Danicopan in addition to the component 5 inhibitor (C5i) ravulizumab for the treatment of adult patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) who have residual hemolytic anemia in Greece: A Cost- Utility analysis

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K. VELLOPOULOU[1], S. RAVANIDIS[1], A. GIANNAKOPOULOU[2], N. KOURKOULAS[2], A. SFIKAS[2], N. MATHIOUDAKIS[2], G. KOURLABA[3]

[1] ECONARE LP, Athens, Greece
[2] AstraZeneca Greece, Marousi, Greece
[3] Department of Nursing, School of Health Sciences, National and Kapodistrian University of Athens, Athens, Greece

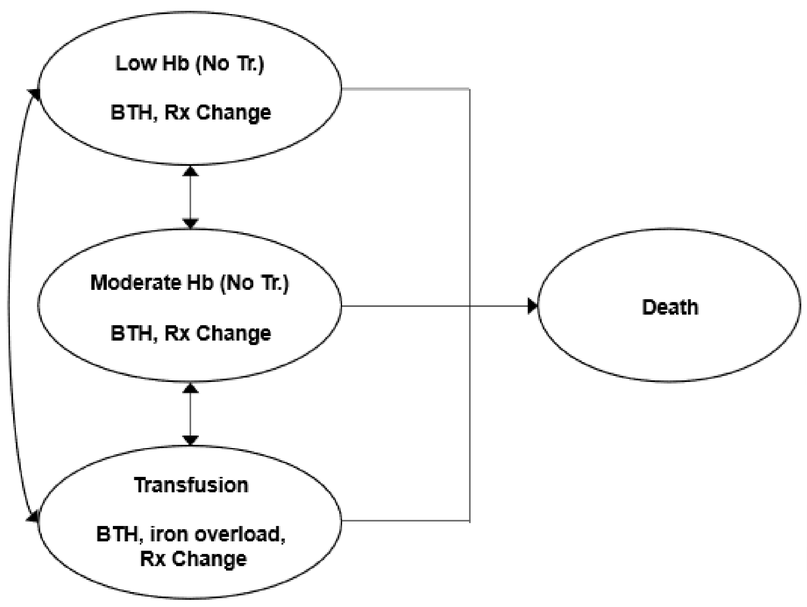
INTRODUCTION

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, chronic, life-threatening disorder driven by terminal complement activity and intravascular hemolysis leading to thrombosis, organ damage and premature mortality.
- Current treatment with C5 inhibitors (ravulizumab, eculizumab) reduces terminal complement activity and IVH; however, in some PNH patients treated with C5 inhibitors may experience residual symptomatic anemia due to extravascular hemolysis (EVH).
- Pegcetacoplan is also indicated as a monotherapy for PNH patients and in some patients who may experience residual symptomatic anemia due to EVH while on treatment with C5 inhibitors. However, these patients are accompanied by increased discontinuation associated with severe risk of breakthrough intravascular hemolysis (BTH).
- Danicopan, an oral factor D inhibitor, as add-on to ravulizumab, controls terminal complement activity and intravascular haemolysis intrinsic to PNH while preventing extravascular haemolysis (improving hemoglobin and reducing transfusions) and severe breakthrough intravascular haemolysis, leading to low risk of morbidity and mortality.
- Besides its clinical and safety profile, its economic values needs to be assessed.

OBJECTIVE

To evaluate the cost-utility of danicopan + ravulizumab versus pegcetacoplan in adult PNH patients under C5 inhibitor treatment and experiencing residual anemia due to EVH in Greece.

Figure 1.Model structure



METHOD

- A Markov cohort cost-effectiveness model (CEM) was developed, reflecting the natural history of PNH-EVH, including four mutually exclusive health states: Hb <9.5 g/dL ("Low Hb"), Hb ≥9.5 g/dL ("Medium Hb"), transfusion, and death (**Figure 1**).
- Within the "Low Hb", "Medium Hb", and "Transfusion states", patients could experience a BTH event, after which they would either undergo dose escalation or discontinue to C5i.
- The CEM was adapted with Greek data to correspond to the local management of PNH-EVH. A lifetime horizon (mean age: 47.6 years), on monthly cycles (28 days) was used, from the public payer perspective (EOPYY), with annual discounting of 3.5% for costs and outcomes [4].
- The patient population characteristics follow the ALPHA trial population [1].
- In the analysis, danicopan in addition to ravulizumab (danicopan/ravulizumab) was compared to pegcetacoplan alone.
- Clinical inputs, such as transition probabilities, BTH event rates, treatment switches and probabilities of transfusion-related iron overload were sourced from ALPHA trial [1] for danicopan/ravulizumab and PEGASUS clinical trial [2] or Hakimi 2022 [3] for pegcetagolan, respectively.
- Utility values using EQ-5D-3L were sourced from ALPHA trial [1]; utility decrements in case of BTH event, iron overload, and intravenous administration were applied [5-7].
- Healthcare resource use data such as drug dose, BTH events, iron overload management, AE management, transfusions and monitoring resources were derived from literature and validated by Greek clinical experts.
- Unit Costs were sourced from Greek official sources (Ministry of Health [8,9], EOPYY [10]) (**Table 1, Table 2**).
- Scenario analyses with different time horizons, discount rates and utility assumptions and one-way sensitivity analysis tested parameters' impact.
- Probabilistic Sensitivity Analysis (PSA) (1,000 iterations) captured uncertainty in the analysis.

RESULTS

- Over a lifetime horizon, the use of danicopan/ravulizumab was estimated to yield more QALYs and lower total costs compared to pegcetacoplan (**Table 3**).
- Incremental cost savings rise up to €484,022; and additional QALYs 0.476.
- The cost of ravulizumab treatment is the parameter that has the greatest impact on the results.
- Treatment with danicopan/ravulizumab remained dominant across all scenarios.
- PSA confirmed the robustness of the results, with all iterations providing lower cost and more QALYs (**Figure 2**).

Table 1. Drug acquisition costs (€, 2024)

	Prescribed dose (mg)	Dose scheme	Strength(mg)	Ex-factory price	Cost per mg	# doses per treatment cycle **	Cost per cycle**
Danicopan	150	3x/day	50, 100	€ 6.808	€ 0.44 /mg	84	€ 5,509
	200	3x/day	100	€ 7.293	€ 0.35 /mg	84	€ 5,901
Ravulizumab*	3,000	1x/8 weeks	1,100	€ 15.736	€ 12.40	1	€ 37,207
	3,300	1x/8 weeks				1	€ 40,928
	3,600	1x/8 weeks				1	€ 44,669
Pegcetagoplan	1,080	2x/week	1,080	€ 3.077	€ 2.47	2	€ 5,335
	1,080	1x/3 days				1	€ 2,668
	1,080	2x/week				3	€ 8,003

Source: Drug Price List bulletin Sep 2024 [8], Source for danicopan ex-factory price: Drug Price List bulletin Nov 2024 [9]
* In co-administration with danicopan
**Monthly

Table 2. Unit cost & cost per cycle of health care resources

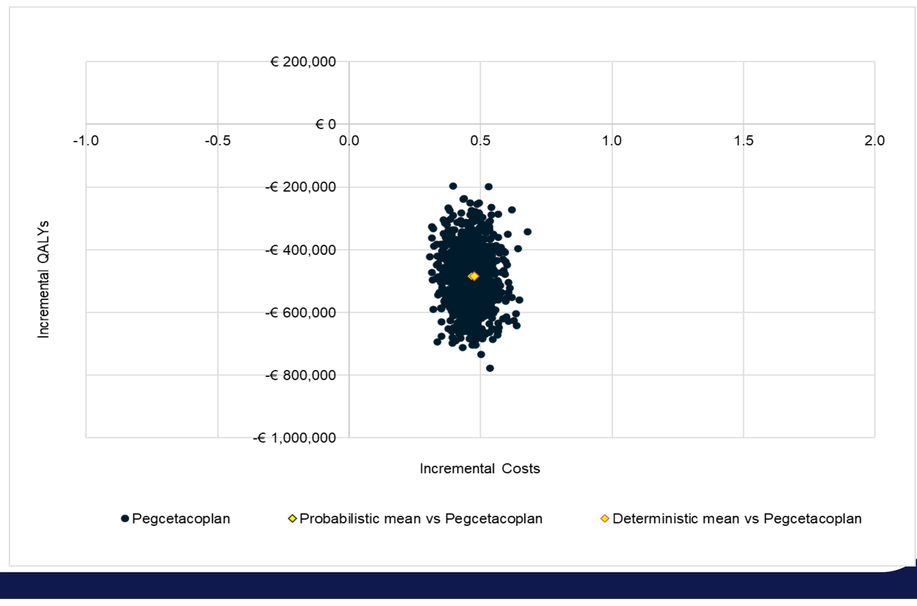
Cost parameter	Cost	Unit costs (€)	Description
Vaccination costs	€ 147.60	Meningococcal: €47.50 Pneumococcal: € 70.98 Influenza: € 28.98	Sum of vaccine costs [11]
Breakthrough hemolysis	€ 61.64	15% Hospitalization in GW (€ 80) 1% hospitalization in ICU (€ 200) 4% 7-days dialysis (€ 170.16)	Weighted average of hospitalization costs [11]
Administration cost	€ 40	50% of Daycare tariff per infusion (€ 80)	Administration cost per model cycle* [11]
Transfusions	€ 80	Daycare tariff (€ 80)	Per transfusion [11]
Iron overload	€ 859.57	54.8% deferasirox (€ 1,094.24) 45.2% Deferoxamine mesylate (€ 495.60)*	4-week average cost [8]
Follow-up & monitoring costs	'No transfusion' health state: € 13.35 'Transfusion' health state : € 96.47	Frequency at 'No transfusion' Frequency at ' Transfusion' Blood tests: € 38.23 Hematologist visits: € 10	Average cost in each health state [10]

* Administration of ravulizumab: every 4 weeks

Table 3. Base case cost-utility results

Treatment option	Total QALYs	Total costs (€)	Incremental QALYs	Incremental Costs	ICER (€/QALY
Pegcetagoplan	13.71	€ 6,686,190	-	-	Danicopan+ ravulizumab less costs & more effects
Danicopan + ravulizumab	14.18	€ 6,202,168	0.476	- € 484,022	

Figure 2. CE Plane (1,000 iterations)



CONCLUSIONS

- Danicopan as an add-on to ravulizumab is more effective and cost-saving compared to pegcetagoplan for the treatment of PNH-EVH in Greece.
- Findings were robust across scenario and sensitivity analyses.

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CONTACT INFORMATION & ACKNOWLEDGMENTS

Katerina Vellopoulou: k.vellopoulou@econcare.gr
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Abbreviations: CE: cost-effectiveness, CEM: cost-effectiveness model, GW: general ward, QALYs: quality adjusted life years, HP: hospital price, ICER: incremental cost-effectiveness ratio, ICU: intensive care unit, PNH-EVH: Paroxysmal nocturnal hemoglobinuria, BTH: breakthrough hemolysis, OWSA: one-way sensitivity analysis, PSA: probabilistic sensitivity analysis

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