Poster EE233

Cost-effectiveness of ravulizumab compared with eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) in the Netherlands

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INTRODUCTION

- PNH is a rare, progressive, chronic disease predominantly diagnosed during young adulthood (30–45 years of age), characterized by chronic intravascular haemolysis and thrombosis [1].
- Complement C5 inhibitor eculizumab has significantly improved the survival and quality of life of patients with PNH [2,3]. However, the frequent infusions of eculizumab and the occurrence of breakthrough haemolysis (BTH) impact quality of life of the patients and their caregivers [4,5].
- In 2019, the long-acting complement C5 inhibitor ravulizumab was approved by the European Medicine Agency [6]. Ravulizumab has shown to be non-inferior compared with eculizumab, but due to its longer half-life time it requires 8-weekly instead of biweekly infusions [7,8].

Objective

- This study evaluates the cost-effectiveness of ravulizumab compared with eculizumab in patients with PNH from a Dutch societal perspective.

METHODS

Model design (Figure 1)

- A Markov cohort model was developed in Excel to assess the cost-effectiveness of ravulizumab compared with eculizumab from a Dutch societal perspective. The model was developed in accordance with the Dutch guideline for economic evaluations in healthcare [8].
  - All patients entered the model in the "No BTH" health state, in which patients were stable on eculizumab or ravulizumab and had no history of BTH caused by Incomplete C5 Inhibition (IncC5Inhib).
  - A history of IncC5Inhib BTH events is a predictive factor for subsequent events and, therefore, patients experiencing a IncC5Inhib BTH move to one of the history of IncC5Inhib BTH health states.
  - After a second IncC5Inhib BTH event, patients were assumed to be permanently up-dosed and cannot experience any subsequent IncC5Inhib BTH events.
  - The two mortality-related health states were "background mortality" and "PNH-related mortality". Background mortality was modelled for each living state and was based on Dutch general population mortality. PNH-related mortality is modelled as an excess mortality risk associated with BTH events.
  - Ravulizumab-treated patients were assumed to experience no InC5Inhib BTH events because no IncC5Inhib BTH were seen in clinical trials [7, 8].

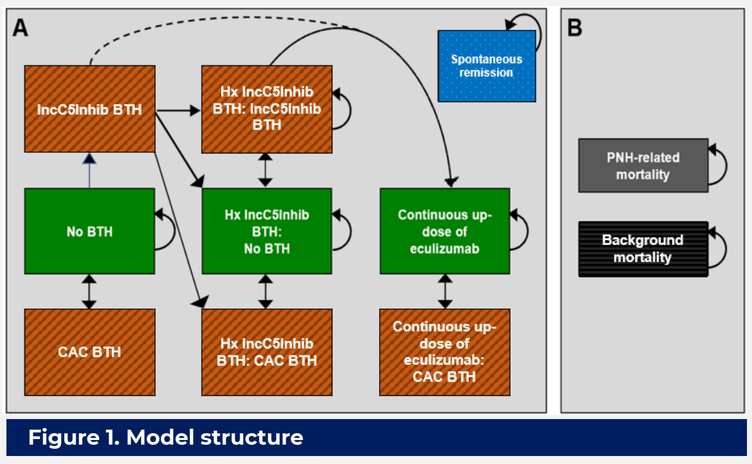

Figure 1. Model structure

Definitions

BTH: a new or worsening sign or symptom of intravascular haemolysis in the presence of elevated lactate dehydrogenase (LDH) (≥2 × ULN) after prior LDH reduction to <1.5 × ULN on therapy.

Complement—amplifying (CAC) BTH: BTH events that are related to an underlying complement-amplifying condition such as an infection, surgery, or pregnancy.

IncC5Inhib BTH: BTH events that are related to incomplete C5 inhibition

Model inputs

- The transition probabilities for BTH events were based on the 52-week data from ALXN1210-PNH-301 for Cohort 1 and ALXN1210-PNH-302 for Cohort 2 (Figure 12) [7,8].
- Health state-specific utilities were based on mapped trial data [7,8]. A utility increment related to the reduced infusion frequency was included based on a discrete choice experiment (DCE) in patients with PNH [10].
- Both medical (i.e., treatment, BTH, and general disease related) and societal (i.e., travel and productivity losses) costs were included. Input values for costs were based on literature and the Dutch manual for costing studies in health care [9].
- Costs were discounted with 4.0%, effects with 1.5% [9].

Sensitivity analyses

- A probabilistic sensitivity analysis, deterministic sensitivity analysis, and scenario analyses were performed.

Cohort 1
Adults who are naive to treatment with a complement-inhibitor.

Data source: ALXN1210-PNH-301 trial [6].

Cohort size was based on Dutch incidence (n= 7 patients).

Cohort 2
Adults who are clinically stable on eculizumab at the labelled dosing for at least six months.

Data source: ALXN1210-PNH-302 trial [7].

Cohort size was based on Dutch prevalence (n= 77 patients).

Aggregate population
In the base case, the outcomes were calculated for the aggregate population (n=84 patients).

Aggregate population was based on a mix of Cohort 1 and Cohort 2 (n=84 patients).

Figure 2. Patient cohorts represented in the analysis

RESULTS

- Results show that patients treated with ravulizumab incurred a total of €5,626,490 costs over a life-time, whereas patients treated with eculizumab incurred a total of €5,893,333 costs over a life-time (Table 1).
- A total of 24.85 QALYs were found in the ravulizumab cohort vs 23.28 QALYs in the eculizumab cohort (Table 1).
- Ravulizumab saved a total of €266,843 while gaining 1.57 QALYs over lifetime compared with eculizumab, resulting in a dominant ICER.

Table 1. Outcomes of the base-case analysis (per patient over life-time horizon)

	Ravulizumab	Eculizumab	Difference
Cohort 1			
Drug and administration costs	€5,518,020	€5,811,145	-€293,125
Medical costs	€14,942	€23,270	-€8,329
Societal costs	€102,594	€107,220	-€4,627
Total costs	€5,635,555	€5,941,635	-€306,081
Total effects (QALY)	24.30	22.70	1.60
ICER (€/QALY)			**Dominant**
Cohort 2			
Drug and administration costs	€5,521,074	€5,778,703	-€257,629
Medical costs	€5,484	€6,448	-€964
Societal costs	€99,107	€103,791	-€4,684
Total costs	€5,625,665	€5,888,942	-€263,276
Total effects (QALY)	24.90	23.33	1.57
ICER (€/QALY)			**Dominant**
Aggregate population			
Drug and administration costs	€ 5,520,820	€ 5,781,406	-€ 260,587
Medical costs	€ 6,272	€ 7,850	-€ 1,578
Societal costs	€ 99,397	€ 104,076	-€ 4,679
Total costs	€ 5,626,490	€ 5,893,333	-€ 266,843
Total effects (QALY)	24.85	23.28	1.57
ICER (€/QALY)			**Dominant**

CONCLUSIONS

- Ravulizumab is cost saving (-€266,843 per patient) and more effective (1.57 QALYs gained per patient) compared with eculizumab in patients with PNH in the Netherlands.
- Cost savings were mainly driven by the difference in total drug and administration costs of ravulizumab compared with eculizumab.
- The gain in QALYs is predominantly attributed to the lower administration frequency associated with ravulizumab and the absence of incomplete inhibition of C5 (IncC5Inhib) BTH events after initiation of ravulizumab treatment.

Sensitivity analyses

Univariate sensitivity analysis (Figure 3)

- The input with the greatest impact on the incremental costs for the aggregate population was drug costs (i.e., -€3,345,061 for the upper bound and €2,147,285 for the lower bound of eculizumab, and -€2,516,968 for the lower bound and €2,602,256 for the upper bound for ravulizumab). Because including these parameters would marginalize the impact of the other parameters in the tornado diagram, they have been left out for presentation purposes.
- Other parameters with a substantial impact on costs include transition probabilities for IncC5Inhib BTH events, administration costs and age at baseline. Parameters with a substantial impact on QALYs were the utility in the no BTH event health state, age at baseline, and utility increment related to the reduced treatment burden.

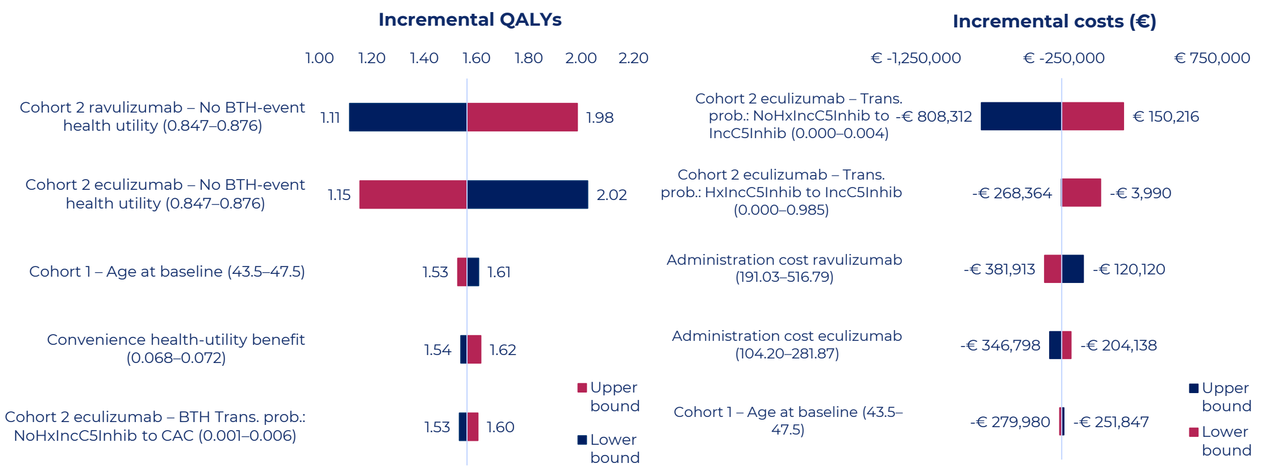

Figure 3. Tornado diagram presenting the five most influential parameters

Probabilistic sensitivity analysis (Figure 4)

- The cost-effectiveness acceptability curve represents the probability of cost-effectiveness against the willingness-to-pay (WTP) threshold. The probability of ravulizumab being cost-effective at a WTP of €20,000/QALY was 75.5%.

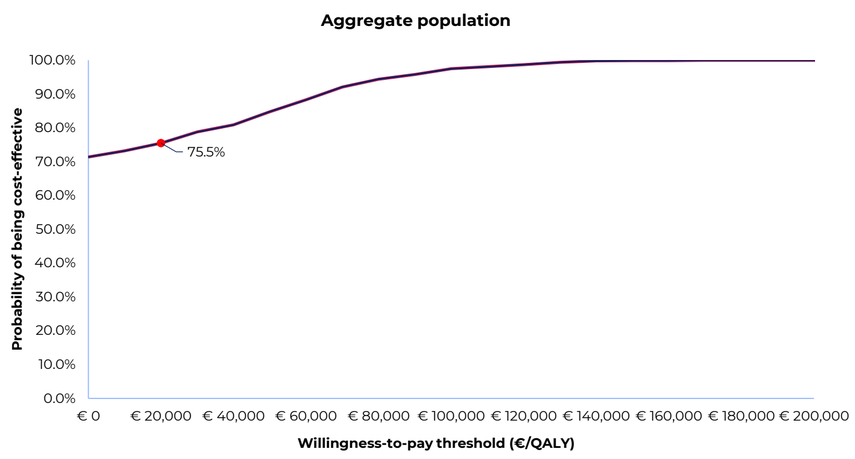

Figure 4. The cost-effectiveness acceptability curve

Scenario analyses – Impact on Costs and QALYs

Scenarios with most impact on incremental costs:
1) excluding up-dosing in eculizumab patients (incremental costs were €117,874)
2) setting the discount rate to 0% (costs and outcomes) (incremental costs were-€766,356).

Scenarios with most impact on incremental QALYs:
1) The incremental utility from a less frequent infusion regimen as based on the DCE (incremental QALYs were 0.60)
2) setting time horizon to 10 years (incremental QALYs were 0.95).

The scenario analysis showed that the new 100mg/mL formulation is more cost-saving than the 10mg/mL formulation, mainly due to reduced administration costs and productivity losses (Incremental costs of were -€388,939). However, the scenario does not consider the beneficial effects of a reduced infusion duration on the QoL of patients with PNH.

The use of a different mapping algorithm of EORTC to EQ-5D had minimal impact on the results. The difference between the two mapping algorithms was only 0.01. When the utility increment of ravulizumab vs. eculizumab was based on trial data and the DCE was excluded, ravulizumab still led to a gain in incremental QALYs of 0.60.

The scenario analysis showed that applying a no excess mortality risk during BTH events did not lead to significantly different outcomes (Incremental costs were -€274,22 and incremental QAYs were 1.53).

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