320 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

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Heinz Gisslinger1, Christoph Klade, PhD2, Pencho Georgiev, MD3, Dorota Krochmalczyk4, Liana Gercheva, MD, Ph.D5, Miklos Egyed, MD, PhD6, Viktor Rossiev7, Petru Dulicek8, Arpad Illés, MD, PhD9, Halyna Pylypenko, MD10, Lyvia Sicheva11, Jiri Mayer, MD12, Vera Yablokova13, Kurt Krefczy, Ph.D14, Barbara Grohmann-Izay, MD, MSc15, Hans Carl Hasselbalch, MD, Professor, DMSc16, Robert Kralovics, PhD15 and Jean-Jacques Kiladjian, MD, PhD16

1 Department of Internal Medicine I, Division of Hematology and Blood Coagulation, Medical University of Vienna, Vienna, Austria
2 AOP Orphan Pharmaceuticals AG, Vienna, AUT
3 University Multiprofile Hospital for Active Treatment “Sveti Georgi” and Medical University, Plovdiv, Bulgaria
4 Reaching Unit of the Hematology Department, University Hospital in Krakow, Krakow, Poland
5 Clinical Hematology Clinic, Multiprofile Hospital for Active Treatment “Sveta Marina”, Varna, Bulgaria
6 Kaposi Mor Teaching Hospital, Kaposvar, HUN
7 Samara Kalinin Regional Clinical Hospital, Samara, Russian Federation
8 FN Hospital Hradec Kralove, Praha 7, CZE
9 Department of Hematology, Institute for Medicine, Clinical Center, University of Debrecen, Debrecen, Hungary
10 Regional Treatment and Diagnostics Hematology Center, Department of Hematology, Cherkassy Regional Oncology Center, Cherkassy, Ukraine
11 First Department of Internal Medicine, Multiprofile Hospital for Active Treatment – Hristo Botev, Vratsa, Bulgaria
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 during 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. Ropeginterferon alfa–2b will provide a valuable and safe new long–term treatment option for PV patients.

**Disclosures:** Gisslinger: *AOP Orphan Pharmaceuticals AG*: Consultancy, Honoraria; *Novartis*: Consultancy, Honoraria; *PharmaEssentia*: Consultancy, Honoraria; *Shire*: Honoraria; *Takeda*: Honoraria; *Janssen Cilag*: Honoraria. Georgiev: *Alnylam*: Consultancy. Mayer: *Eisai*: Research Funding; *Johnson & Johnson*: Research Funding; *Novartis*: Research Funding. Hasselbalch: *Novartis*: Membership on an entity's Board of Directors or advisory committees, Research Funding; *AOR Orphan*: Membership on an entity's Board of Directors or advisory committees. Kiladjian: *AOP Orphan*: Membership on an entity's Board of Directors or advisory committees, Research Funding; *Celgene*: Membership on an entity's Board of Directors or advisory committees; *Novartis*:Membership on an entity's Board of Directors or advisory committees, Research Funding.