THE FUTURE OF INTERFERON IN MYELOPROLIFERATIVE NEOPLASMS

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Paris, France
Besremi
ropeginterferon alfa-2b

On 13 December 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Besremi, intended for the treatment of polycythaemia vera without symptomatic splenomegaly. Besremi was designated as an orphan medicinal product on 9 December 2011. The applicant for this medicinal product is AOP Orphan Pharmaceuticals AG.

The full indication is: "Besremi is indicated as monotherapy in adults for the treatment of polycythaemia vera without symptomatic splenomegaly." It is proposed that Besremi is prescribed by physicians experienced in the management of the disease.
EVIDENCE FOR SUPERIOR EFFICACY AND DISEASE MODIFICATION AFTER THREE YEARS OF PROSPECTIVE RANDOMIZED CONTROLLED TREATMENT OF POLYCYTHEMIA VERA PATIENTS WITH ROPEGINTERFERON ALFA-2B VS. HYDROXYUREA/BEST AVAILABLE TREATMENT

HEINZ GISSLINGER, CHRISTOPH KLADE, PENCHO GEORGIEV, DOROTA KROCHMALCZYK, LIANA GERCHEVA-KYUCHUKOVA, MIKLOS EGYED, VIKTOR ROSSIEV, PETR DULICEK, ARPAD ILLES, HALYNA PYLYPENKO, LYLIA SIVCHEVA, JIRI MAYER, VERA YABLOKOVA, KURT KREJCY, BARBARA GROHMANN-IZAY, HANS C. HASSELBALCH, ROBERT KRALOVICS, AND JEAN-JACQUES KILADJIAN

ASH 2018
Ropeginterferon alfa-2b phase III development in PV: PROUD-PV and CONTINUATION-PV Studies

PROUD-PV:
- Stratified Rand. by Age, prev. HU, prev. TE
- n=127
- Ropeginterferon
- n=106
- EOT PROUD
- Inclusion CONTI
- n=111
- Hydroxyurea
- n=76

CONINUATION-PV:
- n=95
- Ropeginterferon
- n=76
- BAT/Control
- n=73

Month 0
Month 12
Month 24 Efficacy Analysis
up to 3.6 years Safety Analysis
### Treatment-related adverse events in >10% of patients

<table>
<thead>
<tr>
<th>Treatment-related AE</th>
<th>Ropeg (n=95) n (%)</th>
<th>Control (n=76) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>24 (25.3%)</td>
<td>25 (32.9%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>21 (22.1%)</td>
<td>23 (30.3%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>10 (10.5%)</td>
<td>22 (28.9%)</td>
</tr>
<tr>
<td>Increased gamma-GT</td>
<td>11 (11.6%)</td>
<td>2 (2.6%)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>10 (10.5%)</td>
<td>-</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>-</td>
<td>8 (10.5%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>10 (10.5%)</td>
<td>3 (3.9%)</td>
</tr>
</tbody>
</table>
Complete hematologic response (CHR)

<table>
<thead>
<tr>
<th>Study Month</th>
<th>Responder/N</th>
<th>Responder %</th>
<th>Responder/N</th>
<th>Responder %</th>
<th>P-value</th>
<th>RR [95% CI] (AOP2014/Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ropeg (N=95)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MONTH 12 (EOT in PR)</td>
<td>59/95</td>
<td>62.1</td>
<td>57/76</td>
<td>75.0</td>
<td>0.1201</td>
<td>0.85 [0.70-1.04]</td>
</tr>
<tr>
<td>MONTH 24</td>
<td>67/95</td>
<td>70.5</td>
<td>33/67</td>
<td>49.3</td>
<td>0.0111</td>
<td>1.42 [1.08-1.87]</td>
</tr>
<tr>
<td>MONTH 36</td>
<td>67/95</td>
<td>70.5</td>
<td>38/74</td>
<td>51.4</td>
<td>0.0122</td>
<td>1.38 [1.07-1.79]</td>
</tr>
<tr>
<td><strong>Control (N=76)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CHR + improvement in disease burden

<table>
<thead>
<tr>
<th>Study Month</th>
<th>Responder/N</th>
<th>Responder %</th>
<th>Responder/N</th>
<th>Responder %</th>
<th>P-value</th>
<th>RR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ropeg (N=95)</td>
<td>Control (N=76)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MONTH 12 (EOT in PR)</td>
<td>44/95</td>
<td>46.3</td>
<td>39/76</td>
<td>51.3</td>
<td>0.5245</td>
<td>0.91 [0.67-1.23]</td>
</tr>
<tr>
<td>MONTH 24</td>
<td>47/95</td>
<td>49.5</td>
<td>27/71</td>
<td>38.0</td>
<td>0.1832</td>
<td>1.27 [0.89-1.81]</td>
</tr>
<tr>
<td>MONTH 36</td>
<td>50/95</td>
<td>52.6</td>
<td>28/74</td>
<td>37.8</td>
<td>0.0437</td>
<td>1.42 [1.01-2.00]</td>
</tr>
</tbody>
</table>
**JAK2 (V617F) - Molecular response**

**Study Month** | **Responder/N** | **Responder %** | **Responder/N** | **Responder %** | **P-value** | **RR [95% CI]** (AOP2014/Control) |
--- | --- | --- | --- | --- | --- | --- |
**Ropeg (N=95)** | **Control (N=76)** | | | | | |
MONTH 12 (EOT in PR) | 41/94 | 43.6 | 38/75 | 50.7 | 0.5001 | 0.84 [0.62-1.15] |
MONTH 24 (LOCF) | 64/94 | 68.1 | 25/75 | 33.3 | 0.0001 | 1.99 [1.40-2.84] |
MONTH 36 (LOCF) | 62/94 | **66.0** | 20/74 | **27.0** | <0.0001 | 2.31 [1.56-3.42] |
Conclusions

• Results from three years of treatment in this large, prospective, controlled trial in PV confirm the previously reported efficacy and safety of ropéginterferon alfa-2b

• Ropég showed high and **durable hematologic responses** and **symptom control** with **good tolerability**

• Ropég reduced not only \( JAK2V617F \) but also additional mutations and cytogenetic aberrations confirming **disease modification** capability of IFNa

• Ropéginterferon alfa-2b will provide a valuable and safe new long-term treatment option with features clearly **distinct from other treatment modalities** including HU
COMPARISON OF LONG-TERM EFFICACY AND SAFETY OF ROPEGINTERFERON ALFA-2B VS. HU IN POLYCYTHEMIA VERA PATIENTS AGED BELOW OR ABOVE 60 YEARS: TWO-YEAR ANALYSIS FROM THE PROUD/CONTINUATION PHASE III TRIALS

Heinz Gisslinger, Christoph Klade, Pencho Georgiev, Dorota Krochmalczyk, Liana Gercheva-Kyuchukova, Miklos Egyed, Viktor Rossiev, Petr Dulicek, Arpad Illes, Halyna Pylypenko, Lylia Sivcheva, Jiri Mayer, Vera Yablokova, Barbara Grohmann-Izay, Gabriele Maurer, Hans Hasselbalch, Robert Kralovics and Jean-Jacques Kiladjian
Background

Off-label IFNα as first-line therapy is primarily used in patients of younger age, partly because of the misconception that the risk-benefit ratio is not so favorable in elderly patients.

**Aim:**
To analyze the efficacy and safety of Ropeginterferon alfa-2b and HU in two age cohorts (<60 years and ≥60 years).
Ropeginterferon alfa-2b induced higher CHR rates compared to control, irrespective of age.
Ropeginterferon alfa-2b induced higher maintenance rates of CHR compared to control, irrespective of age.
Ropeginterferon alfa-2b induced a higher molecular response compared to control, irrespective of age.
**Long-term Safety:** up to 3.6 years of treatment; mean 2.7 years

<table>
<thead>
<tr>
<th></th>
<th>Ropeg</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;60 years N=49</td>
<td>≥60 years N=46</td>
</tr>
<tr>
<td>Patients with AE</td>
<td>44 (89.8%)</td>
<td>43 (93.5%)</td>
</tr>
<tr>
<td>Patients with serious AE</td>
<td>3 (6.1%)</td>
<td>10 (21.7%)</td>
</tr>
<tr>
<td>Patients with adverse drug reaction (ADR)</td>
<td>38 (77.6%)</td>
<td>29 (63.0%)</td>
</tr>
<tr>
<td>Patients with serious ADR</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Patients with ≥ Grade 3 AE</td>
<td>10 (20.4%)</td>
<td>16 (34.8%)</td>
</tr>
</tbody>
</table>

- Comparable numbers of AEs and serious AEs in the treatment arms, irrespective of age.
- Number of ADRs was comparable in the patients <60 years but a trend towards a lower number of ADRs (serious and non-serious) was evident for Ropeginterferon alfa-2b vs. control in patients ≥60 ys

*Acute Leukemia, Anemia, Leukopenia, Granulocytopenia*
Summary - Conclusion

• A high CHR, symptom improvement and molecular response (JAK2V617F) as well as maintenance of response achieved by long-term treatment with Ropeginterferon alfa-2b was shown, with an advantage over HU independent of age.

• Ropeginterferon alfa-2b was well tolerated in all age groups. The safety analysis in patients ≥60 years showed a positive trend regarding less ADRs and less serious ADRs for Ropeginterferon alfa-2b vs. HU.

• Ropeginterferon alfa-2b provides a valuable, efficacious and safe new treatment option for PV patients of all ages, including those older than 60.
IFN TREATMENT DISCONTINUATION
PVN1 study – *peg-IFNα-2a discontinuation*

- Causes of *peg-IFNα-2a discontinuation*
  - 38% for hematol. CR
  - 27% for toxicity

- Fatigue (n= 2)
- Depression (n= 1)
- Auto-antibodies (n=2)
- Thyroiditis (n= 1)
- Arthralgia (n= 1)
- Neutropenia (n= 1)
- Neuropathy gr. 2 (n= 1)
- LFTs elevation gr. 2 (n=1)
OUTCOME OF PATIENTS AFTER DISCONTINUATION?
Objectives

• Single center study of outcome of MPN patients treated with IFN after discontinuation (whichever the cause)

• Endpoints (competing risk) :
  • hematological relapse
  • thrombosis
  • hematological transformation
  • EFS (thrombosis, transformation, death)

• Predictive factors
Results

• Since 2000 in St-Louis hospital, 333 MPN patients received IFNa
  • 149 stops
    • 78 PV, 61 ET, 10 MF
  • Reasons for stopping:
    • Toxicity : 79 (53%)
    • Prolonged CHR: 52 (35%)
  • Median time on IFN : 28.3 months
Results

- Last follow-up:
  - 109 (73%) patients were in CHR for a median time after IFN discontinuation of 42 months [23-58]
  - including 46 (42%) without cytoreductive therapy after 33 months [19-53]
Impact of molecular response on clinical outcomes

Influence of JAK2V617 allele burden on the predicted probability of persistent complete hematological response without cytoreductive therapy

Kiladjian et al., ASH 2016
COMBINATION THERAPY WITH IFN
RUXOPEG, a Multi-Center Bayesian Phase 1/2 Adaptive Randomized Trial of the Combination of Ruxolitinib and Pegylated Interferon Alpha 2a in Patients with MPN-Associated Myelofibrosis

**Phase 1:** a Bayesian dose finding study to assess the safety of the combination of different doses of ruxolitinib and peg-IFN alpha-2a

**Phase 2:** a secondary randomized evaluation of the 2 optimal doses found in the first part of the study

ClinicalTrials.gov Identifier: NCT02742324
RUXOPEG study design - phase 1

Primary tolerance criterion: occurrence of dose limiting toxicity within 45 days

<table>
<thead>
<tr>
<th>Ruxolitinib (started D1)</th>
<th>10 mg BID</th>
<th>15 mg BID</th>
<th>20 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg-IFN 45 mcg/w (started D15)</td>
<td>n= 3</td>
<td>n= 3</td>
<td>n= 3</td>
</tr>
<tr>
<td>Peg-IFN 90 mcg/w</td>
<td></td>
<td></td>
<td>n= 3</td>
</tr>
<tr>
<td>Peg-IFN 135 mcg/w</td>
<td>n= 3</td>
<td>n= 3</td>
<td></td>
</tr>
</tbody>
</table>

18 patients enrolled from Sept 2017 to Nov 2018

Analysis on the first 16 patients allowing for DLT assessment
Phase 1 - Conclusion

- No DLT was observed among the 18 enrolled patients
- **Starting Phase 2**: a secondary randomized evaluation of the 2 optimal doses found in the first part of the study
  - Ruxolitinib 15 mg BID + Peg-IFN 135 mcg/w
  - Ruxolitinib 20 mg BID + Peg-IFN 135 mcg/w
- **Primary efficacy criterion**: > 50% reduction in spleen length within 6 months
- Will include up to a total of **42 patients** (24 additional patients)
RUXOPEG study - phase 1 preliminary efficacy results

- Efficacy of the combination for reducing the spleen size

Mean: 9.7 5.0 4.7 4.0 5.0
RUXOPEG study - phase 1 preliminary efficacy results

- Efficacy of the combination for reducing the MPN clone
RUXOPEG study - phase 1 preliminary efficacy results

- Efficacy of the combination for reducing the MPN clones

Patient #110-002
5 mutations at baseline

Dose level 1:
Rux 10 mg BID
Peg 45 mcg/w
Efficacy of the combination for reducing **cytokine levels**

Multiplex assay of 45 cytokines at different time points

Different Cytokine Profiles: screening/end of treatment (n=8 first patients)
Ancillary study of immune cells

Phenotype evolution during treatment

- At baseline
- After Rux alone
- After Rux + Peg IFN
- At 12 months

Cytokine expression in T lymphocytes

Population of Treg

Population of naïve and memory T lymphocytes

Checkpoint expression in T lymphocytes

Activation of immune cells during treatment

Claude Capron
RUXOPEG study - phase 1 preliminary efficacy results

- Efficacy of the combination for improving **bone marrow histology**
Specific and Synergistic Targeting of JAK2\textsuperscript{V617F} Cells by Interferon Alpha (IFN) and Arsenic (As\textsubscript{2}O\textsubscript{3}) in Myeloproliferative Neoplasms (MPNs)

Nabih Maslah, Tracy Dagher, Valérie Edmond, Bruno Cassinat, Valérie Lallemand-Breitenbach, Emmanuelle Verger, Isabelle Plo, Jean-Jacques Kiladjian, Jean-Luc Villeval, and Hugues de Thé

ASH 2018
Preclinical model: Chimeric KI JAK2^{V617F} / JAK2^{WT} grafted model

KI JAK2^{V617F\_loxF} TG Ubi GFP

KI JAK2^{VF} / Ubi GFP donor

WT donor

40% BMT

60%

recipient WT

40% BMT

9,5 Gy

IFN

Molecular response

Hematological response

Relapse after treatment discontinuation

2\text{nd} BMT

As_{2}O_{3}

5 weeks

9,5 Gy

Disease in transplanted mice?
Arsenic increases the hematological response induced by IFN in blood and tissues.
IFN+As$_2$O$_3$ in vivo treatment in chimeric KI JAK2$^{V617F}$ / JAK2$^{WT}$ mice: Improvement of Molecular response

Addition of Arsenic to Interferon eradicates JAK2$^{V617F}$ leukemic stem cells?

4 independent experiments
n=25-28 animals
ANOVA Dunnet test

1 out of 2 experiments
n=3 animals
IFN+As$_2$O$_3$ in vivo treatment in chimeric KI JAK2$^{V617F}$ / JAK2$^{WT}$ mice:  
Eradication of disease-initiating cells in secondary transplants

arsenic greatly increases the suppression of disease-initiating cells induced by IFN

*from hematocrit and allele burden.  
4 independent experiments  
n-12-15 animals  
ANOVA Dunnet test
IFN+As$_2$O$_3$ in vivo treatment in chimeric KI JAK2$^{V617F}$ / JAK2$^{WT}$ mice: Lower risk of disease recurrence after treatment discontinuation

Arsenic decreases the percentage of disease relapse observed after discontinuation of the IFN treatment.*

* from hematocrit and allele burden.
4 independent experiments
n=12-15 animals
ANOVA Dunnet test

Disease relapse
9 weeks after treatment discontinuation
Conclusion