Abstract #106570

Ropeginterferon Alfa-2b Induces High Rates of Clinical, Hematological and Molecular Responses in Polycythemia Vera: Two-Year Results from the First Prospective Randomized Controlled Trial

Heinz Gisslinger¹, Christoph Klade, PhD², Pencho Georgiev, MD³, Dorota Krokmalczyk⁴, Liana Gercheva, MD, Ph.D⁵, Miklos Egyed, MD, PhD⁶, Viktor Rossiev⁷, Petr Dulicek⁸, Árpád Illés, MD, PhD⁹, Halyna Pylpenko, MD¹⁰, Lylya Sicheva¹¹, Jiri Mayer, Prof, MD, Scs¹², Vera Yablokova¹³, Kurt Krejcy, PhD², Barbara Grohmann-Izay, MD, MSc², Hans Carl Hasselbalch, MD, Professor, DMS¹⁴, Robert Kralovics, PhD¹⁵ and Jean-Jacques Kiladjian, MD, PhD¹⁶

¹Department of Internal Medicine I, Division of Hematology and Blood Coagulation, Medical University of Vienna, Vienna, Austria; ²AOP Orphan Pharmaceuticals AG, Vienna, AUT; ³University Multiprofile Hospital for Active Treatment “Sveti Georgi” and Medical University, Plovdiv, Bulgaria; ⁴Reaching Unit of the Hematology Department, University Hospital in Krakow, Krakow, Poland; ⁵Clinical Hematology Clinic, Multiprofile Hospital for Active Treatment “Sveta Marina”, Varna, Bulgaria; ⁶Kaposi Mor Teaching Hospital, Kaposvar, HUN; ⁷Samara Kalinin Regional Clinical Hospital, Samara, Russian Federation; ⁸FN Hospital Hradec KraLOve, Praha 7, CZE; ⁹Department of Hematology, Institute for Medicine, Clinical Center, University of Debrecen, Debrecen, Hungary; ¹⁰Regional Treatment and Diagnostics Hematology Center, Department of Hematology, Cherkasy Regional Oncology Center, Cherkasy, Ukraine; ¹¹First Department of Internal Medicine, Multiprofile Hospital for Active Treatment - Hristo Botev, Vratsa, Bulgaria; ¹²Clinic of Internal Medicine, Hematology and Oncology, University Hospital Brno, Brno, Czech Republic; ¹³Department of Hematology, Yaroslavl Regional Clinical Hospital, Yaroslavl, Russian Federation; ¹⁴Department of Hematology, Roskilde Hospital, Roskilde, Denmark; ¹⁵CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Wien, Austria; ¹⁶Hôpital Saint-Louis et Université Paris Diderot, Paris, France

Background: Interferon-alpha (IFNa) based therapies have been successfully used in myeloproliferative neoplasms (MPN) for over thirty years. Ropeginterferon alfa-2b (Ropeg) is a novel mono-pegylated IFNa, which is administered once every 2 weeks, or monthly on long-term maintenance. Ropeg is developed in polycythemia vera (PV), and 12-month data from the randomized controlled phase III PROUD-PV study comparing Ropeg with hydroxyurea (HU) have been presented. Here we report 2 years treatment data obtained from the follow-up phase III CONTI-PV study.

Study design: 254 PV patients (WHO2008 criteria, naïve to cytoreduction or HU pretreated but not resistant) had been randomized to receive Ropeg or HU in the PROUD-PV study. After 12 months of treatment patients were rolled over to the CONTI-PV study: 95 of 106 (89.6%) patients completing the 12-month Ropeg arm, and 76 of 111 (68.5%) patients completing the 12-month HU arm continued in the second year. The latter cohort was also allowed to switch from the HU regimen to best available therapy (BAT) at the investigators discretion; a cross-over between groups was not allowed. Efficacy assessment consisted of complete hematological
response (CHR) rate according to ELN criteria, and the CHR rate plus symptom improvement (PV-related symptoms and signs including clinically significant splenomegaly). Secondary endpoints included the effect of treatment on mutant JAK2 allele burden assessed as rate of molecular response (modified ELN criteria) as surrogate for disease modification.

**Results:** 88 (Ropeg) and 73 (HU/BAT) patients completed the 24-month efficacy analysis time point, the mean treatment duration for safety analysis was 2.7 years (both after initial randomization in the PROUD study). Median drug doses in the second year remained at the same level as during the first year: 450 µg Ropeg every 2 weeks and 1000 mg HU per day. In the HU/BAT arm over 98% of patients remained treated with HU, a switch to other BAT was rare. Discontinuation rates during the second year were comparable with 8.4% in the Ropeg and 6.6% in the HU/BAT arm, respectively.

At 24 months, treatment with Ropeg achieved a high CHR rate of 70.5%. This was significantly better than a CHR of 49.3% with HU/BAT, (p=0.0101, full-analysis-set). Importantly, in contrast to HU/BAT, response rates increased steadily in the Ropeg-treated group throughout the two-year treatment period. The composite endpoint CHR plus symptom improvement also favored Ropeg with 49.5% vs. 36.6% for HU/BAT (p=0.1183) at 24 months. The advantage of Ropeg was most pronounced in the effect on mutant JAK2 allele burden: at 24 months 69.6% of patients in the Ropeg arm but only 28.6% in the HU/BAT arm had achieved partial molecular response (p=0.0046).

Regarding safety, a comparable number of patients (70.1% for Ropeg, 77.2% for HU) experienced treatment-related adverse events. Anemia, thrombocytopenia and leukopenia occurred more frequently with HU, whereas GGT increase was observed only with Ropeg in some patients. Events of special interest for the class of IFNa (in particular thyroid disorders and depression) were below 5% in the Ropeg arm. Disease- or treatment-related secondary malignancies occurred only in the HU cohort, including 2 cases of acute leukemia, 1 melanoma and 2 basaliomas, whereas in the Ropeg cohort 3 malignancies (glioblastoma, seminoma, adrenal neoplasm) - most likely unrelated to IFNa treatment - were reported.

**Conclusions:** These data confirm a) the high and durable hematologic response and symptom improvement achieved with Ropeg, b) the excellent safety and tolerability profile of Ropeg, and c) the disease modification capability of Ropeg suggested by its ability to significantly reduce the mutant JAK2 allelic burden. Ropeg interferon alfa-2b will provide a valuable and safe new long-term treatment option for PV patients.