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ORIGINAL RESEARCH

Estimated Long-Term Durability of Valoctocogene Roxaparvovec Treatment in Male patients with Severe Hemophilia A: An Extrapolation of Clinical Data

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ABSTRACT

***Introduction*:** Valoctocogene roxaparvovec is a single administration gene therapy treatment that enables endogenous factor VIII (FVIII) production to prevent bleeding in people with severe hemophilia A. Valoctocogene roxaparvovec is associated with a higher probability of being bleed-free, improvements in annualized bleed rates, and improvements in health-related quality of life compared with FVIII prophylaxis. The economic value of valoctocogene roxaparvovec will be determined, in part, by the duration of time over which the treatment effect is maintained, and the consequences associated with loss of response. Therefore, this analysis aimed to estimate the long-term durability of valoctocogene roxaparvovec treatment effect by extrapolating pivotal and longer-term trial data (Phase 3 GENEr8-1 4- to 5-year and a Phase 1/2 study 7-year data) to inform decision-making.

***Methods*:** Using data from the pivotal Phase 3 study GENEr8-1 and longer-term data from the 6E13 vg/kg cohort of Phase 1/2 Study 270–201, time to loss of response was analyzed within a time-to-event analysis framework. Loss of response was defined as a combination of: FVIII level decline < 5% and return to continuous prophylactic treatment and experiencing ≥ 2 treated bleed events in the previous 6 months at the time of return to prophylactic treatment.

***Results*:** Data were available for 134 participants from GENEr8-1, and 7 participants from Study 270–201. The main analysis results for predicted median durability ranged from 11.0 to 17.0 years considering the three statistically best-fitting parametric distributions; considering five plausible distributions, results ranged from 8.1 to 25.6 years. In scenario analyses using different definitions of loss of response, the results were broadly similar, with median durability ranging from 7.2 to 31.8 years.

***Conclusion*:** This analysis demonstrates the potential therapeutic benefit of valoctocogene roxaparvovec may be sustained beyond the follow-up period in existing clinical trials and

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across all parametric extrapolations and definitions analyzed, indicating that gene therapy may offer long-term benefits beyond what has been previously reported (i.e., 7 years).
Trial Registration number: GENEr8-1: ClinicalTrials.gov identifier, NCT03370913. Study 270–201: ClinicalTrials.gov identifier NCT02576795.

PLAIN LANGUAGE SUMMARY

Hemophilia A is a condition where blood is unable to properly clot because of a missing protein (factor VIII [FVIII]). People with hemophilia A are at increased risk of prolonged bleeding that can be fatal. To prevent bleeding, people with severe hemophilia A routinely inject treatment into the skin or vein (known as prophylaxis). While this is generally effective, many people still have bleeds, and some people find the frequent injections difficult and time-consuming. Valoctocogene roxaparvovec is a gene therapy where a single injection helps the liver to make the missing protein (FVIII) and prevent bleeding episodes. Valoctocogene roxaparvovec clinical trials have compared the number of treated bleeding episodes participants had prior to gene therapy while using FVIII prophylaxis, with the number of treated bleeding episodes after gene therapy. On average, after gene therapy, participants had 4.1 fewer treated bleeding episodes per year. In this analysis of the trial data, different definitions of loss of response were used to explore how differences in the criteria used to stop treatment might impact how long the therapeutic benefits might last. Across the different combinations of criteria used to define loss of response, the median durability ranged from 7.2 years to 31.8 years, showing that valoctocogene roxaparvovec has the potential to keep having therapeutic benefits beyond what has previously been reported (7 years).

Keywords: Gene therapy; FVIII prophylaxis; Severe hemophilia A; Valoctocogene roxaparvovec; Loss of response

Key Summary Points

Why carry out this study?

Valoctocogene roxaparvovec provides endogenous factor VIII (FVIII) production for people with severe hemophilia A.

This analysis applies different definitions of loss of response to estimate the long-term durability of valoctocogene roxaparvovec.

What was learned from this study?

This analysis suggests that the therapeutic benefits of valoctocogene roxaparvovec are predicted to extend beyond the duration of current clinical trials, highlighting its potential for long-term efficacy and sustained impact in real-world settings.

The use of such an analysis when combined with appropriate characterization of uncertainty may therefore be of value in informing the long-term outcomes for participants treated with valoctocogene roxaparvovec.

INTRODUCTION

Hemophilia is a rare, X-linked congenital bleeding disorder comprising two subtypes, hemophilia A and hemophilia B, which result from the deficiency or complete absence of clotting factor VIII (FVIII) or factor IX (FIX), respectively [1, 2]. People with hemophilia experience persistent, spontaneous bleeding in muscles and/or joints, chronic pain, reduced mobility, and reduced quality of life [3].

Hemophilia A is the more common subtype, accounting for approximately 80% of hemophilia cases [4], and is more common in men due to the X-linked pattern of inheritance [5]. Severe hemophilia A often manifests in the first months of life, whereas mild or moderate disease usually presents later in childhood or adolescence, often incidentally or following trauma [6].

The primary goal of treatment is to prevent bleeding and to improve long-term outcomes (e.g., joint health), which can be at least partially

achieved by continuous FVIII prophylaxis [7]. Hemophilia A prophylaxis involves regular administration of hemostatic agents to reduce or prevent bleeding episodes [5], and consists of regular injections of FVIII replacement therapy or substitution therapy (e.g., emicizumab) [8]. Dose frequency of prophylactic treatments can vary, but can involve treatment multiple times per week, weekly, or in some cases monthly, for life [9]. Pain and discomfort relating to prophylaxis administration is frequently reported and, as such, prophylaxis is associated with a lifetime treatment burden [10, 11]. It is also associated with a high economic burden, with annual treatment costs accounting for 80–95% of total direct expenditure related to hemophilia management in high-income countries [12, 13].

Valoctocogene roxaparvovec is a replication-incompetent adeno-associated virus (AAV) gene therapy that is infused as a single administration, and enables endogenous FVIII production to prevent bleeding in people with severe hemophilia A. In the Phase 3, single-arm, open-label GENEr8-1 study, valoctocogene roxaparvovec was investigated in 134 adult males with severe hemophilia A. The results of GENEr8-1 demonstrated that valoctocogene roxaparvovec was associated with a higher probability of no bleeds, improvements in annualized bleed rates, and improvements in health-related quality of life 4 years after infusion compared with outcomes while on FVIII prophylaxis during the baseline period [14, 15]. In Study 270–201, a Phase 1/2, single-arm, open-label study of 15 participants, 7 of whom received a dose of 6E13 vg/kg, valoctocogene roxaparvovec administration resulted in sustained, clinically relevant benefit, as measured by a substantial reduction in annualized rates of bleeding events and complete cessation of prophylactic factor VIII use in all participants [15, 16]. The most common adverse events (AEs) reported were transient alanine aminotransferase (ALT) elevations and AEs related to the glucocorticoid regimens to manage ALT elevations [17].

As valoctocogene roxaparvovec is a single administration, there are concerns that any treatment benefits may reduce over time, with some patients returning to prophylaxis, although data are currently limited [17]. Notably, the year-over-year rate of decline in FVIII activity over the course of the GENEr8-1 study diminished each year, suggesting a potential plateauing of effect [17]. Accordingly, evidence for valoctocogene roxaparvovec at the present time is limited to data covering up to 7 years of follow-up [14, 15]. As the economic value of valoctocogene roxaparvovec will be determined, in part, by the durability of the treatment effect, and the consequences associated with the loss of this treatment effect, the objective of this analysis was to estimate the long-term durability of the valoctocogene roxaparvovec treatment effect by extrapolating the trial data from GENEr8-1 (4- to 5-year data) and Study 270–201 (7-year data) [14, 15].

METHODS

Study Design

The primary analysis to estimate the long-term durability of valoctocogene roxaparvovec consists of the intention-to-treat (ITT) population from the GENEr8-1 study ($n = 134$). In a scenario analysis, the population within Study 270–201 who received a dose of 6E13 vg/kg ($n = 7$) was included. The maximum follow-up from the GENEr8-1 study was 266 weeks, and, in the 6E13 vg/kg cohort of Study 270–201, it was 374 weeks.

The long-term durability of valoctocogene roxaparvovec was defined using a combination of an objectively measurable biomarker (FVIII levels), a clinical endpoint (bleeding events), and a utilization metric (return to continuous prophylaxis). This is a comprehensive definition given it combines criteria that reflect the benefit of the treatment as a whole, in alignment with clinical guidelines and label recommendations [6]. For people with hemophilia A exhibiting a severe phenotype (including those with moderate hemophilia who present a severe phenotype), the World Federation of Hemophilia strongly advises that patients be on continuous prophylaxis to prevent bleeding, but that this prophylaxis should be tailored to each individual, considering their bleeding phenotype,

individual pharmacokinetics, joint health, and self-assessment and preferences [6].

This study is a post hoc analysis of previously conducted studies and does not include the addition of new studies with human participants or animal subjects. As previously reported, the protocols for GENEr8-1 [14] and Study 270–201 [15] were approved by the institutional review boards or independent ethics committees of all participating sites, and all participants provided written informed consent. Both trials were performed in accordance with the ethical principles set forth by the Declaration of Helsinki.

Study Population and Data Sources

The study design, participant characteristics, and inclusion and exclusion criteria for GENEr8-1 [14, 17–19] and Study 270–201 [15, 16] have been detailed previously. GENEr8-1 was a Phase 3, single-arm, open-label study of 134 participants [14, 17–19], all of whom were male, ≥ 18 years old, previously on FVIII prophylaxis, negative for FVIII inhibitors, and negative for AAV5 antibodies. FVIII prophylaxis was continued through 4 weeks post-infusion, and thereafter could be used if required, per the study protocol (4 weeks representing the time by which endogenous production of FVIII following gene transfer was expected to be efficacious; referred to as 'baseline prophylactic FVIII use'). The ITT population included the 134 participants who received valoctocogene roxaparvovec.

Briefly, Study 270–201 was a Phase 1/2, single-arm, open-label study of 15 participants, 7 of whom received a dose of 6E13 vg/kg [15, 16]. All the participants were male, ≥ 18 years old, with no history of factor VIII inhibitor development, and with ≥ 150 days of previous exposure to factor VIII concentrate.

Analysis

Approach

Durability was analyzed within a time-to-event analysis framework. The approach adopted is widely accepted by health technology assessment bodies [20]. The quantity of interest was the rate at which participants experienced loss of response.

Loss of response was defined as a composite of:

- FVIII decline < 5% (reliable hemostatic efficacy in the GENEr8-1 study was chromogenic substrate FVIII ≥ 5%), and
- Return to continuous prophylactic treatment, and
- Experiencing ≥ 2 treated bleed events in the previous 6 months at the time of return to prophylactic treatment.

In the definition of loss of response, the occurrence of the different criteria is sequential, meaning a participant needs to first have a FVIII level < 5% and then have ≥ 2 treated bleeds in the 6 months prior to returning to continuous prophylaxis.

Return to prophylactic treatment was defined as return to continuous prophylaxis with FVIII or emicizumab. Participants who had not returned to continuous prophylaxis by the end of follow-up were censored.

As participants experience increasing FVIII levels after beginning treatment with valoctocogene roxaparvovec, observed FVIII levels < 5% at the start of the study were unlikely to represent loss of response. Therefore, only observations after a participant's observed maximum FVIII was achieved were considered.

The maximum observed FVIII level was defined as the maximum post-baseline FVIII level that was not associated with the use of baseline prophylactic FVIII or exogenous FVIII within 72 h of observation. A single participant in the GENEr8-1 study was also observed to have a maximum FVIII level of < 5% (excluding observations during baseline prophylactic FVIII use, or with the use of exogenous FVIII within the previous 72 h); for this participant, the time at risk was assumed to have begun at week 5 (corresponding to the point after infusion at which FVIII prophylaxis was discontinued in GENEr8-1). To further avoid scenarios where a participant has FVIII levels temporarily < 5%, two consecutive FVIII observations < 5% were required.

The main analysis considers the combination of three criteria using the GENEr8-1 4- to 5-year follow-up data; a scenario analysis using the data

from the 6E13 vg/kg cohort of Study 270–201 in addition to the GENEr8-1 4–5Y data was also considered. Additional scenarios that considered more conservative approaches to defining loss of response consisting of either a combination of two of the following criteria or a single criterion were also considered for completeness of the analysis and to understand the uncertainty regarding the estimations:

1. FVIII levels < 5% and return to continuous prophylactic treatment
2. Return to continuous prophylactic treatment and ≥ 2 treated bleeds in the previous 6 months at the time of return to prophylactic treatment
3. FVIII levels < 5% and ≥ 2 treated bleeds in 6-month rolling windows
4. Return to continuous prophylactic treatment.

When a single criterion is considered, return to continuous prophylactic treatment is the criterion used, as the analysis considers the payer perspective, and continuous prophylactic treatment incurs costs to the healthcare system. However, given that the decision to return to prophylactic treatment can be multifactorial, using just this criterion to define loss of response would not reflect the treatment benefit as a whole.

Statistical Analysis

A time-to-event analysis framework was used to extrapolate outcomes beyond the follow-up duration. Analyses were conducted using parametric regression modelling.

Parametric survival models of time from baseline until event were estimated to extrapolate beyond the time horizon available. Six alternative parametric distributions were estimated (exponential, Weibull, log-logistic, log-normal, Gompertz, and generalized gamma). The Akaike information criterion (AIC) and Bayesian information criterion (BIC) for each distribution are reported. Median and mean time-to return to continuous prophylaxis were calculated, where these could be estimated.

The 95% confidence interval (CI) was calculated using the percentile method with 1000 bootstrap replications.

RESULTS

Data and Population

Data were available for 134 participants from the GENEr8-1 study, and 7 participants from the 6E13 vg/kg cohort of Study 270–201. Within the GENEr8-1 study, 24 participants (18%) had returned to continuous prophylaxis at the end of the 4-year follow-up period (including one participant who only transiently returned to prophylaxis for 6 weeks) [14, 17–19]. Two participants (29%) within the 6E13 vg/kg cohort of Study 270–201 had returned to continuous prophylaxis at 7-year follow-up [3, 15, 16].

Table 1 summarizes the loss of response composite endpoint data. Within the GENEr8-1 study, 12 participants experienced loss of response based on the three-criteria definition.

In the main analysis, and across scenarios, the log-normal distribution was the best statistical fit, followed by log-logistic and Weibull. Table 2 summarizes the alternative scenarios considered.

Durability

Three-Criteria Definition

Using the three-criteria definition of loss of response, the main analysis results ranged from 11.0 to 17.0 years (see Fig. 1 and Table 3); considering all distributions, results ranged from 8.1 to 25.6 years, where all distributions encompass all but the exponential (Supplementary Information). The exponential distribution was not considered to be clinically plausible as the rate of loss of response did not appear to be constant (Fig. 1). The Kaplan–Meier curve for the main analysis is presented in Fig. 2.

In the scenario analysis including the data from the 6E13 vg/kg cohort of Study 270–201, durability

Table 1 Summary of composite endpoint data (GENEr8-1 study only)

Scenario	Event or censored?	Time of event/censored	*n*
First event: FVIII < 5% for 2 consecutive visits Second event: RTP Bleed criteria[a]: met	Event	RTP	12
First event: FVIII < 5% for 2 consecutive visits Second event: RTP Bleed criteria[a]: not met	Censored	RTP	6
First event: RTP before FVIII < 5% for 2 consecutive visits Bleed criteria[a]: not required	Censored	RTP	5
First event: FVIII < 5% for 2 consecutive visits Second event: did not RTP Bleed criteria[a]: not required	Censored	Maximum follow-up	41
First event: Never had FVIII < 5% for 2 consecutive visits Second event: did not RTP Bleed criteria[a]: not required	Censored	Maximum follow-up	70[b]

FVIII factor VIII, *RTP* return to continuous prophylaxis

[a] ≥ 2 treated bleeds in 6 months prior to RTP. Where bleed criteria was 'not required', this was where participants did not meet the other essential criteria for the three-criteria definition of loss of response (i.e., as criteria were assessed sequentially, if participants did not meet FVIII < 5% for 2 consecutive visits prior to RTP bleed criteria were not assessed)

[b] Note this includes one participant who only transiently returned to prophylaxis for 6 weeks during the entire study, not reflecting an RTP per clinical practice but meeting the trial protocol definition; for this participant, the time-to-event or censoring was their RTP time (not max. follow-up)

estimates increased across the three best-fitting distributions compared with the main analysis (Table 3).

Scenario Analysis Using Two-Criteria Definitions

There were 134 participants at risk in the scenario analysis using the various two-criteria definitions of loss of response (Table 4). The scenario for FVIII levels < 5% and ≥ 2 subsequent treated bleeds in 6 months differed in terms of best fit compared with the three-criteria scenario, with the Weibull, Gompertz and log-logistic emerging as the equally best-fitting distributions. As in the main analysis, the exponential distribution was considered implausible for each scenario. Full results for all distributions (excluding exponential) are presented in Supplementary Information.

Return to Continuous Prophylaxis

The analysis of return to continuous prophylaxis included all eligible participants from the GENEr8-1 study. A total of 134 participants entered the analysis and were considered at risk of returning to prophylaxis. Among these participants, the maximum time at risk was 266 weeks, and median time at risk was 214 weeks. Predicted median time to return to continuous prophylaxis was between 6.4 and 16.1 years; the log-normal distribution was associated with the lowest AIC and BIC scores and resulted in a predicted median time to return to continuous prophylaxis of 9.5 years (95% CI: 5.8, 13.1) (Fig. 2 and Table 5). The results for the three best statistical fits (Weibull, log-logistic and log-normal) are presented in Table 5, with full results available in Supplementary Information. The exponential distribution was not considered to be clinically plausible for the same reasons stated previously (Fig. 3).

Table 2 Summary of scenarios and cohorts

Event	Number of criteria	*n*	Number of events
GENEr8-1 study 4- to 5-year data			
FVIII < 5% and ≥ 2 treated bleeds in 6 months prior to RTP	3	134	12
FVIII < 5% and RTP	2	134	18
RTP and ≥ 2 treated bleeds in 6 months prior to RTP	2	134	12
FVIII < 5% and ≥ 2 subsequent treated bleeds in 6 months	2	134	18
RTP	1	134	23
GENEr8-1 study 4- to 5-years and Study 201 (6E13 vg/kg)			
FVIII < 5% and ≥ 2 treated bleeds in 6 months prior to RTP	3	141	12
RTP and FVIII < 5%	2	141	19
RTP and ≥ 2 treated bleeds in 6 months prior to RTP	2	141	12
FVIII < 5% and ≥ 2 subsequent treated bleeds in 6 months	2	141	20
RTP	1	141	25

Annual rate of return is calculated as loss of response/person-time (exposure time)

FVIII factor VIII, *RTP* return to continuous prophylaxis

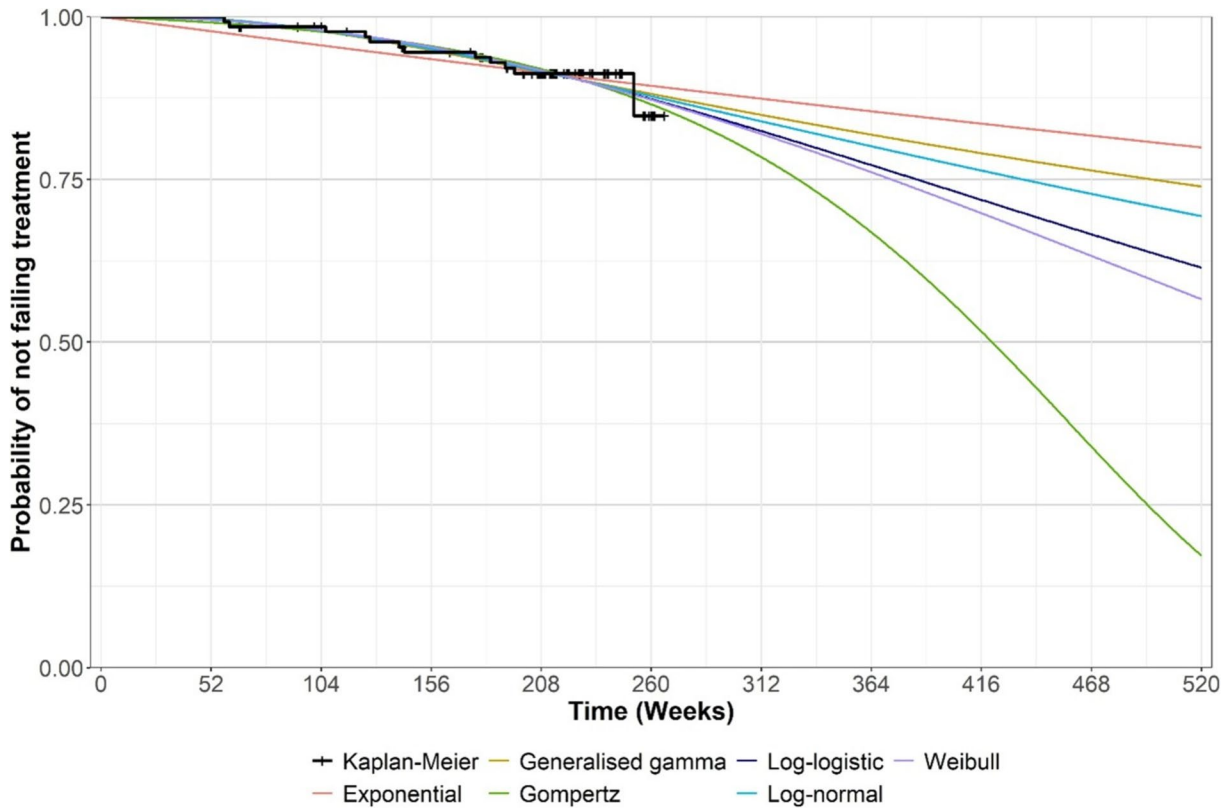

Fig. 1 Main analysis extrapolations (three-criteria loss of response; GENEr8-1 4-year data)

Table 3 Median durability in years

Model	Median (95% CI)	*n*	AIC	BIC
Three-criteria loss of response; GENEr8-1 study 4- to 5-year data				
Weibull	11.0 (4.5, 17.4)	134	90.9	96.7
Log-normal	17.0 (3.4, 30.6)	134	90.6	96.4
Log-logistic	12.4 (4.3, 20.6)	134	90.9	96.7
Three-criteria loss of response; GENEr8-1 study 4- to 5-year data and Study 201 (6E13 vg/kg)				
Weibull	13.2 (4.6, 21.8)	141	94.2	100.1
Log-normal	20.4 (2.6, 38.2)	141	93.4	99.3
Log-logistic	15.0 (4.2, 25.8)	141	94.1	100.0

AIC Akaike information criterion, *BIC* Bayesian information criterion, *CI* confidence interval

DISCUSSION

The objective of this analysis was to estimate the long-term durability of valoctocogene roxaparvovec treatment effect by extrapolating the trial data from GENEr8-1 (4- to 5-year data) and Study 270–201 (7-year data) to better inform healthcare system decision-making. Loss of response was defined in the main analysis to occur when a participant enters the moderate hemophilia range (FVIII levels < 5%), experiences a severe bleeding phenotype (≥ 2 treated

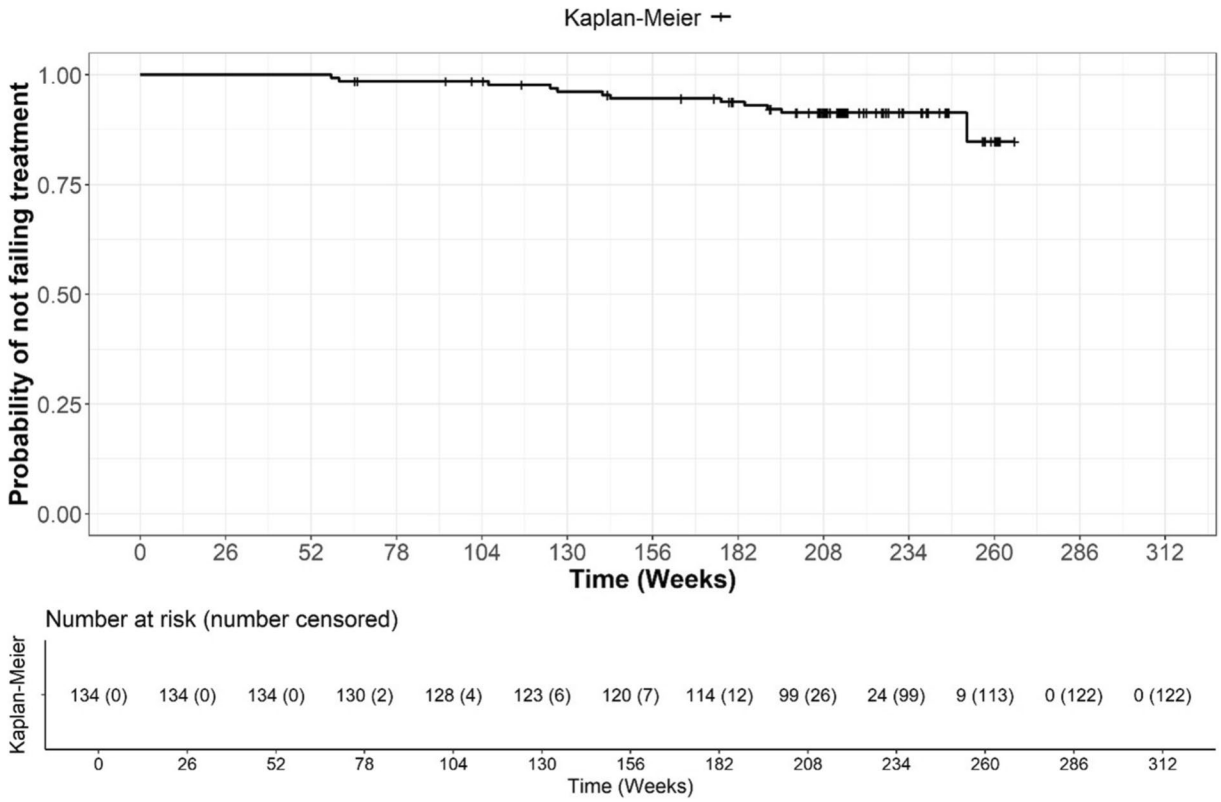

Fig. 2 Main analysis Kaplan–Meier curve (three-criteria loss of response; GENEr8-1 4-year data)

Table 4 Median durability in years: scenario results using two-criteria definitions

Model	Median (95% CI)	*n*	AIC	BIC
Two-criteria loss of response (FVIII < 5% and return to continuous prophylaxis, GENEr8-1 study 4- to 5-year data				
Weibull	8.9 (5.4, 12.5)	134	119.3	125.1
Log-normal	12.2 (5.6, 18.8)	134	118.7	124.5
Log-logistic	9.9 (5.5, 14.3)	134	119.2	125.0
Two-criteria loss of response (returning to continuous prophylaxis and ≥ 2 treated bleeds in 6 months prior to returning to continuous prophylaxis), GENEr8-1 study 4- to 5-year data				
Weibull	11.0 (4.5, 17.5)	134	91.0	96.8
Log-normal	17.0 (3.4, 30.7)	134	90.6	96.4
Log-logistic	12.5 (4.3, 20.6)	134	90.9	96.7
Two-criteria loss of response (FVIII < 5% and ≥ 2 subsequent treated bleeds in 6 months), GENEr8-1 study 4- to 5-year data				
Weibull	16.2 (4.1, 28.3)	134	141.6	147.4
Gompertz	12.2 (–1.4, 25.8)	134	141.6	147.4
Log-logistic	19.8 (3.3, 36.3)	134	141.6	147.4

AIC Akaike information criterion, *BIC* Bayesian information criterion, *CI* confidence interval

bleeds in 6 months), and returns to continuous prophylaxis. When using a three-criteria definition of loss of response, the median durability of treatment effect estimates ranges from 11.0 to 17.0 years when the three best statistical fits are considered.

The comprehensiveness of the definition of loss of response in the main analysis is supported by the different combinations of two criteria only. In the scenario where loss of response was defined by a participant experiencing return to continuous prophylaxis and ≥ 2 treated bleeds in the preceding 6 months, durability estimations are similar to the main analysis results, suggesting that all the participants meeting this definition are already in the moderate hemophilia range (FVIII levels < 5%).

In the scenario only considering FVIII levels and return to continuous prophylaxis, durability decreases compared with the main analysis, which reflects the individual component driving the decision of returning to continuous prophylaxis, including factors such as risk aversion, lifestyle choices, and patient preferences.

Finally, when only considering return to continuous prophylaxis, durability estimates ranged from 7.5 to 9.5 years. The returning of a patient to continuous prophylaxis is a readily observable outcome, and its appeal as a single-criterion definition for loss of response is therefore understandable. However, the decision for a patient to return to continuous prophylaxis is multifactorial and open to environmental

Table 5 Median time to return to continuous prophylaxis in years

Model	Median (95% CI)	*n*	AIC	BIC
Return to continuous prophylaxis, GENEr8-1 study 4- to 5-year data				
Weibull	7.5 (5.4, 9.7)	134	135.3	141.1
Log-normal	9.5 (5.8, 13.1)	134	134.8	140.6
Log-logistic	8.1 (5.5, 10.8)	134	135.2	141.0
Return to continuous prophylaxis, GENEr8-1 study 4- to 5-year data and Study 201 (6E13 vg/kg)				
Weibull	7.8 (5.8, 9.8)	141.0	142.5	148.4
Log-normal	9.6 (6.2, 13.1)	141.0	142.6	148.5
Log-logistic	8.4 (5.9, 10.9)	141.0	142.7	148.5

AIC Akaike information criterion, *BIC* Bayesian information criterion, *CI* confidence interval

factors (e.g., patient lifestyle and physician prescribing habits) that may or may not correlate with bleeding risk. As such, considering it in isolation as a definition for loss of response independent of FVIII levels and/or bleeding events may not fully reflect the treatment attributes of valoctocogene roxaparvovec. Similarly, while the 5% FVIII threshold chosen for the presented analysis is a recognized clinical marker for moderate hemophilia, the evolving treatment landscape for hemophilia A allows many patients to experience FVIII trough levels of (or equivalent to) > 5% with continuous prophylaxis. The definition and relative importance of the three criteria presented in this analysis, and their appropriateness as measures for treatment response in gene therapy, remain as open considerations with the advancing standards in hemophilia care.

By accounting for variability in treatment responses, clinicians may be able to more accurately assess the potential risks and benefits for individual patients, leading to more personalized and informed decision-making. This approach expands the evidence base for valoctocogene roxaparvovec, potentially leading to improved patient care and long-term health outcomes.

Limitations

The primary limitation of the present analysis is the small number of events observed to date in the valoctocogene roxaparvovec clinical trial program. With only a small number of events, small changes in the timing of events may have resulted in very different extrapolated outcomes. In particular, the final observed events occurred when a low number of participants remained at risk, and these events therefore disproportionately affect the Kaplan–Meier estimator and consequent extrapolations.

Although the addition of data from the 6E13 vg/kg cohort of Study 270–201 as a scenario analysis adds further evidence of the long-term risk of returning to prophylaxis, such an analysis using

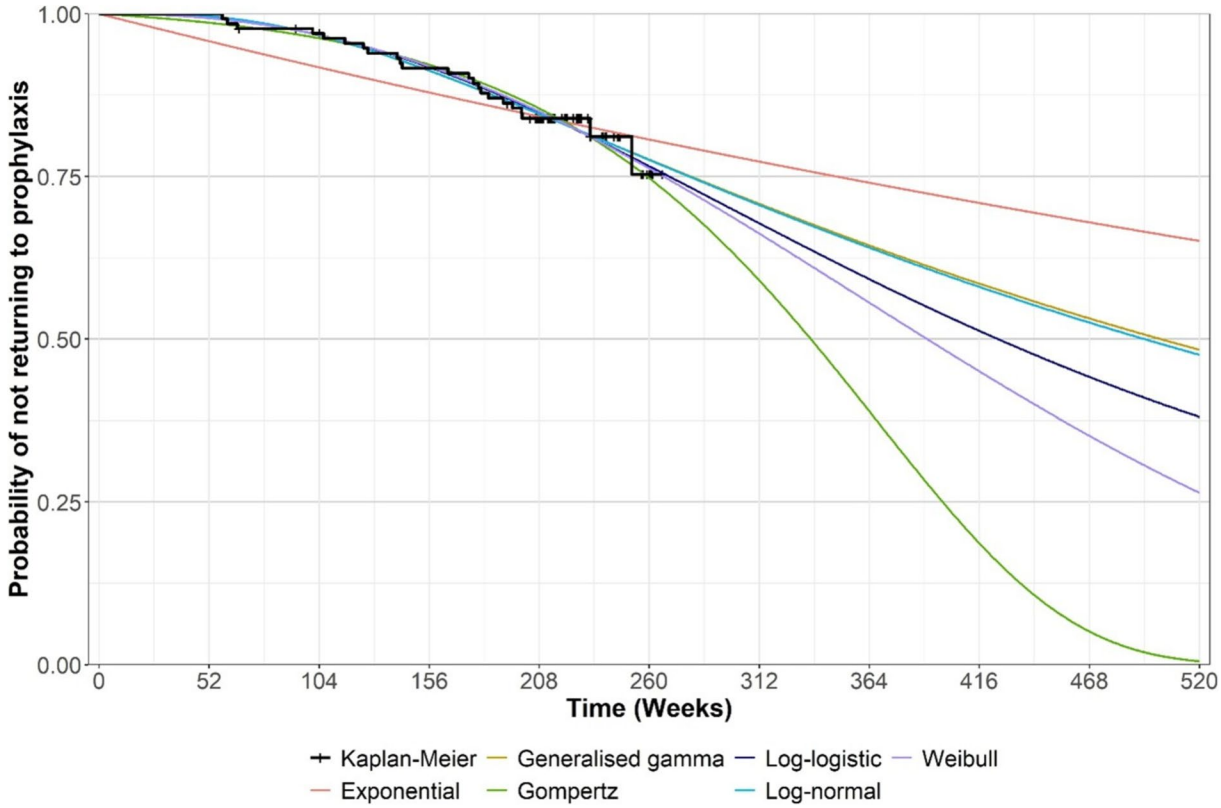

Fig. 3 Main analysis extrapolations for return to continuous prophylaxis (GENEr8-1 study)

a 'pooled' dataset is subject to potential issues of between-study heterogeneity. Furthermore, participants at risk at the end of the Kaplan–Meier curve disproportionately affect the resulting extrapolation, and thus this small number of participants from Study 270–201 are responsible for informing the long-term assumptions around the hazard function. This can be seen in the predicted medians resulting from extrapolation with the exponential distribution, which increase with the addition of Study 270–201 data (6E13 vg/kg cohort). However, the availability of longer follow-up data remains crucial to better understand the durability of the treatment effect.

CONCLUSION

Despite the uncertainties caused by small sample sizes and limited follow-up within GENEr8-1, there are no better alternative sources of information from which to estimate the rate at which participants experience the loss of effect of valoctocogene roxaparvovec. This analysis therefore demonstrates that the potential therapeutic benefit of valoctocogene roxaparvovec may be sustained beyond follow-up in existing clinical trials (7 years). The use of such an analysis when combined with appropriate characterization of uncertainty offers a valuable tool for enhancing the prediction of long-term outcomes in participants treated with valoctocogene roxaparvovec.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. David Trueman is an employee of Source Health Economics, who were funded by BioMarin to undertake this work. Sandra Santos is an employee and stockholder of BioMarin UK Ltd. Tara Robinson was an employee and stockholder of BioMarin Pharmaceutical Inc at the time of study initiation.

Ethical Approval. This study is a post hoc analysis of previously conducted studies and does not include the addition of new studies with human participants or animal subjects. As previously reported, the protocols for GENEr8-1 [14] and Study 270–201 [15] were approved by the institutional review boards or independent ethics committees of all participating sites, and all participants provided written informed consent to participate. Both trials were performed in accordance with the ethical principles set forth by the Declaration of Helsinki.

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