrograms pegylated interferon alfa-2a once weekly resulted in a 34% lower drug exposure than in patients with normal renal function.

Patients with renal impairment receiving a single dose of 1.0 micrograms/kg pegylated interferon alfa-2b showed an increased relation of C_{max}, AUC, and half-life to the degree of renal impairment. Following multiple dosing of pegylated interferon alfa-2b (1.0 micrograms/kg subcutaneously administered every week for four weeks), the clearance of pegylated interferon alfa-2b was reduced by a mean of 17% and 44% in patients with moderate or severe renal impairment, respectively, compared to subjects with normal renal function. Based on single dose data, clearance was similar in patients with severe renal impairment not on haemodialysis and in patients who received haemodialysis.

Elderly

Only limited pharmacokinetic data are available from the use of ropeginterferon alfa-2b in the elderly. Based on the results from the PROUD-PV and CONTINUATION-PV Study on drug

exposure, pharmacodynamic response and tolerability, a dose adjustment for ropeginterferon alfa-2b is not considered necessary in the elderly population.

Obese or underweight patients

The pharmacokinetic profile of ropeginterferon alfa-2b has not been determined in obese and underweight patients.

2.0 SUMMARY REPORT

2.1 Quality

2.1.1 Active Substance

Ropeginterferon alfa-2b is the INN name for PEGylated Proline-Interferon alfa-2b Drug Substance (DS). It is also called mono-PEGylated Proline-Interferon alfa-2b or PEG-Proline-IFN alfa-2b. The molecular mass of ropeginterferon alfa-2b is approximately 60 kilodaltons (kDa). Ropeginterferon alfa-2b is a covalent conjugate of a recombinant proline-interferon alfa-2b and a two-arm methoxypolyethylene glycol (mPEG) moiety. Pro-IFN alfa-2b, produced in Escherichia coli, is an approximately 19 kDa non-glycosylated polypeptide of 166 amino acids; a 40 kDa two-arm PEG moiety attaches to its N-terminal proline. Ropeginterferon alfa-2b contains two pairs of disulfide bonds (cys-2 pairing with cys-99 and cys-30 pairing with cys-139) as those found in other interferon alpha-2b products. The secondary and tertiary structures elucidated by biophysical characterisation suggest ropeginterferon alfa-2b a monomeric globular protein with a high content of alpha helices.

The DS manufacturing process is divided into upstream process, downstream process-1 (proline-interferon alfa-2b AS intermediate purification), synthesis of the 40 kDa PEG intermediate and downstream process-2 (ropeginterferon alfa-2b purification). The process starts with fermentation in *E. Coli* that starts with two 40-L fermentation in which a working cell bank (WCB) cell acts as a starting material to produce Pro-IFN alfa-2b. The product is expressed as an intracellular protein in the form of inclusion bodies. The product is extracted by lysing the cells followed by washing with buffers, and then solubilizing the inclusion bodies that contain the product.

Each fermentation batch is individually subjected to the downstream processes including refolding, ammonium precipitation (ASP), and chromatography purification. Two purified batches are then combined into one batch of Pro-IFN alfa-2b Drug Intermediate followed by PEGylation with PEG-aldehyde. Then the PEGylated products are purified by chromatography. The final products are compounded to the desired concentration becoming the Ropeginterferon alfa-2b DS.

Four consecutive process validation runs for Ropeginterferon alfa-2b Drug Substance and the validation for 40kDa mPEG-Aldehyde manufacture have been successfully performed. All validation runs were completed successfully proving consistency of the manufacturing process in PharmaEssentia.

The stability program is designed in accordance with the requirements of ICH guideline Q1A (R2) and Q5C to assess the stability behavior of Ropeginterferon alfa-2b Drug Substance (DS) upon storage under defined conditions, confirming its stability during the intended storage period. Representative batches of ropeginterferon alfa-2b DS under long-term storage at 5°C ± 3°C and accelerated condition at 25°C ± 2°C with 60% ± 5% relative humidity (RH) are presented. Three commercial batches of ropeginterferon alfa-2b DS at 2.0 mg/mL are presented for stability evaluation. The product was stored in a 100-mL bottle with a screw cap. This is equivalent to those used for storage during the production process. The stability testing protocols for long-term storage at 5°C ±3°C and accelerated condition at 25°C ±2°C with 60% ±5% relative humidity (RH) are provided.

All three lots passed stability requirements with meet-specification results for up to 12 months under long-term condition at 5±3°C. The results of all parameters monitored in the course of the long-term stability study are within the range of the specifications and prove the stability and unimpaired quality behavior of the product over the period of observation.

The GMP compliance for the DS manufacturer, PharmaEssentia Corporation, Taichung Plant, Taiwan. has been verified by the PIC/S authority Taiwan Food And Drug Administration (TFDA).

2.1.2 Finished Product

Since the active pharmaceutical ingredient (API) is delivered in a formulation buffer that had been shown to be stable, and is physiologically feasible for subcutaneous injection, no further formulation changes were made. The formulation buffer composition is used to compound drug product to the desired concentration. There is no manufacturing or stability overage applied.

Ropeginterferon alfa-2b drug substance (DS) is diluted and formulated at Pharma Essentia Corporation (PEC) Taichung Plant followed by filtration. Subsequent steps include sterile filtration, aseptic filling/closing, 100% visual inspection, labeling and packaging. The fill/finished prefilled syringes (PFS) are sampled for the releasing test and stability test.

Three consecutive process validation runs at commercial-scale for manufacturing of Ropeginterferon alfa-2b Drug Product (DP) have been successfully performed at PEC Taichung Plant. The validated DP manufacturing process includes buffer preparation, dilution and formulation, sterile filtration, aseptic filling and closing, 100% visual inspection, labeling and packaging. The defined process conditions and parameters, homogeneity of the bulk and filling of minimum and maximum batch sizes as well as successful pen assembly have been confirmed. Hold times were microbiologically and physico-chemically verified. Filter flush volume for the sterilizing filter was also checked. Release data for all batches support the reproducibility of the manufacturing process. Therefore, these data confirm that the process is validated and capable of producing consistent product quality in the commercial manufacturing site and at scale.

A comparability assessment of the ropeginterferon alfa-2b prefilled pen (PFP) and ropeginterferon alfa-2b prefilled syringe (PFS) that includes the detailed quality evaluation and comparison on the manufacturing process steps and controls, container closure systems, specifications, analytical procedures, impurities profiles, long-term stabilites, and accelerated stabilites showed that they are comparable.

Batch analyses have been provided for 3 commercial scale batches. The analytical results of ropeginterferon alfa-2b DP lots for process validation, stability program, clinical trials, and specification justification are provided. All batches are well controlled and meet the set specification for the intended use.

Three process validation lots manufactured by PharmaEssentia Taichung Plant in 2019 passed stability requirements by meeting all specification limits for up to their real time 36-month stability time points for the long-term condition at 5±3°C. Based on the long-term stability data, a shelf-life of 36 months is proposed for ropeginterferon alfa-2b drug product stored at 5±3°C.

The product has passed the laboratory evaluation on analytical protocol and validation.

The GMP compliance for the DP manufacturer, PharmaEssentia Corporation, Taichung Plant, Taiwan has been verified by PIC/S authority, Taiwan Food And Drug Administration (TFDA), Taiwan.

An endorsement letter for Drug-Medical Device Combination Product from Medical Device Authority concerning the ancillary medical device components for Besremi has been submitted.

Primary packaging: The prefilled syringe (PFS) is designed for single-use injection of ropeginterferon alfa-2b DP at 0.5 mg/mL.

Secondary packaging: Each finished PFS with ropeginterferon alfa-2b DP is packed together with a separate safety needle in a syringe holder (thermoform tray) then enclosed in a carton for patient administration.

2.2 Non-Clinical

- A total of 12 non-clinical studies were conducted as part of the non-clinical development programme: 4 safety pharmacology studies, 1 combined pharmacodynamic and pharmacokinetic (PD/PK) study and 7 toxicology studies.
- A pivotal toxicity study was completed with ropeginterferon alfa-2b (P1101) in cynomolgus monkeys. It was conducted at sites in the United States which are in accordance with Organization for Economic Co-operation and Development (OECD) GLPs.
- Safety pharmacology studies did not identify any specific concerns towards the use of P1101 in clinics, when tested at adequately high dose levels.
- The in vivo combined PD/PK study was performed with the aim to demonstrate the biological activity of P1101 in cynomolgus monkeys and compare it to Pegasys®. P1101 elicited PD effects that were similar in magnitude but of longer duration in comparison to Pegasys®.
- The toxicological evaluation of P1101 was limited to studies of not more than 1 month in duration due to the production of neutralizing anti-drug antibodies (ADAs) in cynomolgus monkeys (4-Weeks) and the lack of biologic activity in Sprague Dawley rats (14-Days).
- The toxicity studies used clinical route of administration (subcutaneous) and formulation intended for marketing, did not reveal any serious adverse effects after repeated treatment up to the dose of 6.75 mg/kg. The major findings such as slight weight loss, decreased appetite, reduced red blood cell mass, reticulocytes and platelets, prolonged activated partial thromboplastin clotting time (APTT), transient decrease in mean total protein, albumin and calcium levels in serum and ketonuria were all of mild non-adverse character and reversible after the four-week recovery phase.
- Safety margin between no observed adverse effect level (NOAEL) in the pivotal toxicity study (6.75 mg/kg) and the maximum human dose of 500 µg, i.e. 7.1 µg/kg assuming 70 kg body weight, was calculated to be 307.04.
- The local tolerance evaluation included in the GLP repeated dose toxicity studies were performed with formulation and route of administration intended for marketing, and thus a separate local tolerance study was not considered necessary.

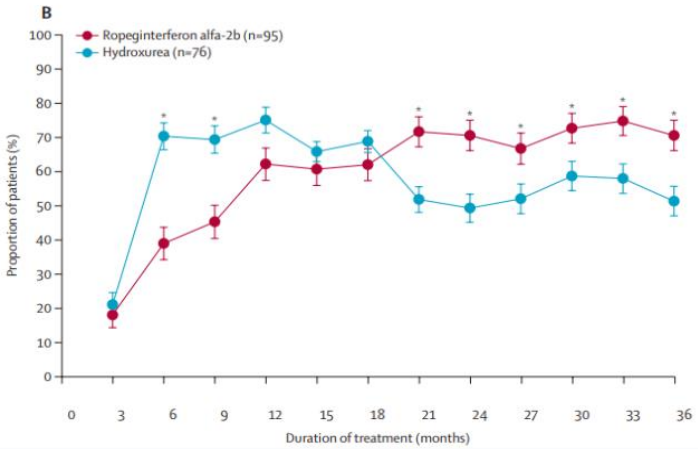
- The non-clinical toxicology program is considered to fulfil the ICH S6 (R1) guidelines. The completed non-clinical studies of Ropeginterferon alfa-2b (P1101) that supported the clinical development programme are considered acceptable.
- The information relevant to the non-clinical studies have been reflected in the package insert.

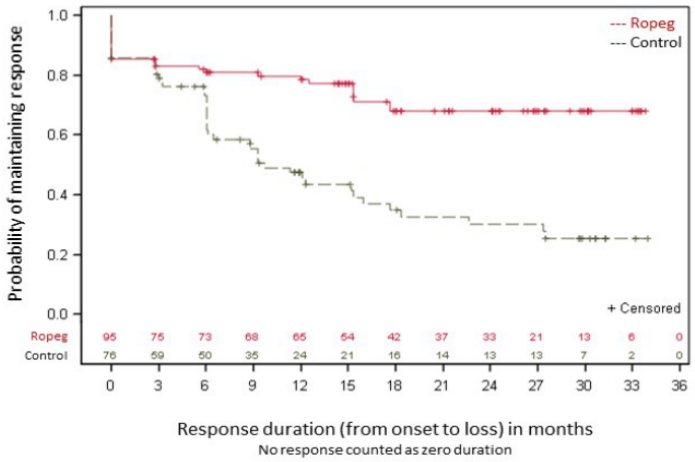
2.3 Efficacy

- The following clinical studies have been conducted to evaluate the efficacy of ropeginterferon alfa-2b in the treatment of PV in adults.
- Dose finding in study **PEGINVERA-PV**- An open-label, prospective, multicentre, phase I/II dose escalation study to determine the maximum tolerated dose and to assess the safety and efficacy of P1101, PEG-Proline-interferon alpha-2b in patients with Polycythaemia Vera.
- **A single pivotal phase 3 trial (PROUD-PV)** and the supportive follow-up trial, **CONTINUATION-PV.**
    - PROUD-PV trial- an **open-label, randomized (1:1),** controlled, parallel-group, non-inferiority study comparing the efficacy and safety of ropeginterferon over hydroxyurea over 12 months in randomised PV patients.
    - CONTINUATION-PV trial- an **open-label extension study** to PROUD-PV designed to provide **long-term evaluation** of safety as well as efficacy of ropeginterferon alfa-2b in patients with PV who were previously treated in the PROUD-PV Study.

- The results of the pivotal clinical studies are summarised in the table below:

Study Type & Design (N)	Objectives of the Study	Results
Study PROUD-PV and CONTINUATION-PV [Gisslinger H et al *et al. Lancet Lancet Haematol.* 2020& Clinical Study Report, 2020]	● The assessment of non-inferiority of ropeginterferon alfa-2b versus hydroxyurea regarding disease response.	**Primary efficacy results:** *Primary endpoint - non-inferiority of ropeginterferon alfa-2b versus hydroxyurea regarding complete haematological response with normal spleen size (longitudinal diameter of ≤12 cm for women and ≤13 cm for men) at 12 months.* *-non-inferiority margin of -10.5%; p>0.05*

A multicentre, phase 3, randomised, controlled, open-label, trials done in 48 clinics in Europe. Randomized **1:1 ratio** to ropeginterferon alfa-2b or hydroxyurea **PROUD-PV:** ropeginterferon alfa-2b=127 hydroxyurea= 127 **CONTINUATION-PV** ropeginterferon alfa-2b=95 best available treatment= 76 The final results of PROUD-PV and an **interim analysis at 36 months** of the CONTINUATION-PV study (per statistical analysis plan) are presented.		**PROUD-PV:** 26 (21%) of 122 patients in the ropeginterferon alfa-2b group and 34 (28%) of 123 patients in the standard therapy group met the composite primary endpoint of complete haematological response with normal spleen size at 12 months. The 95% CI of the difference in response was –17.23 to 4.09; non-inferiority was not shown (p=0·23). **CONTINUATION-PV** *Primary endpoint - The co-primary efficacy endpoints were the proportion of patients achieving a complete haematological response and normal spleen size (as defined in PROUD-PV) and a complete haematological response with improved disease burden (ie, resolution or clinical improvement of disease-related splenomegaly, microvascular disturbances, pruritus and headache, or a combination).* *The proportion of patients with a complete haematological response was significantly higher in the ropeginterferon alfa-2b group than in the hydroxyurea group.*  *p< 0·05. Proportion of patients with complete haematological response during a treatment period of 36 months among patients who participated in the extension study, CONTINUATION-PV

		The difference in response between the treatment groups was significant at 36 months. Complete haematological response including normalisation of spleen size among patients treated with ropeginterferon alfa-2b also increased steadily over time, from 27 (30%) of 91 patients at month 12 to 38 (42%) of 90 patients at month 36. However, no significant difference was reported between the ropeginterferon alfa-2b and hydroxyurea groups (p=0.16). Complete haematological response with improved disease burden was met in 50 (53%) of 95 patients in the ropeginterferon alfa-2b group versus 28 (38%) of 74 patients in the hydroxyurea group, p=0·044 at 36 months. Over the 36-month treatment period, the proportion of patients who maintained their response were significantly higher in the ropeginterferon alfa-2b group compared with the hydroxyurea group regarding complete haematological response as well as complete haematological response with improved disease burden (37 [39%] of 95 vs 11 [15%] of 76, p=0·0011; 28 [30%] of 95 vs 11 [15%] of 76, p=0·025, respectively). The probability of maintaining complete haematological response over time is shown below. **Figure S6 Probability of Maintaining Complete Haematological Response** 

		Conclusion: Ropeginterferon alfa-2b offers a new treatment option for patients with polycythaemia vera that has greater benefits than standard therapy with hydroxyurea after the second year of exposure, suggesting that ropeginterferon alfa-2b treatment should be considered as early as possible in the course of disease.
[Gisslinger H. *et al. Leukemia.* 2023& Clinical Study Report, 2021] 72 Months of Treatment - Pegylated-proline-interferon α-2b (AOP2014, marketed as BESREMi®)	● To assess the long-term efficacy of BESREMi or standard first line treatment (HU or best available treatment, referred to as 'Control') in terms of disease response rate in patients diagnosed with PV, who previously participated in the PROUD-PV Study and who completed this study. ● To assess the long-term efficacy including changes in disease burden in patients	**CHR and normal spleen size** At 72 months of treatment, the disease response rate defined as (1) was 32/86 (37.21%) for BESREMi and 15/60 (25.00%) for the control. The response rate ratio (RR) was 1.48 (0.89 to 2.46), indicating higher (but not statistically significant; p=0.1289) response rates in the BESREMi treatment arm at 72 months of treatment. **CHR and resolution and/or clinical improvement of disease-related signs (clinically significant splenomegaly defined per Investigator) and symptoms** At Month 72, the disease response rate defined as (2) was 39.77% (35/88) in the BESREMi arm and 25.76% (17/66) in the control treatment arm, with a response rate ratio of 1.58 (95% CI: 0.98 to 2.52), indicating higher (but not statistically significant; p=0.0584) response rate at 72 months of treatment for the BESREMi treatment arm. **Maintenance rate** CHR was maintained over the entire 6-year treatment period by 21.1% of patients who received BESREMi and 1.4% of HU/BAT-treated patients from Month 60 to Month 72 (RR: 13.85 [95% CI: 1.92 to 100.00]; p=0.0092). The duration of maintained response was significantly longer in the BESREMi arm than in the control arm.

		diagnosed with PV. Disease burden is defined as disease-related signs (clinically significant splenomegaly) and disease-related symptoms (microvascular disturbances, pruritus, headache), assessed by the Investigators.	<u>Conclusion:</u> Response rates at 72 months remained higher in the BESREMi group compared to control for all disease response definitions for polycythaemia vera.

2.4 Safety

- Study PROUD-PV and CONTINUATION-PV
  - The proportion of serious adverse events and adverse events with a severity of grade three or higher were similar in both treatment groups.
  - Treatment-related serious adverse events occurred in three (2%) of 127 patients in the ropeginterferon alfa-2b group and five (4%) of 127 patients in the hydroxyurea group.
  - 72 months: The intensity of most AEs was mild or moderate. Safety results were comparable between patients across ropeginterferon alfa-2b group dose levels (4-week average of µg, 250–500 µg, or >500 µg) and ropeginterferon alfa-2b group administration schedules (dosing every 2 weeks, or every 3 to 4 weeks), with respect to the rates of adverse events, treatment-related AEs, SAEs, AESIs and AEs leading to discontinuation.

3.0 CONCLUSION

Drug Control Authority (DCA) on the 397th meeting on 10th June 2024 has decided to approve the registration of this product with the following indication:

Besremi is indicated as monotherapy in adults for the treatment of polycythaemia vera without symptomatic splenomegaly.