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Modeling Benefits, Costs, and Affordability of a Novel Gene Therapy in Hemophilia A

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ABSTRACT

The objective was to undertake an early cost-effectiveness assessment of valoctocogene roxaparvovec (valrox; Roctavian) compared to factor (F)VIII prophylaxis or emicizumab (Hemlibra; Roche HQ, Bazel, Switzerland) in patients with severe Hemophilia A (HA) without FVIII-antibodies. We also aimed to incorporate and quantify novel measures of value such as treatment durability, maximum value-based price (MVBP) and break-even time (ie, time until benefits begin to offset upfront payment). We constructed a Markov model to model bleeds over time which were linked to costs and quality-of-life decrements. In the valrox arm, FVIII over time was estimated combining initial effect and treatment waning and then linked to bleeds. In FVIII and emicizumab arms, bleeds were based on trial evidence. Evidence and assumptions were validated using expert elicitation. Model robustness was tested via sensitivity analyses. A Dutch societal perspective was applied with a 10-year time horizon. Valrox in comparison to FVIII, and emicizumab showed small increases in quality-adjusted life years at lower costs, and were therefore dominant. Valrox' base case MVBP was estimated at €2.65 million/treatment compared to FVIII and €3.5 million/treatment versus emicizumab. Mean break-even time was 8.03 years compared to FVIII and 5.68 years to emicizumab. Early modeling of patients with HA in The Netherlands treated with valrox resulted in estimated improved health and lower cost compared to prophylactic FVIII and emicizumab. We also demonstrated feasibility of incorporation of treatment durability and novel outcomes such as value-based pricing scenarios and break-even time. Future work should aim to better characterize uncertainties and increase translation of early modeling to direct research efforts.

INTRODUCTION

Hemophilia A (HA) is a rare hereditary X-linked bleeding disorder caused by a mutation in the *FVIII-gene* coding for coagulation factor (F)VIII.[1] This mutation results in activity impaired hemostasis causing bleeding tendency.[2] Treatment of severe HA focuses predominantly on bleed prevention, especially prevention of joint bleeds.[3] In The Netherlands, guidelines recommend prophylactic treatment of severe HA patients with intravenous (recombinant) FVIII every 1–3 days.[4] Recently, several FVIII products with extended half-life have been added to the treatment formularies, as well as the first monoclonal antibody emicizumab (Hemlibra; Roche HQ, Bazel, Switzerland). Emicizumab, a nonfactor replacement therapy, is administered subcutaneously every 1–4 weeks and is expected to have rapid global uptake. Longer-acting FVIII substitutes and nonfactor replacement therapies allow less frequent (intravenous) administrations increasing patient mobility and quality-of-life.[5] The latest innovation in HA-treatment is the emergence of gene therapies.[6] The promise of one-time treatments inducing prolonged or sustained near-normal FVIII is considered a potential transformative innovation and creates high expectations among patients and physicians.[7]

The first gene therapy indicated for severe HA is in advanced clinical trials: valoctocogene roxaparvovec (valrox; Roctavian by BioMarin, San Rafael, CA).[8,9] Valrox' developer applied for centralized market authorization in the late 2019.[10,11] However, in November of 2020, the application was withdrawn after the European regulator—following the US Food and Drug Administration—requested additional data from an ongoing phase III trial. The full results are not expected until November 2024.[12,13] In addition to clinical uncertainties, high upfront and irrecoverable costs are expected to create additional market access challenges.[14] Specifically, uncertainties around the extent and persistence of the potential benefits raise both practical and affordability concerns among health technology assessment (HTA)-bodies and payers (eg, will the intervention result in a net population health gain and over what time horizon?).[15–18]

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To inform HTA, cost-effectiveness analyses (CEAs) are used to quantify benefits, costs, as well as uncertainties and the net impacts on population health (ie, whether the health gained by the patient exceeds the health forgone elsewhere by the same resources not being available for other purposes). Few published CEAs have assessed gene therapies for hemophilia. Machin et al[19] was the first to assess the cost-effectiveness of a hypothetical gene therapy intended for HA in a US setting and found the gene therapy to dominate (being cost saving and more effective) compared to FVIII prophylaxis. More recently, Cook et al[20] explored the cost-effectiveness of valrox and incorporated individual patient FVIII. This allowed for incorporation of an initial treatment effect (max FVIII) and treatment waning over time, which are used more widely to determine gene treatment durability.[20–22] Cook et al[20] also estimated a cost-saving but with high variance (ie, large 95% confidence intervals [CIs]), but did not provide insight on affordability. Last, the US-based Institute for Clinical and Economic Review (US ICER institute) conducted assessments of emicizumab compared to FVIII prophylaxis and more recently of valrox versus emicizumab.[23,24] Awaiting availability of more clinical data, early cost-effectiveness analyses can be performed to quantify key areas of uncertainty. This is helpful both for the developers as well as policy makers, for example, to anticipate on upcoming dossiers, possible challenges, or inform access schemes such as Coverage with Evidence Development programs.[25,26] So far, no (early) assessments of the benefits, costs, and affordability of valrox have been conducted for the Dutch situation.

The objective of this study is to undertake an early cost-effectiveness assessment of valoctocogene roxaparvovec (Roctavian; valrox) compared to prophylactic FVIII or emicizumab (Hemlibra; Roche HQ) in patients with severe HA without detectable FVIII-antibodies in The Netherlands. We also explore the use of novel measures to aid product development and direct research efforts, such as treatment durability, maximum value-based price (MVBP), and break-even time (time for benefits to offset high upfront payment to improve population health).

MATERIALS AND METHODS

Study design

To model the expected benefits and cost of valrox in patients with severe HA in The Netherlands, a Markov state transition model was constructed in Microsoft Excel (Microsoft, Redmond, WA). We compared a hypothetical cohort of patients who received valrox to a cohort receiving FVIII prophylaxis and to a cohort receiving emicizumab. The model takes a societal perspective and adheres to the Dutch guidelines on economic evaluations in health care.[27] Costs were assessed from a Dutch societal perspective. The primary health outcome was quality-adjusted life years (QALYs). Cost-effectiveness was expressed in terms of incremental cost-effectiveness ratios (ICERs) and net benefits where appropriate.

As no list price is available for valrox we used a price of €2,125,000 in the base case based on previous research but also examined the MVBP of valrox,[28] the MVBP analysis also accounted for uncertainty in the confidential price discounts of FVIII and emicizumab with different discounts to list prices considered. In the emicizumab MVBP analysis, a dose reduction scenario was also included.[29] In both scenario's, the MVBP reflects where the intervention would still be considered as cost-effective condition on different prices of FVIII and emizumab.[30] Furthermore, we examined the point at which the intervention would break-even compared to the standards of care in terms of net health (eg, where the upfront cost, and resulting forgone health, is exceeded by the health benefits to the patient).

Model overview

A Markov model was constructed, based on a previously published model: The University of Washington Comparative Health Outcomes, Policy, and Economics (CHOICE) Institute Hemophilia A Cost-Effectiveness Model, which assessed prophylactic emicizumab versus FVIII in patients with inhibitors.[23] This model was adapted to the Dutch situation and to include an additional gene therapy arm. The gene therapy arm incorporated mean patient FVIII and treatment waning (Figure 1). This was done by translation of FVIII of patients treated with valrox from the literature to annual bleed rates (ABRs) based on work from den Uijl et al.[31–33]

The adapted model included 5 health states and 3 submodels. The model distinguished 5 health states reflecting different types of bleeds with more severe bleeds incurring higher costs and utility decrements: No bleed, untreated bleed, treated bleed not into target joint, treated target joint bleed and death (any cause). A target joint was defined as a single joint with ≥3 spontaneous bleeds within a consecutive 6-month period.[34] The cycle length of the model was 1 week with patients returning to the no-bleed health state at the end of each cycle. A time horizon of 10 years was considered based on reported sustained benefits and the absence of retreatment data.[10]

Within the model three sub-models were defined to incorporate joint damage: (1) no target joint; (2) 1 target joint; and (3) 2+ target joints (Figure 1).[23] The transitions between submodels was driven by the mean number of joint bleeds linked to Pettersson score (PS) increase.[35] PS ≥28 was assumed to indicate a target joint whereafter a patient transitioned to subsequent submodel after acquiring cost increase and utility decrement for a total joint replacement therapy (assumed 50% knee/50% hip).[36]

All input parameters and assumptions, including ranges for sensitivity analyses are reported in Table 1.

Population

The model simulated a hypothetical cohort of patients with severe uncomplicated HA (defined as adults with congenital FVIII deficiency, FVIII < 1%, and without detectable FVIII antibodies or adeno-associated virus serotype 5). The patient characteristics matched the phase I/II study by Pasi et al[9] (cohort 3), and are similar to the Dutch population.[31]

It was assumed that our cohort had the same life-expectancy as the general Dutch population.[37] Consequently, Dutch life-tables for background mortality were applied.[37] A mean age of 31 years (23–42) and mean weight 85 kg (68–102) were applied in line with cohort 3 from the phase I/II study by Pasi et al[9] (see Table 1). Weight was varied by age and was sex-adjusted using 2019 Dutch population statistics.[9,37] The prevalence of existing target joints was assumed to be 70%, of which 70% had >1 target joint. The baseline PS in submodels ii and iii was 24.1.[35]

Interventions

The primary intervention of interest was valrox (dosed 6×10^{13} vg/kg in one intravenous admission).[9] Mean FVIII and adverse events were derived from a phase I/II study and extrapolated beyond study duration.[9,51] In the first 2 months after valrox-treatment, patients received additional FVIII prophylaxis (including costs and adverse events) reflecting the trial protocol.[9] Patients also received prophylactic glucocorticosteroids (40 mg/d), which were tapered from week 3 onward.[8] In addition, the phase I/II study showed 1 of 7 patients (15%) in cohort 3 demonstrated limited response (FVIII < 5% after 2 y).[9] This is in line with more recent unpublished preliminary data from an ongoing phase III trial.[13,52] Therefore, 15% of patients in the base case were characterized as limited-responders and, in line with treatment protocol, switched back to FVIII prophylaxis.

The first comparator is standard (recombinant) FVIII concentrate prophylaxis (dosed 30I E/kg 3 times a week intravenously) and current main standard of care for patients with severe uncomplicated HA in The Netherlands.[38,45] The model also included an emicizumab arm. This nonreplacement therapy was

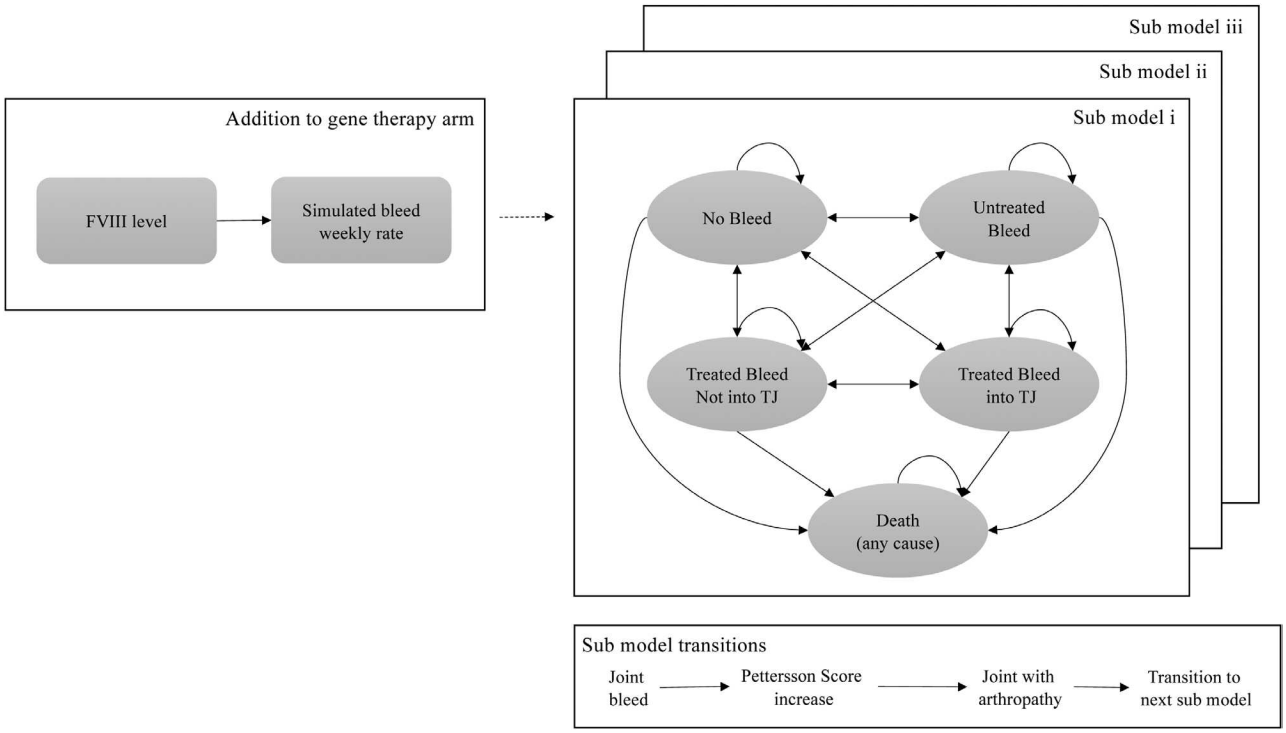

Figure 1. Structure of Markov model. Submodels have the same structure. Joint with arthropathy was defined as Petterson Score ≥28. Sub model i: No target joints. Sub model ii: 1 target joint. Sub model iii: 2+ target joints. FVIII = Factor VIII clotting factor; TJ = target joint.

approved for reimbursement in The Netherlands in July 2020 and is expected to have rapid uptake.[33] Following guidelines, emicizumab was dosed at 3 mg/kg/wk subcutaneous in the first month followed by maintenance dose of 3 mg/kg biweekly.[45]

Efficacy

Differences in treatment effects in the FVIII prophylaxis and emicizumab arm were driven by treatment specific ABRs (see Table 1). ABRs and adverse events were derived from the clinical trial to evaluate prophylactic emicizumab versus no prophylaxis in the HA without inhibitors (HAVEN-3) trial and the technology assessment of emicizumab conducted by The Dutch Health Care Institute (Zorginstituut Nederland, ZIN) and transformed to weekly rates.[32,38]

In the valrox arm, ABRs were deduced from FVIII reported by Pasi et al and translated to bleed rates using a relation described in the Dutch population by den Uijl et al.[31] This study found an S-curved association between the FVIII level and annual joint bleeds. A sigmoid-curve was fitted on the S-curve published by den Uijl et al[31] to simulate weekly joint bleed rates, which were translated to all bleed rates assuming 70% of all bleeds were joint bleeds.[20,24] After initial treatment with valrox, it was assumed after week 26 that maximum FVIII% were achieved (ie, initial treatment effect) based on trial data.[9] Treatment waning was incorporated by incorporating a mean linear decline of −5.7% FVIII/year based on public available developer materials.[9,10] Assumptions around the initial treatment effect and treatment waning were discussed in expert elicitation and found appropriate. FVIII was measured with one-stage assay, both by Pasi et al and den Uijl et al.

To best reflect the bleed rates, bleed types, and translation to clinical presentation of different HA severity and disease stages over time in the valrox arm, several additional decision rules were applied to the modeled sigmoid curve based on the previous work and expert opinion.[20] When FVIII >15% a base case spontaneous ABR of 1.0 (joint bleeds) was modeled.[20] Bleeds were modeled to be treated the same across treatment arms with demand FVIII dosed according to Dutch treatment formulary: 25 units/kg bolus followed by twice daily 15 units/kg for 3.5 d).[4,33,45] If FVIII >5% but ≤15% (corresponding to mild HA), 60% of bleeds were assumed joint bleeds of which 40% target joint bleeds.[20] When FVIII >1% but ≤5% (corresponding to moderate-to-severe HA), 25% of patients returned to prophylactic FVIII and when FVIII ≤1%, it was assumed 100% returned to chronic prophylactic FVIII therapy.

Expect elicitation was conducted to inform decision rules to translate FVIII to bleeds rates. Elicitation was conducted via semi-structured 60-minute interviews with clinicians (n = 3).[53] Additionally expert advisors were included to assess validity of modeled disease progression, treatment assumptions, clinical validity, and generalization to Dutch population.

Outcomes

Health outcomes were expressed in life years (LYs), QALYs, PS, and (joint) bleeds. A QALY is a generic measure capturing both survival and quality of life, which allows for meaningful comparison of health across different diseases.[54]

Baseline utility (eg, a standardized quality of life score with 0 reflecting death and 1 perfect health) was set at 0.82 for patients in the no-bleed health state in submodel i (no target joints) (see also Table 1).[42,55] In the 1 and 2+ target joint submodels, baseline utilities were related to PS derived from a study by Fischer et al[43] based on the SF-6D (utility derived from the Short Form-36) questionnaire with higher PS reflecting lower quality of life.[56] Patients experiencing a bleed were assigned an utility of 0.66 for 2 days across submodels.[42] A target joint bleed was assigned an additional disutility of −0.12.[55] Patients undergoing orthopedic surgery were assigned a 1-month disutility of −0.39.[44]

Resource use and costs

Drug costs were expressed in 2019 euros (€). At time of analysis, no price of valrox had been disclosed in The Netherlands by the developer; therefore, our base case scenario used the US price converted to 2019 Euros (Table 1).[24] As previously described,

Table 1.

Input Variables and Ranges Used in Deterministic and Probabilistic Sensitivity Analyses.

Input variables	Base Case	Low Estimate	High Estimate	Distribution	Source
Characteristics and disease progression					
Age	31	23	42	Normal	9
Weight	85	68	102	Normal	37
Sex (%male)	100%	—	—	Fixed	9
Prevalence existing target joint (%)	70%	56%	84%	Beta	32
Prevalence existing > 1 target joint (%)	70%	56%	84%	Beta	32
Pettersson score (baseline submodel ii/iii)	24.1	20.0	30.0	Lognormal	35
Number of joint bleeds per Pettersson Score increase	12.6	11.1	14.7	Lognormal	35
Valrox intervention					
Initial FVIII level (week 26)	67.00	20	84	Lognormal	9
FVIII waning (annual)	–5.72%	–1.56%	–10%	Lognormal	10
Limited responders (%)	15%	0.4%	45.9%	Lognormal	8,9
FVIII ≥15%: all bleeds (ABR)	1.0	0	2.0	Lognormal	Expert elicitation
FVIII ≥5% and <15%: joint bleeds (%)	60%	48%	72%	Lognormal	20
FVIII% >5% and <15%: joint bleeds into target joint (%)	40%	32%	48%	Lognormal	20
FVIII% ≥1% and <5%: patients receiving FVIII prophylaxis	25%	5%	40%	Lognormal	Expert elicitation
FVIII prophylaxis					
All bleeds (ABR)	4.80	3.20	7.10	Lognormal	32,38
Treated bleeds (ABR)	4.33	3.46	5.20	Lognormal	32,38
Treated joint bleeds (ABR)	2.90	2.32	3.48	Lognormal	32,38
Treated target joint bleeds (ABR)	2.50	2.00	3.00	Lognormal	32,38
Adherence during trial (0–24 wks)	100%	80%	100%	Beta	39
Adherence posttrial (>24 wks)	89%	71%	100%	Beta	40
Emicizumab					
All bleeds (ABR)	2.60	1.60	1.92	Lognormal	32,38
Treated bleeds (ABR)	1.30	0.80	1.70	Lognormal	32,38
Treated joint bleeds (ABR)	0.90	0.40	0.96	Lognormal	32,38
Treated target joint bleeds (ABR)	0.70	0.30	0.84	Lognormal	32,38
Adherence during trial (0–24 wks)	100%	80%	100%	Beta	41
Adherence post trial (>24 wks)	86%	69%	100%	Beta	41
Quality of life					
Utility, no bleed submodel i	0.88	0.66	0.98	Beta	42
Utility, bleed submodel i	0.66	0.53	0.79	Beta	42
Disutility target joint bleed submodel i	–0.12	–0.10	–0.14	Beta	42
Duration disutility bleed	2 d	—	—	Fixed	24
Utility PS 4–12, submodel ii/iii	0.82	0.78	0.86	Beta	43
Utility PS 13–21, submodel ii/iii	0.79	0.75	0.83	Beta	43
Utility PS 22–39, submodel ii/iii	0.73	0.69	0.77	Beta	43
Utility PS 40–78, submodel ii/iii	0.72	0.68	0.76	Beta	43
Disutility orthopc surgery	–0.39	–0.31	–0.46	Beta	44
Duration disutility orthopedic surgery	1 mo	—	—	Fixed	24
Cost (2019 Euro)					
Healthcare cost: pharmaceutical					
Cost/unit valrox	2,125,000	1,700,000	2,550,000	Gamma	24
Cost/unit FVIII prophylaxis (per IE)	0.89	0.20	1.10	Gamma	30
Cost/unit emicizumab (30 mg/mL vial)	2476	1980	2971	Gamma	45,46
Cost/bleed FVIII on demand (IE)	119.7/kg	95.78	143.67	Gamma	45,46
Healthcare cost: nonpharmaceutical					
Bleed-related, 19–44 y	904.55	723.64	1085.46	Gamma	47,48
Bleed-related, >44 y	3735.80	2988.64	4482.95	Gamma	47,48
Not bleed-related, no TJ (weekly)	112.38			Gamma	48,49
Not bleed-related, >1 TJ (weekly)	176.21			Gamma	48,49
Arthropathy surgery cost (50%TKR/50%THR)	11,850	9480	14,221	Gamma	48,50
Surgery related on demand FVIII (valrox and emicizumab arm)	8278	6622	9934	Gamma	4
Surgery related on demand FVIII (prophylactic FVIII arm)	66,225	52,980	79,470	Gamma	4
Surgical follow-up	20 y	—	—	Fixed	24
Adverse events valrox (week 1)	401.29	321.03	481.55	Gamma	8, 9, 48
Adverse events, FVIII prophylaxis (weekly)	2.01	1.61	2.41	Gamma	32, 38, 48
Adverse events, emicizumab prophylaxis (weekly)	2.06	1.65	2.47	Gamma	32, 38, 48
Nonhealthcare cost					
Lost productivity after bleed	1 d			Fixed	24
Lost days of productivity after hospitalization	Duration of stay + 2 d			Fixed	24
Hourly wage 2019 (adjusted for sex)	40.46	32.27	48.55	Gamma	27

Low and high estimates are extracted from literature (ie, confidence intervals) and used to explore impact on outcomes in sensitivity analyses.

ABR = annual bleed rate; FVIII = factor VIII; QALY = quality-adjusted life year.

FVIII costs are considerably lower than public available list prices as discounts are negotiated between hospitals and manufacturers.[30,57] This notion was supported by our expert advisors. Based on a procurement survey, a mean FVIII unit price of €0.89 per unit corresponding with 11% discount was applied (€0.56 per unit adjusted to 2019 Euros).[30,37] Impact of different discounts informed by the procurement survey and expert opinion was further explored in a scenario analysis. For emicizumab, the Dutch list price was used in the base case analysis (€2476 per 30 mg/mL vial).[46] The effect of dose reduction and a discount scenario were further explored in a second scenario analysis.

Healthcare utilization was derived from the literature and includes outpatient visits, hospitalization, and emergency room visits. Per bleed resource use was obtained from a real-world study and assumed similar across treatment arms.[47] Nonbleed-related healthcare utilization was divided into 19–45 years of age and >45 years old and also assumed the same across treatment arms.[49] Healthcare utilization was matched with Dutch Treatment and Diagnosis Combination Codes and tariffs from the Dutch Healthcare Authority (Nederlandse Zorgautoriteit; NZa) to calculate costs.[27,47–49] Untreated bleeds were assumed to accrue no cost, but they did incur a utility decrement (i.e., disutility), therefore these will not be further reported.[23]

Costs were split into healthcare and non-healthcare costs. Healthcare costs were further divided pharmaceutical costs (prophylactic and on demand treatment) and nonpharmaceutical costs (healthcare utilization; bleed-related; and nonbleed-related). To adhere to the societal perspective, nonhealthcare cost included costs for patients and family (rehabilitation after surgery and travel expenses) and loss of productivity.[27,58] This is in line with Dutch guidelines for economic evaluations.[27]

Analyses

Incremental benefits and costs between treatment arms were expressed as ICERs.[54] The ICER captures the incremental cost per unit of outcome of one intervention compared to another. Here, valrox was compared to prophylactic FVIII and separately to emicizumab yielding 2 ICERs. Prophylactic FVIII and emicizumab were not compared to each other. The ICER is calculated as: $(Cost_{intervention} - Cost_{control})/(QALY_{intervention} - QALY_{control})$.[54,59] Costs and (QA)LYs were discounted at 4.0% and 1.5% per annum, respectively, in line with Dutch guidance.[27]

Uncertainty around parameter estimates were explored via deterministic (DSA) and probabilistic sensitivity analyses (PSA).[54,60] The DSA explores impact of individual parameters by alternately varying input values between pre-set minimum and maximum values (Table 1) and can be considered parameter specific best- and worst-case scenarios. Minimum and maximum values were derived directly from the literature (eg, via reported 95% CIs, standard deviation [sd], or standard error [se]) or indirectly (by deriving 95% CI, sd, or se from patient characteristics using epidemiological methods).[54] When no variability measures were available, parameters were varied ±20%. A PSA provides a more comprehensive combined uncertainty estimate by simultaneously sampling uncertainty across all parameters. This was done by sampling 1000 iterations of random values for all model input parameters according to their individual distributions (Table 1).[61] PSA results are typically presented as a scatterplot in a cost-effectiveness plane. The PSA output was used to estimate the probability of a treatment being cost-effective for a given willingness-to-pay threshold, which was presented in a cost-effectiveness acceptability curves (CEACs). The Dutch informal willingness-to-pay-threshold of €80,000/incremental QALY was applied.[27]

In 2 scenario analyses, the mean MVBP was calculated for valrox at which its net monetary benefits (NMBs) equaled zero.[62] Given discounts of FVIII clotting factors are unknown, in the first scenario analysis, the impact of a range of discount scenarios (0%–80%) on MVBP was explored.[30] A 0% discount corresponds with the Dutch list price (€1.00/unit) and an 11% discount was applied in the base case (€0.89/unit).[30] In a second scenario analysis, MVBP for valrox was estimated in comparison to emicizumab.

Similar to the FVIII scenario, discounted emicizumab prices informed by expert opinion were explored and estimated to be plausible up to 50%. The price discount scenario was combined with a dose reduction scenario informed by recent research efforts. Donners et al[29] describes up to 50% emicizumab dose reduction could be possible, without loss of efficacy. This resulted in the inclusion of combined dose reduction and discount scenario for emicizumab, ranging from 0%–80%. Here, 0% discount corresponds with the Dutch list price and was used as base case (€2476 per 30 mg/mL vial).[46]

Last, a break-even point was expressed as the estimated time in years needed before treatment of a patient with valrox results in a net improvement in population health (ie, the health gains to the patient exceed the health losses elsewhere from the high upfront costs).[54]

RESULTS

Base case

The estimated cumulative bleeds and costs per treatment over time derived from the base case model are shown in Figure 2. The base case results in Table 2 show the cost and benefits per treatment arms over the model time horizon (10 y). Major cost drivers were the drug acquisition costs, with mean prophylactic drug costs accounting for 91%, 80%, and 92% of total cost for the valrox, prophylactic FVIII, and emicizumab arm, respectively. Valrox patients experienced 6.7 treated bleeds (ie, target and nontarget joints) compared to 42.1 in the FVIII arm and 11.5 with emicizumab over 10 years. This reduction in treated bleeds compared to FVIII prophylaxis is also reflected in lower PSs, higher total QALYs, and less on demand drug cost across in valrox and emicizumab arms (Table 2).

Results of the incremental analysis are shown in Table 3. Valrox was found to dominate both FVIII and emicizumab—meaning valrox results in higher incremental benefits at lower total costs. The CEAC shows valrox has a 54.8% probability of being cost-effective when compared to FVIII prophylaxis (Supplemental Digital Figure S1; http://links.lww.com/HS/A215). This means 54.8% of ICER-estimates in the PSA were lower than €80,000/QALY. In the comparison between valrox and emicizumab the estimated percentage was 38.9%. Given the dominant base case, these low CEAC-percentages suggest large uncertainty.

The DSA (Supplemental Digital Figures S2 and S3; http://links.lww.com/HS/A215) shows that similar parameters have most impact on outcomes across both comparisons, specifically: cost/unit of drug (valrox, emicizumab, and FVIII); initial treatment effect; distribution of limited responders and treatment waning. The PSA outcome (Supplemental Digital Figure S4; http://links.lww.com/HS/A215) is shown as a scatter plot of ICER-estimates in a cost-effectiveness plane, providing a visual depiction of the directions and extent of uncertainty of our estimates.

Mean MVBP and discount scenarios are shown in Figure 3. Base case MVBP of valrox (11% discount) compared to FVIII prophylaxis was estimated at €2,650,512 and varied from €2,929,004 in the most conservative discount scenario (0% discount) to €701,067 under the most optimistic scenario (80% discount) (Figure 3A). When compared to emicizumab, the most conservative discount scenario and base case MVBP (0% discount) was €3,527,984, and decreased to €779,405 under the most optimistic scenario (80% discount) (Figure 3B).

The base case break-even point was estimated after 8.03 years for valrox compared to FVIII prophylaxis and 5.68 years when compared to emicizumab (see Figure 4).

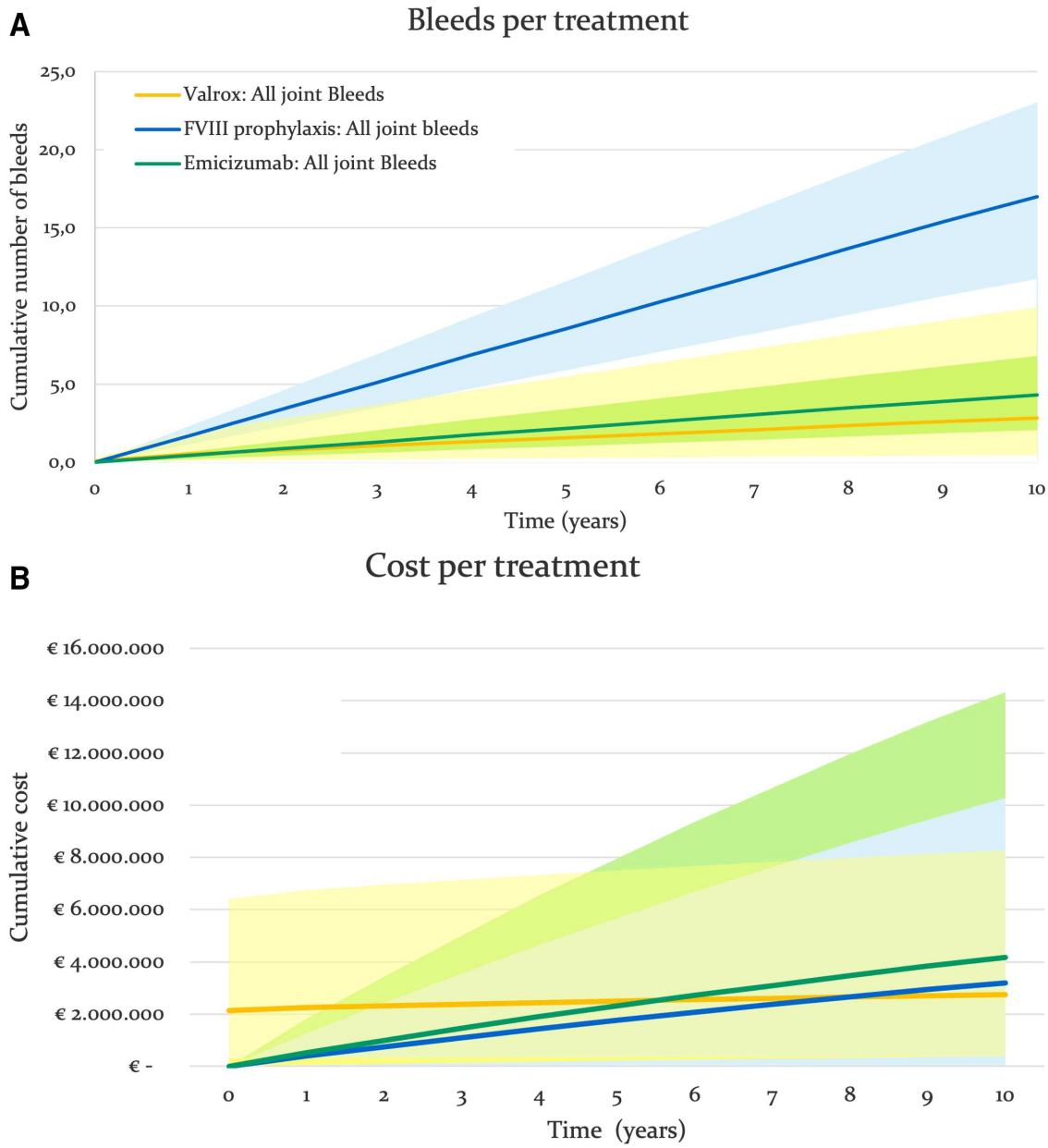

Figure 2. Simulated outcomes per treatment including 95% confidence interval over time in the base case analysis (cumulative over time). (A) Simulated bleeds (all bleeds and joint bleeds) per treatment. (B) Simulated costs per treatment. FVIII = Factor VIII clotting factor.

DISCUSSION

This early CEA shows that the intervention of the novel gene therapy valoctocogene roxaparvovec (valrox; Roctavian) compared to prophylactic FVIII as well as to emicizumab were estimated to result in greater QALYs gains for less costs resulting in dominated ICERs. Base case MVBP for valrox when compared to prophylactic FVIII was estimated at €2,622,663 and when compared to emicizumab €3,527,984. These estimates decreased to €701,067 and €779,405 under the most optimistic discount scenarios of FVIII and emicizumab, respectively. The cost-effectiveness and MVBP of valrox were found to be closely linked to price discounts of the FVIII clotting factor. To break-even on the initial irrecoverable upfront investment of valrox and to ensure net population health gains, it was estimated that the benefits (defined as FVIII > 5%) would need to be sustained at least 8.03 years compared to FVIII prophylaxis and 5.68 years compared to emicizumab. Although these estimates were associated with considerable uncertainty, they are in line with previous analyses of gene therapies in severe HA.[19,20] To our knowledge, this is the first early CEA of valrox compared to prophylactic FVIII and emicizumab.

The economic evaluation conducted by Machin et al[19] showed a dominated ICER over a 10-year time horizon but at lower cumulative costs and higher benefits. The lower costs can be explained as Machin et al[19] included only direct medical costs, lower FVIII dosage, and lower valrox price (ie, $850,000/treatment). Additionally, the study assigned a utility of perfect heath (ie, 1.0) to patients after successful gene therapy treatment and did not include loss of efficacy over time, which in light of recent clinical findings may be an overestimation.[9] Cook et al[20] constructed a microsimulation model and was the first to include treatment waning. The incremental results reported by Cook et al[20] also estimate valrox to be dominant compared to FVIII prophylaxis, but at higher costs.[20] This difference can

Table 2.

Estimated Base Case Benefits and Costs per Treatment Over a 10-year Time Horizon.

	Valrox		FVIII Prophylaxis		Emicizumab	
	Deterministic Analysis	95% Credible Range PSA	Deterministic Analysis	95% Credible Range PSA	Deterministic Analysis	95% Credible Range PSA
Costs						
Prophylactic drug cost	€2,570,885	(€296,326–€9,830,835)	€2,626,284	(€42,454–€9,041,070)	€3,930,144	(€100,531–€14,368,43)
On demand drug cost	€57,022	(€971–€767,311)	€355,193	(€5819–€1,225,133)	€108,241	(€1.872–€363,847)
Nonpharmaceutical cost	€89,035	(€81,690–€156,761)	€120,181	(€89.241–€197,420)	€94,766	(€85,203–€210,534)
Societal cost	€122,268	(€4492–€672,249)	€183,032	(€6250–€945,622)	€119,015	(€4389–€638,335)
Total cost	€2,839,210	(€487,449–€10,545,521)	€3,284,690	(€282,686–€10,444,562)	€4,252,167	(€408,737–€14,853,421)
Benefits						
Maximum Pettersson score	24.2	(11.59–40.21)	25.1	(12.26–40.92)	24.4	(11.51–40.07)
Treated non target joint bleeds	2.8	(0.49–21.89)	17.9	(9.35–27.61)	4.6	(1.39–7.23)
Treated target joint bleeds	3.8	(0.64–24.79)	24.3	(19.85–29.4)	6.9	(4.1–10.95)
Total QALYs	7.03	(5.86–8.14)	6.38	(5.59–7.36)	6.90	(5.98–7.96)
Total life years	9.29	(8.04–10.48)	9.28	(8.05–9.94)	9.28	(8.05–9.94)

FVIII = factor VIII; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; Valrox = valoctocogene roxaparvovec (Roctavian).

partially be explained by the US rates of FVIII costs which were approximately 3 times higher.[20] After initiation of this study, the US Institute for Clinical and Economic Review (ICER-institute) published a report assessing valrox in HA.[24] The biggest change compared to their previous report—assessing emicizumab and FVIII—is model structure.[23] The latest US ICER-institute model uses a Markov model preceded by a decision tree and puts more emphasis on joint damage. Due to early onset FVIII prophylaxis used in The Netherlands since the 1970s, arthropathy is likely to be most relevant to the elderly HA population and, therefore, less appropriate in the younger population assessed in this study.

During this study, the European regulator issued a negative interim market authorization opinion for valrox and requested additional data.[13] Consequently, the developer withdrew valrox' market authorization application. Some preliminary (unpublished) interim evidence from an ongoing phase III trial has since became available, but full trial results are not expected until November 2024.[12,13] In light of these events, our study was characterized as an early CEA in contrast to the studies previously published and discussed earlier.[63] Early cost-effectiveness analyses are often conducted with less robust clinical data in early clinical development to explore major uncertainties and inform further, among other purposes, evidence generation and development strategies.[25,64] Reassessment when new the evidence becomes available may decrease some uncertainty, but mostly will add to learnings of interpretation of early clinical data.[65] To add, full pipelines of novel therapies are observed for HA, including extended half-life FVIII, nonreplacement therapies, and other gene therapies.[66] By adding arms to this model, (early) economic evaluations will allow more rapid assessment of their relative-effectiveness and cost-effectiveness.

Although achieving incremental health benefits at lower costs sounds attractive, there are additional considerations which require further discussion. First, as previously mentioned, gene therapies with a sustained or curative claim are administered in the present time, as is the payment. The irreversible upfront treatment cost is only offset by future health benefits. Hence, benefit durability over time is critical and have so far not been clinically confirmed. If a therapy turns out to be less effective than initially claimed this treatment cannot be discontinued due to the one-off nature of provision, nor can the cost be recouped.[67] Second, the initial budget impact and/or the proposed timing of payments may pose affordability challenges among payers.[68] This raises the question whether affordability may not only be associated with high prices but also with timing of payment. Third, our results reflect benefits and cost on a population level. From the clinical evidence supporting this analysis, as well as previous work, it is known that intrapatient variability is considerable.[9,20,51,69] This means that some patients may achieve incremental benefits for less costs, but also vice versa. Increasing insights and predictability of benefits on a patient level is of great interest in the hemophilia space and may decrease decision uncertainty.[70,71] Last, cost-effectiveness is expressed a ratio between therapies. Therefore, the ICER measure may suggest an intervention is cost-effective—or even cost-saving—even when the comparator itself is not. This supports the interpretation of cost-effectiveness and affordability of novel interventions in a wider context than ICER estimates only. Additional research is needed to best interpret cost-effectiveness and affordability of one-off therapies with sustained effect, this may include additional measures such as—but not limited to—budget impact, break-even point, MVBP, and treatment durability.

Despite best efforts this study has some limitations. First, our analyses rely mostly on clinical data from a small clinical trial.[9,51] Key parameters describing treatment durability are uncertain and showed considerable impact on outcomes. Also, the single arm design of the trial required indirect comparisons between model arms. Together with the different simulation approaches taken in the valrox arm (simulation of bleed rates using FVIII) and prophylactic arms (bleeds rates derived from the literature), this may cause additional bias which has not explicitly been quantified in our sensitivity analyses. However,

Table 3.

Estimated Incremental Base Case Benefits, Costs and Probability of Being Cost-effective Compared to Valrox of a 10-year Time Horizon.

[B] Treatment	Benefits (QALYs)	Costs €	Incr Benefit	Incr Cost	ICER	Probability of Being Cost-effective[a] (%)
Valrox	7.03	€2,839,210	—	—	—	—
FVIII prophylaxis[b]	6.38	€3,284,690	0,65	–€358,970	Dominated	54.8
Emicizumab[b]	6.90	€4,252,167	0,13	–€1,412,957	Dominated	38.9

[a]Probability of being cost-effective using a willingness-to-pay threshold of €80,000/incremental QALY.

[b]Proper interpretation of the table results.

FVIII = factor VIII; ICER = incremental cost-effectiveness ratio; incr = incremental; QALY = quality-adjusted life year; Valrox =valoctocogene roxaparvovec (Roctavian).

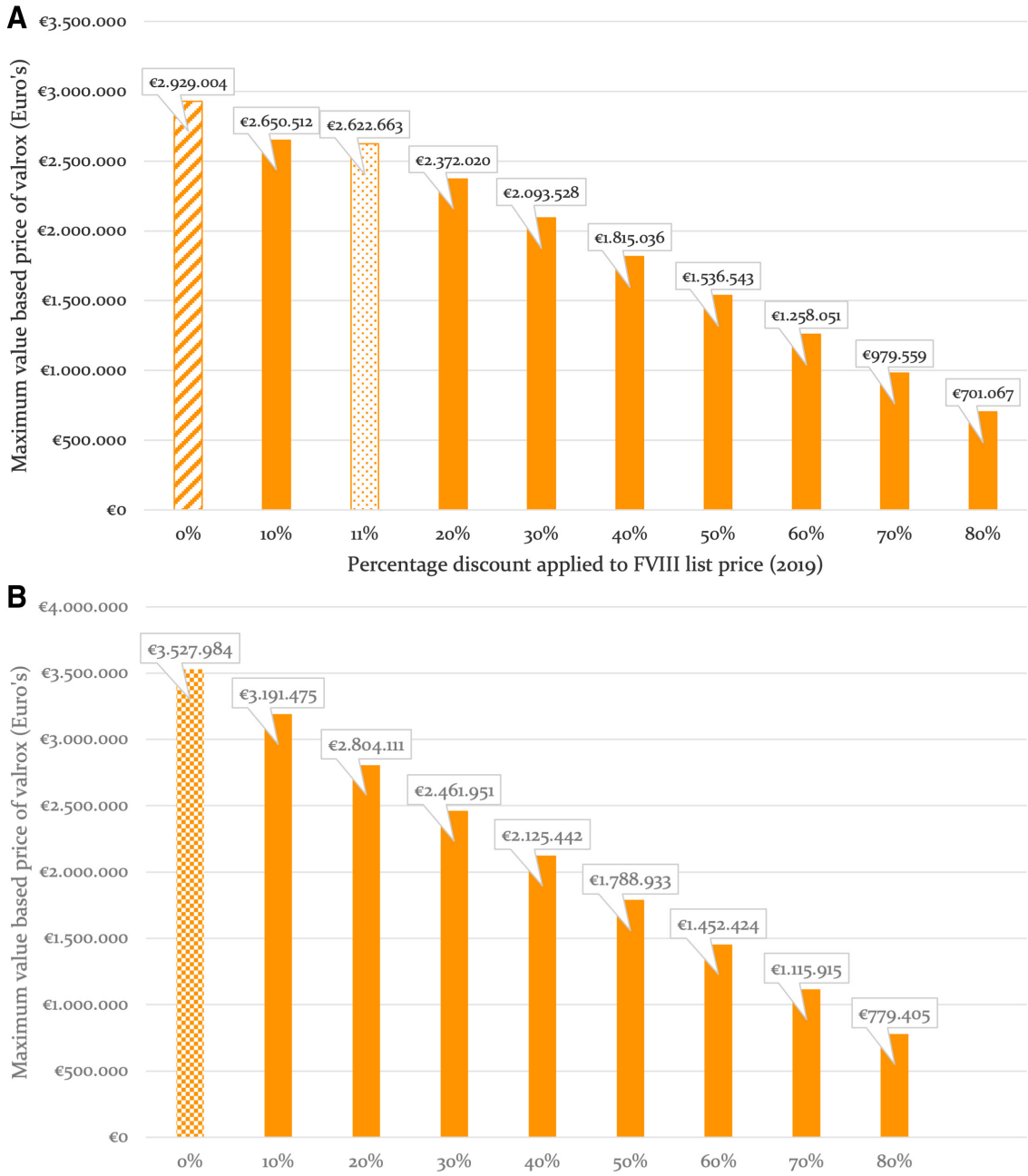

Figure 3. Maximum value-based price (MVBP) of valrox under discount scenarios. (A) Simulated MVBP with discounted FVIII scenarios with 0% discount represents Dutch list price (striped bar at €1.0/unit), and 11% discount aligns with the base case analysis (dotted bar at €0.89/unit) based on the literature.[30] (B) Simulated MVBP with discounted emicizumab scenario's with 0% discount represents Dutch list price and base case (checked bar at €2476 per 1 mL vial 30 mg/mL), Time horizon: 10 years. FVIII = Factor VIII clotting factor.

these are limitations which decision makers will likely increasingly encounter. We aimed to address these limitations by, as described in guidelines, matching inputs based on patient characteristics and using effectiveness parameters from meta-analyses where possible.[24,27,33] In addition, (irreversible) future side effects were not included as no supporting clinical evidence was available. Short-term side effects are immunological responses, which may lead to liver function abnormalities, decrease of FVIII and failure of therapy. We aimed to address the latter by including nonresponse in our estimates. Furthermore, the utilities applied in the model reflect HA patients with inhibitors as these were the only available estimates at that time for emicizumab.[23] However, patients without inhibitors are expected to have a higher quality of life; therefore our utilities may be underestimated.[5] Also, our approach to use FVIII to simulate bleeding rates in the gene therapy arm was done to incorporate treatment durability as well overcome the limitation that valrox and prophylactic FVIII benefits are FVIII-level driven, and emicizumab is not.[72] The last limitation is that we did not take into account the costs and burden of administration of FVIII (intravenously) and emicizumab (subcutaneously) by the patients at home 3 times a week (around 1500 times and 250 times over 10 years, respectively), which may mean we underestimated societal costs and burden.

By modeling treatment waning, this is the first study comparing a gene therapy in HA to both FVIII prophylaxis and emicizumab. Other strengths of this study are demonstration of feasibility to include break even time and MVBP, which are

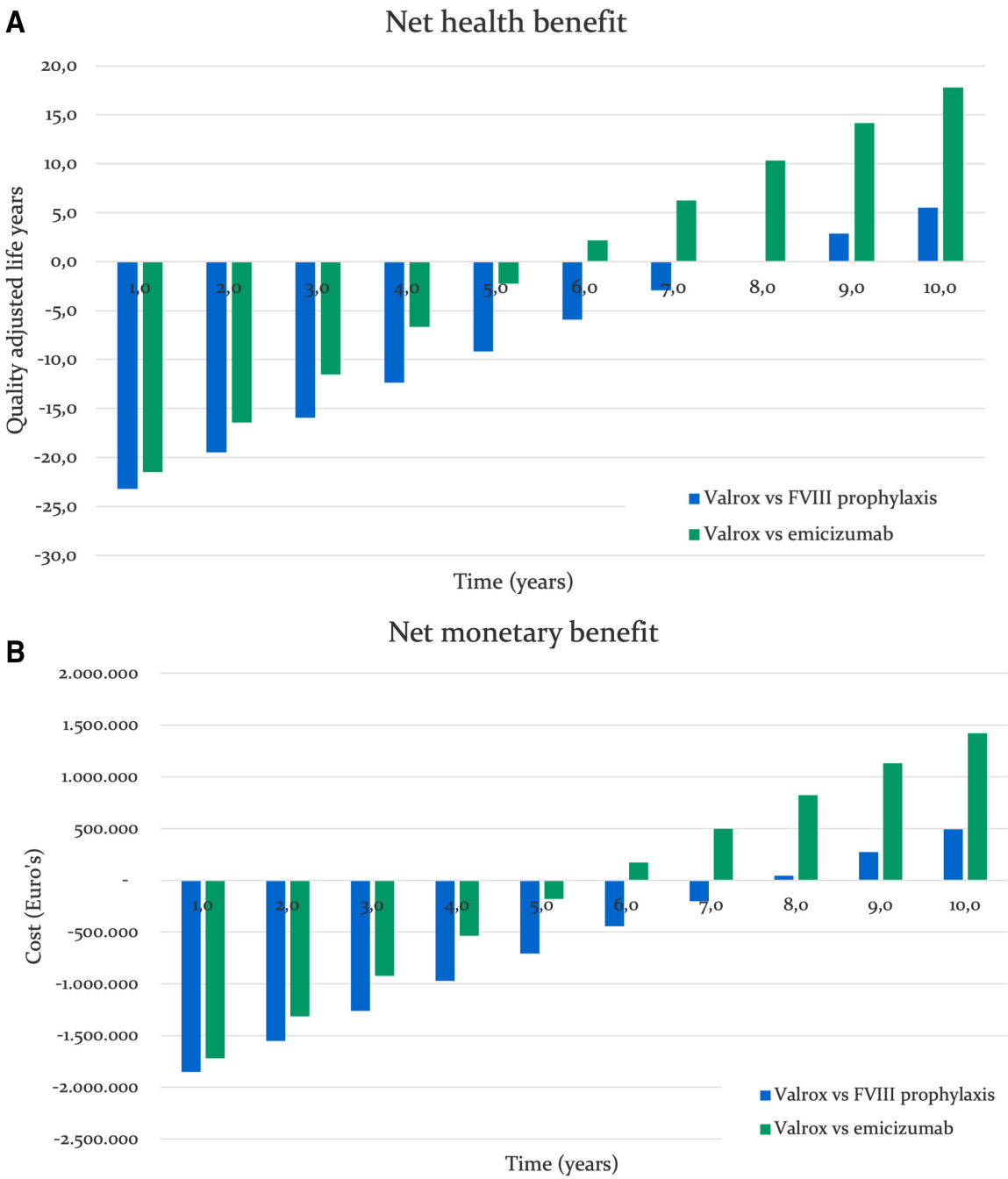

Figure 4. Return on investment expressed as breakeven point of net benefit. Return on investment expressed as breakeven point of net health benefit (A) and net monetary benefit (B). FVIII = Factor VIII clotting factor.

not routinely included in (early) cost-effectiveness analyses. Estimation of break-even time can improve contextualization of the ICER for curative therapies, also outside the hemophilia field.[68] Future research can further explore feasibility and informativeness to include expected value of information analyses (EVIs). EVIs provide strategic information when a "wrong" strategy is adopted, expected cost of uncertainty, and parameters for which additional research is most useful.[73,74] This may be useful to design coverage-with-evidence development payment models and can also be applied earlier on in decision making. EVIs, together with a forgone-health-assessment, can also quantify net benefits (or losses) of postponement of market authorization, informing decision-making and prioritize additional data requests.[54]

Clinical interpretation

In this model, the decrease of FVIII expression over time in patients treated with valrox is portrayed as a gradual process. However, translation of FVIII expression to bleeding tendency in clinical practice is more dichotomous. As similar joint bleeding rates are observed when FVIII > 100% or FVIII > 15%.[31] When FVIII intercepts approximately 10%, annual bleed rates increase considerably. Therefore, perhaps, the initial treatment effect and decrease in FVIII over time are less important than modeled here, as long as patients remain above FVIII > 15%. Also, reduction in FVIII treatment cost due to tenders, discounts, and other reasons were in general seen as a positive trend from a healthcare perspective.[30] Although the introduction of new treatment options are welcomed by patients and physicians, they are also

associated with high prices. This increases pressure on (hospital) budgets and raises economic and ethical concerns.[69]

To conclude, the results of this early CEA comparing valoctocogene roxaparvovec (valrox; Roctavian) to standard-half-life FVIII prophylaxis, and to emicizumab in severe hemophilia A without FVIII antibodies in The Netherlands estimated—in both comparisons—that incremental health gains were achieved for less costs. Second, we were able to incorporate treatment durability, a novel gene therapy-specific measure, in an early cost-effective model. In addition, the novel measures MVBP and break-even time were modeled and quantified. Base case MVBP was for valrox was €2,622,663 and €3,527,984 when compared to prophylactic FVIII and emicizumab, respectively. Break-even time was 8.03 and 5.68 years compared to FVIII and emicizumab, respectively. Future work should aim to better characterize uncertainties and increase translation of early cost-effectiveness analyses to inform product development and direct research efforts.

DISCLOSURES

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