Comparative EQ-5D utilities for valoctocogene roxaparvovec gene therapy and emicizumab in people with severe hemophilia A using a matching-adjusted indirect comparison

PCR239

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Background

- Novel therapies in hemophilia aim to deliver quality of life benefits beyond those associated with reductions in bleeding events because novel therapies avoid frequent regular infusions and thereby may deliver benefits such as a reduction in pain or an improvement in conducting usual activities
- Two novel approved non-factor replacement therapies are valoctocogene roxaparvovec (Roctavian®), a gene therapy that enables endogenous FVIII production in people with severe hemophilia A, and emicizumab (Hemlibra®), a bispecific monoclonal antibody with subcutaneous injection
- Head-to-head data from valoctocogene roxaparvovec with emicizumab are not available; thus, an indirect comparison is required to compare the two treatments on quality of life benefits

Objective

- This study aimed to compare the health-related quality of life benefits of valoctocogene roxaparvovec with those of emicizumab using a matching-adjusted indirect comparison (MAIC) approach

Methods

GENEr8-1 utilities

- The pivotal study for valoctocogene roxaparvovec was the GENEr8-1 study[1] in 134 adult males (≥18y) with severe hemophilia A
- In study year 1, health-related quality of life was captured using the EQ-5D-5L questionnaire at baseline and in weeks 4, 12, 26, and 52
- Utilities were calculated using the crosswalk approach for consistency. Linear mixed-effects models were fitted to estimate health-state utility values, accounting for repeated measures at the patient level

Estimating HAVEN-3 Arm D utilities

- Data from participants in HAVEN 3 Group D who were treated previously with prophylactic FVIII replacement therapy[2] were used for this study
- Because Arm D utilities were not reported they had to be estimated. Unreported HAVEN 3 Arm D utilities were estimated at baseline, week 25, and week 49 using a linear programming method[3]
- Constraints guiding the linear programming method were derived from public sources:
  - Cross-arm utilities aggregated on selected patient characteristics for the adult population were taken from Skinner et al[4]
  - The number of adults who reported their utility per week was estimated using data from G-BA, EudraCT, and clinicaltrials.gov

Matching-adjusted indirect comparison

- Utilities from GENEr8-1 were reweighted using the weights from the published MAIC by Astermark et al[5]. This study compared valoctocogene roxaparvovec and emicizumab HAVEN 3 Arm D before and after balancing for patient baseline characteristics[5]
- The main analysis of Astermark et al[5] matched on a set of key baseline variables (see **Table 1**)

Table 1. Baseline characteristics of participants in HAVEN 3 and GENEr8-1 before and after MAIC

Time point	HAVEN 3 (n = 63)	GENEr8-1 unweighted (n = 132)	GENEr8-1 weighted (ESS = 76.2)
Mean age (y)	36.4	31.4	36.4
Percent white race	74.6%	71.2%	74.6%
Mean BMI	25.56	25.31	25.56
Mean ABR	6.4	6.0	6.4
Percent with <9 bleeds in 24 weeks prior to enrolment	84.1%	90.9%	84.1%
Percent with SHL FVIII product used before trial entry	84.1%	72.0%	84.1%

Adapted from Astermark et al[5]. ABR, annualized bleed rate; BMI, body mass index; ESS, effective sample size; FVIII, factor VIII; SHL, standard half-life

Results

- After reweighting, the effective sample size was 76.2, 57.7% of the original 132 HIV-negative participants. Baseline parameters of interest were comparable between GENEr8-1 and HAVEN 3[5] (**Table 1**)
- GENEr8-1 weighted mean utilities were 0.725 at baseline, 0.773 at 26 weeks, and 0.791 at year 1 (**Table 2**)**.** Utilities for emicizumab were calculated as 0.79 for baseline, 0.82 for week 25, and 0.82 for week 49
- At week 52, the utility improvement was 0.07 for valoctocogene roxaparvovec compared to 0.03 for emicizumab, resulting in a greater increase by 0.04 for valoctocogene roxaparvovec

Table 2. UK cross-walk EQ-5D-5L summary statistics for valoctocogene roxaparvovec (following MAIC re-weighting) compared with emicizumab (estimated via linear programming)

Time point	Sample size	Mean utility after MAIC	Change from baseline
GENEr8-1 – valoctocogene roxaparvovec – weighted means incorporating MAIC weights			
Baseline	131	0.725	-
26 weeks	129	0.773	+ 0.05
52 weeks	132	0.791	+ 0.07
HAVEN 3 Arm D - emicizumab			
Baseline	52	0.79	-
25 weeks	[53, 54]*	0.82	+ 0.03
49 weeks	[51, 54]*	0.82	+ 0.03

*There was insufficient evidence to identify the exact numbers of patients who reported their utility on weeks 25 and 49. Therefore, a range is given.

Conclusions

- This study demonstrates the feasibility and importance of reweighting utility outcomes via MAIC, enabling a comparison of QoL between two products and providing valuable insights for pharmacoeconomic evaluation
- After accounting for differences in patient characteristics and incorporating linear programming assumptions, **valoctocogene roxaparvovec shows a greater utility increase than emicizumab by 0.04 (0.07 vs. 0.03) per year**
- These findings support the hypothesis that gene therapy offers benefits beyond reducing bleeds, as reflected in the utility data. These results can be incorporated into cost-effectiveness modeling by informing treatment arm-specific utilities

References

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