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Ropeginterferon alfa-2b is cost-effective to manage low-risk patients with polycythemia vera as compared to phlebotomy only

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Objectives

- Polycythemia vera (PV) is a rare myeloproliferative neoplasm associated with high risk of thrombosis, progression to myelofibrosis (MF), acute myeloid leukemia (AML) and reduced survival. Patients younger than 60 years without prior thrombosis are defined at "low risk" and typically managed with low-dose aspirin and phlebotomy.
- In a multicenter, open-label, two-arm, parallel-group, investigator initiated, randomized phase 2 trial, ropeginterferon alfa-2b (ropeg) on top of the standard phlebotomy regimen was superior to phlebotomy alone in steadily maintaining hematocrit (HCT) on target (<45%) in low-risk PV patients (Barbui et al. 2021).
- Recognizing its potential to change the standard management of low-risk PV, especially since treatment guidelines (NCCN, ELN) already recommend ropeg for certain patient groups, we aimed to evaluate the cost-effectiveness of ropeg from the perspective of the Austrian healthcare system over a 30-year period.

Methods

- Two therapeutic approaches were compared:
  - **Phlebotomy + aspirin** (300 mL for each phlebotomy) to maintain the HCT values of lower than 45%, and low-dose (100 mg daily) aspirin (if not contraindicated), as recommended by clinical guidelines (Barbui et al. 2018).
  - **Ropeginterferon alfa-2b** (BESREMi®; AOP Orphan Pharmaceuticals AG, Vienna, Austria) subcutaneously every 2 weeks at a fixed dose of 100 µg, by means of a ready-to-use injection pen, on top of conventional therapy.
- We combined a 12-month decision tree with a semi-Markov cohort model (**Figure 1**)
  - The decision tree was developed based on the Low-PV study (Barbui et al. 2021, Barbui et al. 2023 and Barbui et al. 2024).
  - The semi-Markov model considered the following health-states:
    - **Myelofibrosis-free survival (MFS) with HCT control** defined as maintenance of median recommended value HCT ≤ 45%, WBC <10 x109/l and PLT <400x109/l per cycle. The probability of thrombosis depends on HCT target achievement.
    - **MFS without HCT control** defined as HCT values > 45%. The probability of thrombosis depends on HCT target achievement.
    - **Post-PV MF** transition with increased leukocytes (leukocytosis) and platelets (thrombocytosis) and splenomegaly.
    - **AML** transition, higher for patients with post-PV-MF.
    - **Death.**
- The model considers the possibility to receive follow-up therapy with:
  - Interferon (IFN): Recombinant interferon alpha-2a, recombinant interferon alpha-2b or pegylated interferon alpha-2a
  - Hydroxyurea (HU)
  - Other: Ruxolitinib or anagrelide
- Additional details on methods are provided in **Table 1.**

Figure 1: Model structure

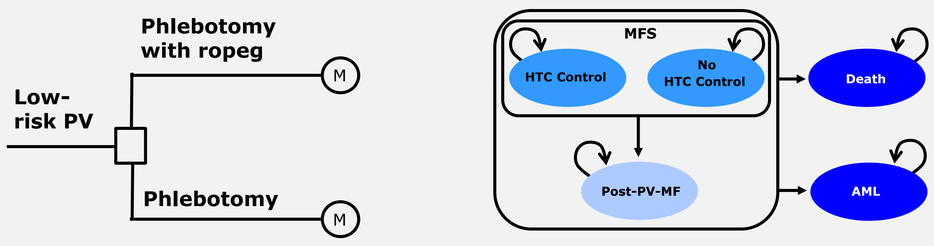


Table 1: Overview of methods applied

Type of study	Cost-utility analysis (CUA)
Type of model	Combined decision tree and semi-Markov cohort model
Perspective	Austrian health care payers perspective (direct costs)
Time horizon **Cycle length**	30 years 3 months
Discount rate	5% for costs and 5% for outcomes
Population	Eligible patients were adults aged 18–60 years with a diagnosis of PV, a HCT <45% and in need of phlebotomy. All patients met the definition of low-risk PV according to the ELN and the NCCN
Intervention	Ropeg plus standard therapy with phlebotomy + aspirin
Comparator	Phlebotomy + aspirin
Direct costs	• Medication, PHL and monitoring and thrombosis, AE and end-of-life costs represent reimbursements prices and tariffs and were extracted from published price lists • Post PV-MF and AML costs are derived from the literature
Outcomes	• Quality-adjusted life-years (QALYs) of the defined health-states were derived from the literature (Gerds et al. 2021) • Disutilities due to the symptoms burden from the low PV-study were used (Barbui et al. 2023)
Results	Incremental cost utility ratio (ICUR) Probabilistic sensitivity analysis (PSA) and deterministic one-way sensitivity analysis (OWSA) to examined the robustness of the model
Timing	2024

Clinical Data

- The primary composite end point in the Low-PV study, used in the decision three, was the percentage of patients who maintained HCT ≤45% for 12 months in the absence of progressive disease (Barbui et al. 2021).
- Transition probabilities for progression to post-PF MF and AML were extracted from a retrospective cohort study that specifically analyzed low-risk patients (Abu-Zeinah et al. 2021) and supplemented with simulation model by Barbui et al. (2023a).
- Survival was modelled using the published 20-year observational data in low-risk patients, divided among treatment groups (Abu-Zeinah et al. 2021).

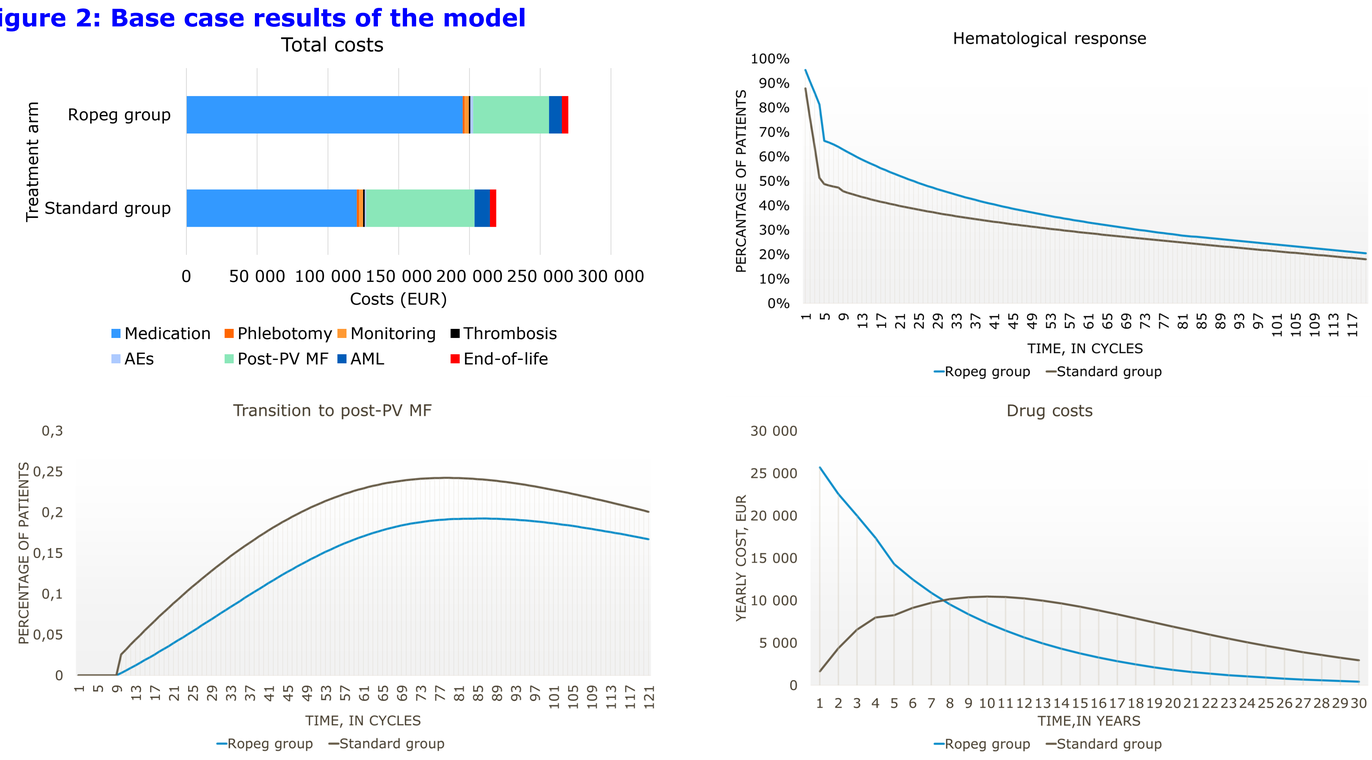
Results

- In our simulation, ropeg led to 1.4 higher QALYs and 50,960 € higher costs compared to phlebotomy alone, with an ICUR of 35,525 €/QALY (**Table 2**). Drug costs accounted for 72% of ropeg and 55% of standard group's costs. From Year 8, yearly drug costs were higher in the standard group (**Figure 2**).
- A higher percentage of low-risk PV patients treated with ropeg achieved the HCT target. After two years, 64% of simulated patients in the ropeg group reached the HCT target compared to 47% in the standard group; this was 53% vs. 40% after 5 years it and 39% vs. 32% after 10 years. As a result, fewer thrombotic events occurred with ropeg with a 12% cost decrease compared to the standard group.
- Earlier use of ropeg delayed the transition to post-PV-MF, reducing associated costs by 30% compared to the phlebotomy group. After 10 years, 11% of the simulated patients progressed to post-PV-MF, compared to 18% in the phlebotomy group.
- More patients in the standard group in our model developed AML (7% vs 6% after 10 years), with 16% higher costs compared to the ropeg group.

Table 2: Base case results

Costs	**Ropeg group**	**Standard group**	**Incremental**
Total costs	269,883 €	218,923 €	50,960 €
Outcomes			
QALYs	10.09	8.65	1.43
ICUR		**35,526 €**	

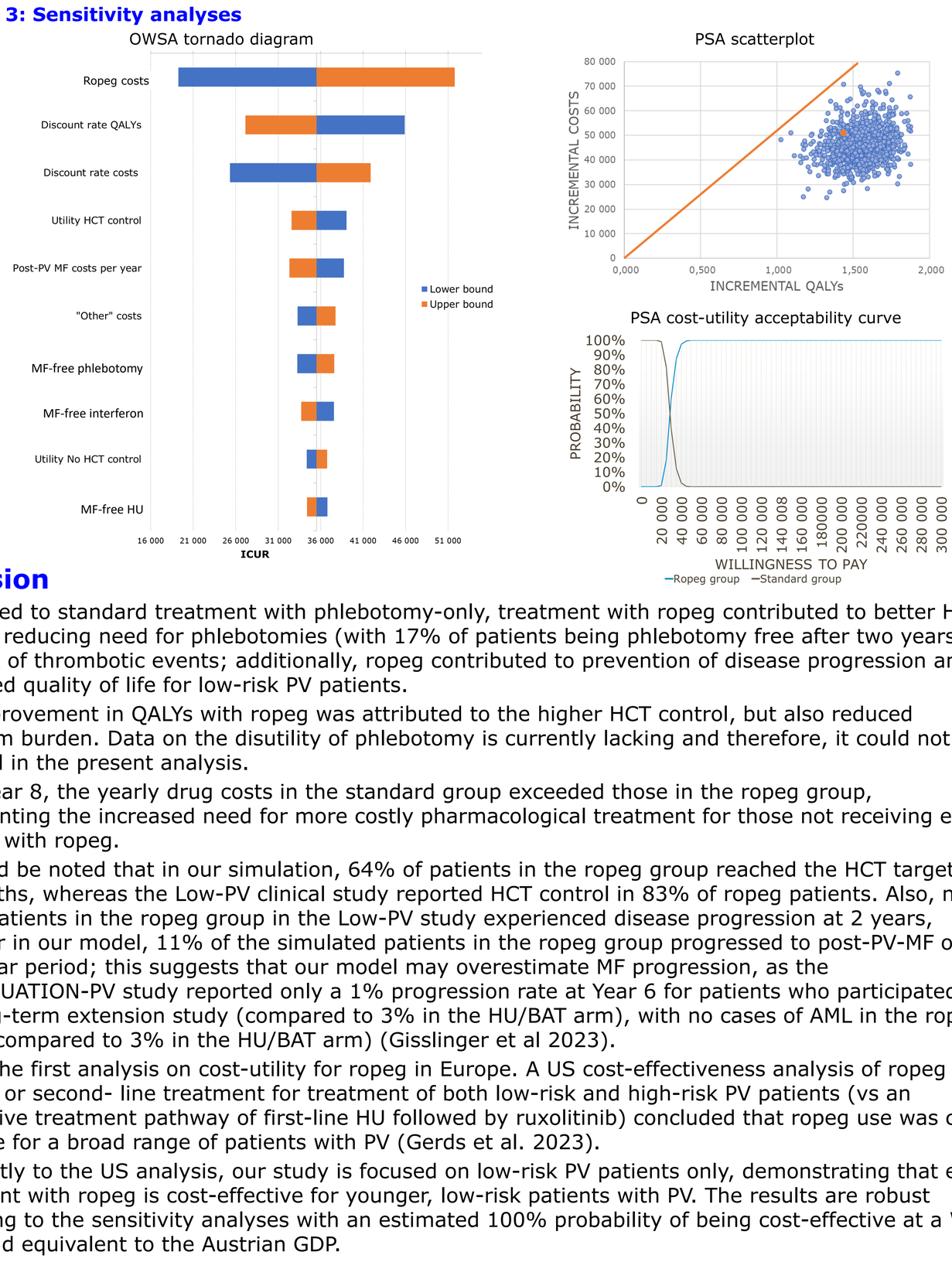
Figure 2: Base case results of the model



Sensitivity analyses

- In the OWSA, variations of ropeg costs, the discount rate (QALYs and costs), followed by the utility value for reaching the HCT target greatest impact results (**Figure 3**).
- The Monte-Carlo PSA results of 1,000 second-order simulations plotting incremental costs versus incremental effects. At a willingness-to-pay of GDP per capita (52,372 €), 100% of simulation are in the cost-effective range.

Figure 3: Sensitivity analyses



Discussion

- Compared to standard treatment with phlebotomy-only, treatment with ropeg contributed to better HCT control, reducing need for phlebotomies (with 17% of patients being phlebotomy free after two years) and risk of thrombotic events; additionally, ropeg contributed to prevention of disease progression and increased quality of life for low-risk PV patients.
- The improvement in QALYs with ropeg was attributed to the higher HCT control, but also reduced symptom burden. Data on the disutility of phlebotomy is currently lacking and therefore, it could not be included in the present analysis.
- From Year 8, the yearly drug costs in the standard group exceeded those in the ropeg group, documenting the increased need for more costly pharmacological treatment for those not receiving early therapy with ropeg.
- It should be noted that in our simulation, 64% of patients in the ropeg group reached the HCT target at 24 months, whereas the Low-PV clinical study reported HCT control in 83% of ropeg patients. Also, none of the patients in the ropeg group in the Low-PV study experienced disease progression at 2 years, however in our model, 11% of the simulated patients in the ropeg group progressed to post-PV-MF over a 10-year period; this suggests that our model may overestimate MF progression, as the CONTINUATION-PV study reported only a 1% progression rate at Year 6 for patients who participated in the long-term extension study (compared to 3% in the HU/BAT arm), with no cases of AML in the ropeg group (compared to 3% in the HU/BAT arm) (Gisslinger et al 2023).
- This is the first analysis on cost-utility for ropeg in Europe. A US cost-effectiveness analysis of ropeg used as first- or second- line treatment for treatment of both low-risk and high-risk PV patients (vs an alternative treatment pathway of first-line HU followed by ruxolitinib) concluded that ropeg use was cost-effective for a broad range of patients with PV (Gerds et al. 2023).
- Differently to the US analysis, our study is focused on low-risk PV patients only, demonstrating that early treatment with ropeg is cost-effective for younger, low-risk patients with PV. The results are robust according to the sensitivity analyses with an estimated 100% probability of being cost-effective at a WTP threshold equivalent to the Austrian GDP.

Conclusions:

- Ropeg is a cost-effective treatment option for patients with low-risk PV. Findings suggest that early treatment with ropeg could ensure optimal resource allocation by preventing costly thrombotic events and progression to MF whilst increasing patient quality of life.

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Abbreviations
AE, adverse event; AML, acute myeloid leukemia; ELN, European LeukemiaNet; HCT, hematocrit; IFN, interferon; ICUR, incremental cost-utility ratio; HU, hydroxyurea; MF, myelofibrosis; MFS, myelofibrosys-free survival; NCCN, National Comprehensive Cancer Network; OWSA, one-way sensitivity analysis; Post-PV MF, post-polycythemia vera myelofibrosis; PSA, probabilistic sensitivity analysis; PV, polycythemia vera; QALY, quality-adjusted life years; WTP, willingness to pay.

References
Abu-Zeinah G et al. Leukemia. 2021 Mar 2; **Barbui** T et al. Lancet Haematol. 2021 Mar;8(3):e175-e184; **Barbui** T et al. NEJM Evid. 2023 Jun;2(6):EVIDoa2200335; **Barbui** T et al. Ann Hematol. 2024 Feb;103(2):437-442; **Barbui** T et al. Blood Cancer J. 2023a Dec 15;13(1):187; **Gerds** AT et al. Journal of Comparative Effectiveness Research. 2023 Sep;12(9):e230066; **Gisslinger**, H., et al. Leukemia. 2023; 37, 2129–2132. Additional literature with the author.