Danicopan a dominant option for the treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH) with residual haemolytic anaemia in Spain

Castanyer M[1], Merino-Montero S[1], Malé N[1], Rubio D[2], Caballero M[2]

[1]Alexion Pharmaceuticals, Barcelona, Spain [2]Omakase Consulting SL, Barcelona, Spain

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BACKGROUND & OBJECTIVES

- Paroxysmal nocturnal hemoglobinuria (PNH) is a **rare, chronic, life-threatening blood disorder** driven by terminal complement activity and intravascular hemolysis (IVH) leading to thrombosis, organ damage and premature mortality (1–3).
- **Complement C5 inhibition with eculizumab and now ravulizumab as the current standard of care (SoC)** for patients with PNH with significant clinical symptoms controls terminal complement activity and intravascular hemolysis, **reduces thrombosis and improves survival** (4). In a subset of patients **with effective terminal complement inhibition**, **residual anemia could persist due to C3-mediated extravascular hemolysis (EVH)**, with anemia and fatigue potentially reaching debilitating levels and impacting patients' functional status and quality of life (5-7).
- **Danicopan**, an oral factor D inhibitor, was evaluated in a pivotal Phase III study (ALPHA), as an **add-on therapy to C5 inhibitors (C5i)** in patients with PNH who present **clinically significant extravascular hemolysis (EVH)** (9). When combined with C5 inhibition (eculizumab or ravulizumab), danicopan helps manage PNH symptoms while reducing the risk of EVH (9).
- The study objective was to determine the **cost-effectiveness (CE) of danicopan as an add-on therapy to the C5i (eculizumab or ravulizumab),** versus pegcetacoplan (C3 inhibitor) in patients with PNH with residual hemolytic anemia from a **Spanish healthcare and societal perspective**.

METHODS: THE MODEL

Model Structure

- A **Markov state-transition model** was developed with 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” health states, patients could experience a breakthrough hemolysis (BTH) event, after which a switch in treatment regimen was assumed (**Figure 2**) (9).
- The model uses a **four-week cycle length**, consistent with the visit schedule in the ALPHA trial (9), with health state transitions occurring every four weeks and no half-cycle correction applied due to the short cycle duration.
- Given the mean age of the population included in the analysis is 54.3 years, and assuming a maximum age of 100 years, the model applies a lifetime time horizon of 45.7 years.
- Costs and outcomes were discounted at 3.0% per year (10).

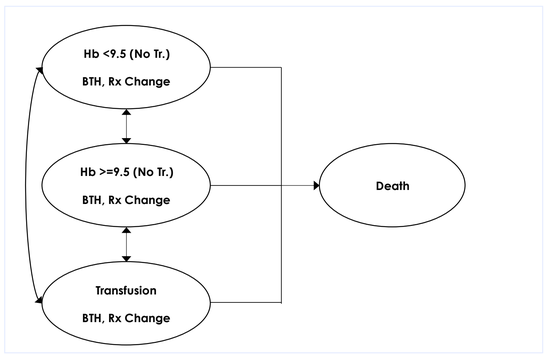

Figure 1. *Model structure*

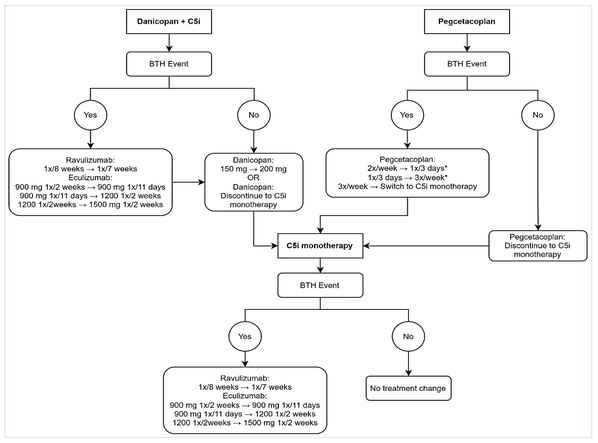

Figure 2. *Application of treatment switch probabilities within a model cycle*

Probabilities & Utilities

- Health state transitions and model probabilities were based on data from **the main pivotal studies for each drug**: ALPHA (9) and PEGASUS (11).
- For patients receiving C5i + danicopan, health state transition probabilities were estimated using a multinomial logistic regression model in SAS version 9.4 (SAS Institute Inc.), based on the approach described by Hakimi et al. 2022 (12) (**Table 1**):

Current health state = Previous health state + Treatment + Age

- For patients receiving pegcetacoplan, transition probabilities were derived directly from the analysis by Hakimi et al. 2022 (12).
- The transition probabilities reported by Hakimi et al. (12) were assumed to be generalizable to the health states defined in the current model framework*, which uses a **9.5 g/dL Hb threshold as in the base case** (**Table 1**).

Table 1. *Health state transition probabilities*

	Danicopan+C5i Final health status			Pegcetacoplan Final health status		
Initial health status	Hb < 9,5 mg/dL	Hb ≥9,5 mg/dL	Transfusion	Hb < 9,5 mg/dL	Hb ≥9,5 mg/dL	Transfusion
Hb < 9,5 mg/dL	0.4299	0.5401	0.0301	0.4370	0.4900	0.0730
Hb ≥9,5 mg/dL	0.0634	0.9217	0.0149	0.0310	0.9660	0.0030
Transfusion	0.1744	0.7573	0.0683	0.2660	0.6120	0.1220

*This was considered the most suitable alternative approach without introducing undue complexity into the model

- BTH events for C5i + danicopan were defined as **LDH (lactate dehydrogenase) levels ≥2xULN**. For pegcetacoplan, BTH probability from weeks 1 to 16 was based on the randomized controlled period of the PEGASUS trial (9,13,14). For the modeled period from week 17 to week 52, probabilities were based on data provided by the PEGASUS open-label literature (14).
- General population mortality was derived from **Spain-specific data** (15). As a conservative assumption it was applied uniformly across all treatment arms, excess mortality related to PNH was not included in the model.
- Health state utilities were estimated using Health-Related Quality of Life (HRQoL) data from the ALPHA trial using the EQ-5D-3L instrument and were assumed to remain constant throughout the model, with age-related adjustment applied multiplicatively based on Health Survey for England (HSE) 2014 data (16). Disutility was applied BTH, for iron chelation therapy and administration of pegcetacoplan and eculizumab.

Model cost assumptions

- Healthcare resource utilization and cost data were sourced from eSalud (17) and Botplus (18). The model includes pharmacological cost, administration associated cost (138€), chelation therapy (561€), antibiotic prophylaxis (10€), monitoring (51€) and transfusion costs (665€). Severe adverse events (headache and vertigo) were assumed to incur no additional cost.
- Given **Spain's dual pricing system**, price scenario analyses were conducted to assess the impact of **different pricing assumptions** -list prices and potential confidential discounts - on cost-effectiveness outcomes (**Table 2**).

Table 2. Price scenarios – pricing assumptions (June 2025)

Treatment	Base-case (List Price)	Scenario 1 (-30%)	Scenario 2 (-50%)
Danicopan (1mg)	0.504 €	List Price	-29%
Ravulizumab (300 mg)	5,018 €	3,513 €	2,509 €
Eculizumab (300 mg)	3,115 €	2,181 €	1,558 €
Pegcetacoplan (1080 mg)	3,338 €	2,336 €	1,669 €

RESULTS

- The **deterministic cost-effectiveness results** for the base case analyses comparing danicopan + C5i (eculizumab or ravulizumab) to pegcetacoplan are presented in **Table 3**, from both the health care system and societal perspectives.
- The societal perspective accounts for productivity losses associated with both health state impairment and time required for treatment administration (negligible in Spain, and conducting to no differences among perspectives).
- **Danicopan was dominant versus pegcetacoplan in the base case scenario** both from the payer and societal perspective with an incremental QALY gain of 0.352.
- When applying a 30% discount to the list prices of pegcetacoplan and C5i, danicopan remained cost-effective (ICER: €7,564). When assuming a 50% discount on pegcetacoplan and C5i, danicopan would retain dominance from a 29% discount applied to its list price (**Table 4**).

Table 3. *Results for danicopan + C5i (eculizumab or ravulizumab) vs pegcetacoplan in the base case scenario*

	Health Care perspective		Societal perspective	
	Danicopán + C5i	Pegcetacoplan	Danicopán + C5i	Pegcetacoplan
Total costs	8,387,643 €	9,096,319 €	8,387,643 €	9,096,319 €
Total QALY	15.19	14.84	15.19	14.84
Incremental cost	-708,676 €	-	-708,676 €	-
Incremental QALY	0.352	-	0.352	-
ICER	**-2,012,192 € (DOMINANT)**		**-2,012,192 € (DOMINANT)**	

Table 4. *Results for danicopan + C5i (eculizumab or ravulizumab) vs pegcetacoplan in the scenarios proposed*

	Health Care perspective Scenario 1 (-30%) Danicopan list Price		Health Care perspective Scenario 2 (-50%) Danicopan list Price -29%	
	Danicopán + C5i	Pegcetacoplan	Danicopán + C5i	Pegcetacoplan
Total costs	6,377,365 €	6,374,701 €	4,555,694 €	4,560,289 €
Total QALY	15.19	14.84	15.19	14.84
Incremental cost	2,664 €	-	-4,596 €	-
Incremental QALY	0.352	-	0.352	-
ICER	**7,564 € (COST-EFFECTIVE)**		**-13,049 € (DOMINANT)**	

- **Probabilistic sensitivity analyses (PSA) confirm the robustness of the cost-effectiveness results**, as incremental costs and QALYs for danicopan vs. pegcetacoplan remain relatively stable across the base case and price scenarios when model parameters are simultaneously varied within their respective probability distributions (**Figure 3**).

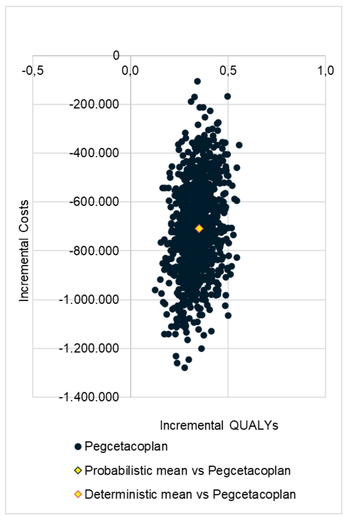

Figure 3. *PSA results base-case*

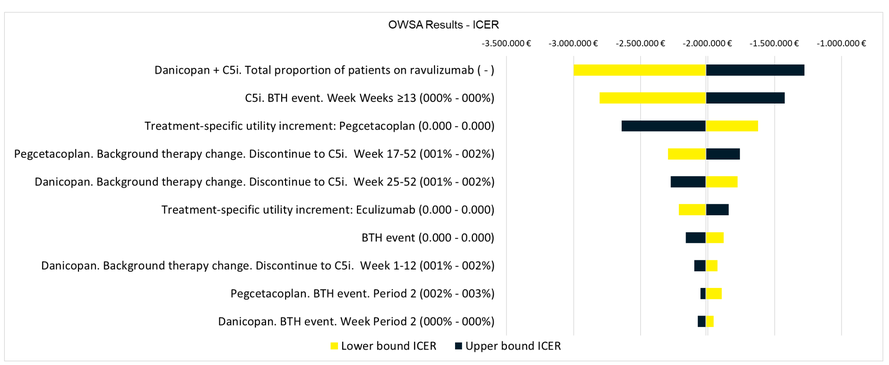

Figure 4. *OWSA results base-case*

The tornado diagram displaying the parameters with the greatest impact on the cost-effectiveness analysis outcomes is presented in **Figure 4**.

CONCLUSIONS

- Danicopan as add-on therapy to the current SoC (eculizumab and now ravulizumab) is a **cost-effective option** for the treatment of patients with PNH and **clinically significant EVH,** across all pricing scenarios.
- Danicopan is the only option available that allows the management of PNH patients **experiencing residual hemolytic anemia** while **ensuring control of terminal complement activity and IVH with C5i** (eculizumab and ravulizumab).
- Danicopan, in combination with C5i is a **dominant option** versus pegcetacoplan using a minimum discount of 29% vs. List price, even considering a discount up to 50% vs. list price for the comparator.

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Corresponding author: Miriam Castanyer (miriam.castanyer@alexion.com)

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