Jawaharlal Institute Postgraduate Medical Education & Research, Puducherry (JIPMER)

Health Technology Assessment Resource Hub (HTARH)

Department of Preventive and Social Medicine, JIPMER, Puducherry

HTA REPORT

On

Cost-effectiveness of Emicizumab prophylaxis versus no prophylaxis among hemophilia A patients with and without inhibitors

Background:

The JIPMER HTA Resource Hub was assigned the task of assessing the cost-effectiveness of Emicizumab prophylaxis versus no prophylaxis among Hemophilia A (HA) patients with and without inhibitors. The purpose was to generate evidence-based recommendations to inform policy decisions for managing HA within Indian healthcare settings.

Development during the study:

While progressing through the model-building phase of the study, a pivotal paper titled *"Cost-Effectiveness Analysis of Emicizumab Prophylaxis in Patients with Hemophilia A in India"* was published in December 2023. The published study closely aligned with the objectives and methodologies of the assigned HTA study.

Presentation to Technical Appraisal Committee (TAC):

The methodology and findings of the published study were presented at the 44th Technical Appraisal Committee (TAC) meeting held on November 28, 2024. The TAC reviewed the overlap between the published study and the assigned HTA topic, raising pertinent questions about the necessity of proceeding with the JIPMER study. After addressing the committee's comments during the meeting, the TAC recommended concluding the study, contingent on submitting a detailed note of the responses provided by the JIPMER team during the meeting. These responses have been documented and shared with the DHR in the *Response to TAC Comments* file.

Conclusion:

Given the considerable alignment between the objectives, and methodologies of the assigned HTA study and the published manuscript, and as per the TAC's recommendations, the JIPMER HTA Resource Hub considers the study completed. The published paper, titled *"Cost-Effectiveness Analysis of Emicizumab Prophylaxis in Patients with Hemophilia A in India"* (1), is attached to this report, providing details on the methodology, results, and conclusions relevant to the assigned HTA topic.

Attachment: Published Manuscript

References:

1. Seth T, John MJ, Chakrabarti P, Shanmukhaiah C, Verma SP, Radhakrishnan N, et al. Cost-effectiveness analysis of emicizumab prophylaxis in patients with haemophilia A in India. Haemophilia. 2024 Mar;30(2):426–36.

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ORIGINAL ARTICLE

Cost-effectiveness analysis of emicizumab prophylaxis in patients with haemophilia A in India

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Abstract

Introduction: Emicizumab is the initial subcutaneously administered bispecific antibody approved as a prophylactic treatment for patients with haemophilia A (PwHA).

Aim: This study assessed the economic evaluation of emicizumab treatment for non-inhibitor severe haemophilia A (HA) patients in India.

Methods: A Markov model evaluated the cost-effectiveness of emicizumab prophylaxis compared to on-demand therapy (ODT), low-dose prophylaxis (LDP; 1565 IU/kg/year), intermediate-dose prophylaxis (IDP; 3915 IU/kg/year) and high-dose prophylaxis (HDP; 7125 IU/kg/year) for HA patients without factor VIII inhibitors. Inputs from HAVEN-1 and HAVEN-3 trials included transition probabilities of different bleeding types. Costs and benefits were discounted at a 3.5% annual rate.

Results: In the base-case analysis, emicizumab was cost-effective compared to HDP, with an incremental cost-effectiveness ratio (ICER) per quality-adjusted life-years (QALY) of Indian rupees (INR) 27,869. Compared to IDP, ODT and LDP, emicizumab prophylaxis could be considered a cost-effective option if the paying threshold is >1 per capita gross domestic product (GDP) with ICER/QALY values of INR 264,592, INR 255,876 and INR 305,398, respectively. One-way sensitivity analysis (OWSA) highlighted emicizumab cost as the parameter with the greatest impact on ICERs. Probabilistic sensitivity analysis (PSA) indicated that emicizumab had a 94.7% and 49.4% probability of being cost-effective at willingness-to-pay (WTP) thresholds of three and two-times per capita GDP.

Conclusion: Emicizumab prophylaxis is cost-effective compared to HDP and provides value for money compared to ODT, IDP, and LDP for severe non-inhibitor PwHA in India. Its long-term humanistic, clinical and economic benefits outweigh alternative options, making it a valuable choice in resource-constrained settings.

KEYWORDS
cost-effectiveness analysis , emicizumab, haemophilia A, Markov economic model, one-way sensitivity analysis, probabilistic sensitivity analysis

1 | INTRODUCTION

Haemophilia A (HA) is a type of X-linked congenital, life-threatening bleeding disorder caused by severe deficiency of factor VIII (FVIII). Globally, 4,29,232 individuals are estimated suffer from haemophilia's, per the World Federation of Haemophilia (WFH) annual survey.[1] Of the known 30,000 haemophilia patients in India, HA accounts for approximately 80%–85%, and around 1300 children with haemophilia are born in the country each year. The exact data in India remain under reported.[1–4]

HA is characterised by spontaneous bleeding into the joints, muscles, soft tissues and potentially life-threatening bleeds (e.g., intracranial, neck, gastrointestinal, etc.).[2,4] Patients with severe HA have residual FVIII activity less than 1 IU/dL experience > 1–2 episodes of spontaneous bleeds per week.[4] These events impact patients' daily lives with reduced productivity, and poor quality of life (QoL).[5] In the absence of proper treatment, people with HA have long-term secondary complications, including detrimental musculoskeletal and psychosocial effects.[3–4]

The current standard of care for HA is intravenous infusion of FVIII concentrates to manage a bleeding episode or to prevent bleeding and its consequential effects on joints and muscles (prophylaxis therapy).[2,6] World Health Organization (WHO) and WFH also recommend early prophylaxis as the standard of care treatment for patients with severe haemophilia.[4] Prophylactic FVIII treatment offers clear benefits for clinical outcomes, but patient adherence is poor, due to frequent intravenous injections. Standard half-life prophylaxis with plasma-derived or conventional recombinant FVIII involves three times a week infusion, plus additional doses for breakthrough bleeds.[4] Extended half-life recombinant clotting factor concentrates offer longer therapy but still require 2–3 per week FVIII infusions.[4,7] Severe haemophilia patients also encounter challenges like difficult venous access. In accordance with the WFH recommendation, episodic therapy also known as on-demand therapy (ODT) should no longer be considered a long-term treatment option for patients with severe haemophilia.[4]

Emicizumab (Hemlibra®, Hoffman-La Roche) is a novel recombinant antibody that brings together factor IXa and factor X proteins to restore blood clotting in individuals with HA. It is the first subcutaneous prophylaxis injection that prevents or reduces the frequency of bleeding episodes and can be used in 1, 2 or 4 weekly doses.[8] Emicizumab has received approval for HA patients with and without FVIII inhibitors in various countries. Clinical trials (HAVEN 1 and 3) demonstrated its efficacy in controlling bleeding and improving health outcomes with good tolerability.[9–11] In April 2019, emicizumab was approved in India for prophylactic treatment of HA.[12] However, an economic evaluation of emicizumab in the Indian setting is currently lacking. This study aims to assess the economics of emicizumab compared to conventional HA treatment for severe HA patients without factor VIII inhibitors within the Indian market context.

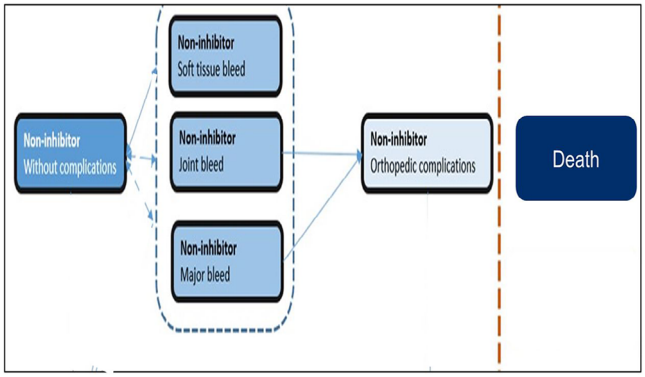

FIGURE 1 Model structure.

2 | METHODS

2.1 | Model structure

We constructed a Markov model in Microsoft Excel® to evaluate the cost-effectiveness of emicizumab prophylaxis for HA patients without inhibitors. Our model, based on state transition models used in haemophilia research, included 1000 hypothetical HA patients without inhibitors (Figure 1).[13–15] Health states considered were 'HA without complications,' 'major bleed,' 'joint bleed,' 'soft tissue bleed,' 'orthopaedic complications/disability,' and 'death.' Patients initially entered the 'alive' state without inhibitors, with the risk of death based on treatment and age. Bleed events could occur in the 'alive' state, and death could happen in any state (Figure 1).

This economic evaluation employed cost-utility analysis to compare the cost-effectiveness of emicizumab prophylaxis with ODT (on-demand therapy), LDP (low dose prophylaxis) with FVIII, IDP (intermediate dose prophylaxis) with FVIII, and HDP (high dose prophylaxis) with FVIII. While HDP and IDP therapy are common in developed countries, ODT is the usual treatment and LDP is emerging as an alternative for better care in resource-limited settings. Several studies have shown positive clinical outcomes with LDP in HA patients, making it a relevant comparator.[2,3,16] The model adopted a monthly time unit to present the result and per year or lifetime time horizon functionality were added. The model used 1-month cycle length for the simulation.

2.2 | Model inputs

2.2.1 | Clinical data

Patients entered the model at age zero. Different average weights were considered for children in different age groups, while adults (above 18 years) were assumed to have an average weight of 50 kg.[17] The clinical effects of emicizumab were established in pivotal HAVEN studies. In HAVEN 1, weekly emicizumab (35 patients) resulted in low rates of treated bleeding events; model-based annualized bleed rate (ABR)

TABLE 1 Transition probabilities across different health states.

	On-demand therapy	LDP with FVIII (10–15 IU/kg)	IDP with FVIII (15–25 IU/kg)	HDP with FVIII (25–40 IU/kg)	Prophylaxis with emicizumab
Non-inhibitor patient without complication					
Non-inhibitor patient without complication	.0500	.2700	.2700	.4900	.9900
Non-inhibitor—soft tissue bleed	.4500	.3500	.3500	.2500	.0100
Non-inhibitor—joint bleed	.4000	.3000	.3000	.2000	.0000
Non-inhibitor—major bleed	.1000	.0800	.0800	.0600	.0000
Non-inhibitor patient with major bleed					
Non-inhibitor orthopaedic complications/disability	.0700	.0700	.0700	.0400	.0000
Non-inhibitor patient with hemophilia without complication	.0000	.0000	.0000	.0000	.0000
Non-inhibitor patient with joint bleed					
Non-inhibitor orthopedic complications/disability	.3000	.2300	.2300	.1100	.0000
Non-inhibitor patient with hemophilia without complication	.0500	.0000	.0000	.0000	.0000
Non-inhibitor patient with soft tissue bleed					
Non-inhibitor patient with hemophilia without complication	.3900	.2800	.2800	.1600	.0100

Abbreviations: HDP, high-dose prophylaxis; IDP, intermediate-dose prophylaxis; LDP, low-dose prophylaxis.

2.9 (95% CI 1.7–5.0) in adolescents and adults with HA, and 63% of patients had zero treated bleeds with emicizumab prophylaxis. HAVEN 3, conducted in adolescents and adults without FVIII inhibitors, showed that weekly (36 patients) and every 2 weeks (35 patients) emicizumab prophylaxis had model based ABRs of 1.5 (95% CI .9–2.5) and 1.3 (95% CI .8–2.3), respectively, with 56% and 60% of patients having zero treated bleeds.[9,10]

For non-inhibitor HA patients, the annual bleeds on ODT, LDP, HDP and emicizumab prophylaxis were assumed to be 38, 15, 4 and 1, respectively, based on inputs from 25 treating physicians in India. Transition probabilities for different bleed types were calculated using ABRs from HAVEN 1 and 3 trials; further validated detailed questionnaires in a holistic manner (Table 1).[9,10] Monthly cycle lengths were used for bleed transition probabilities. Hospitalization days of 12 for ODT and three for prophylaxis therapy were based on a study of Haemophilia Treatment Center and local government facilities.[18]

2.2.2 | Costs

Table 2 displays the costs considered in the model, encompassing direct and indirect expenses. Direct costs included medicine, hospitalization, resource utilization and diagnostic expenses, obtained from tender prices and literature sources.[18–22] Patient costs were estimated by combining the unit cost, dosage, administration frequency, annual bleeds and product consumption based on age and relative weight in each simulated cycle. The assumed dose of FVIII clotting factor concentrates for bleeds in all treatment groups was 40 IU/kg, with a per-unit cost of Indian rupees (INR) 7.00 per IU. For non-inhibitor patients, the dose required for prophylaxis with LDP, IDP and HDP were calculated to be 1565, 3915 and 7125 IU/kg per year, respectively.

Emicizumab is administered subcutaneously with a loading dose of 3 mg/kg weekly for 4 weeks, followed by a maintenance dose of 1.5 mg/kg weekly, 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks. The assumed non-inhibitor HA dose is 78 IU/kg per year, with a unit cost of INR 452.00 per mg. Doctor visit costs were obtained from www.medifee.com, while hospitalization costs (INR 3000) and emergency attendance costs (INR 3000) were sourced from studies in Kerala and Mumbai.[19] Haemophilia Treatment Centre setup and staff costs were referenced from the National Health Profile report of 2018.[20] A consolidated cost of INR 500 was considered for managing adverse events. Indirect costs, including caregiver expenses, school absenteeism, work productivity loss and emotional costs, were sourced from the literature.[21] School absenteeism for ODT and prophylaxis therapy were considered 78 and 2 days.[18] Costs related to travel, caregiver support, work productivity loss and school absenteeism were derived from a study conducted at a non-governmental organization and a civil hospital in Maharashtra.[21]

2.2.3 | Utility data

Table 3 presents the utility values used in the model. Data on QoL parameters were collected through quantitative interviews with 90

TABLE 2 Cost inputs in the model.

Cost	Type of cost	Cost related to	Description	Cost value (in INR)	Source
Hospitalization	Direct	Patient/Payer	Cost of hospitalization	3000.00	Hemophilia Treatment Centre in Kerala[18]
Attendance at emergency	Direct	Patient/Payer	Cost of emergency management like ICU, CCU etc.	3000.00	Tertiary care hospital in private set up in Mumbai region[22]
Non-drug bleed cost	Direct	Patient/Payer	Primary cost incurred to manage or stop bleed like PCP visit, first aid, dressing etc.	2000.00	Using tender prices
Medicine: FVIII CFC (per IU)[a]	Direct	Patient/Payer	Medicine cost for on-demand therapy	7.00	Using tender prices
Medicine: emicizumab (per mg)[a]	Direct	Patient/Payer	Medicine cost for prophylaxis treatment with emicizumab	452.00	Using tender prices
Diagnostic cost	Direct	Patient/Payer	Cost of diagnostic (screening and clotting factor test) like platelet count, bleeding time, FVIII activity	1500.00	Using tender prices
Adverse events cost	Direct	Patient/Payer	Cost of managing any adverse event	500.00	
Surgery cost	Direct	Patient/Payer	Cost of doing a surgery	500.00	
Orthopedic complications	Direct	Patient/Payer	Cost incurred to manage Orthopedic complications and disability	2000.00	
Disability cost	Direct	Patient/Payer	Cost incurred to manage Orthopedic complications and disability	3000.00	
Doc visit	Direct	Patient/Payer	Cost paid by patient/payer per visit to doctor (Hematologist, Orthopedic etc.)	150.00	Doctor visit charges[19]
Travel cost—patient	Direct	Patient	Travel cost of patient	150.00	NGO and civil hospital in Maharashtra[21]
Travel cost—caregiver	Direct	Caregiver	Travel cost of caregiver	100.00	NGO and civil hospital in Maharashtra[21]
Cost per workday lost	Indirect	Patient	Cost per workday lost by patient	350.00	
Caregiver cost	Indirect	Caregiver	Cost per workday lost by caregiver	1500.00	NGO and civil hospital in Maharashtra[21]
Emotional cost of hemophilia	Intangible	Patient/Careg	Cost like Anxiety, pain, suffering, depression etc.	1000	
HTC setup cost	Indirect	Account	Cost involved for account for infrastructure development	150.00	National Health Profile 2018 report[20]
HTC utilization	Indirect	Account	Cost involved for account for facility maintenance	150.00	National Health Profile 2018 report[20]
Paramedics fees	Indirect	Account	Cost involved for account to pay support staff	100.00	
School performance loss	Indirect	Patient/Society		300.00	
Early retirement	Indirect	Patient/Society	Because of diseases people go for early retirement	1,000.00	
Less working cost	Indirect	Patient/Society	Because of diseases patient productivity is hampered during general days	100.00	
Unemployment rate impact cost	Indirect	Patient/Society / Caregiver	In some cases, patient or caregiver decides to quit the job which impact unemployment rate	75.00	
Absenteeism from school	Indirect	Patient/Society	School days are impacted for patients which results into impact on education	200.00	Hemophilia Treatment Centre in Kerala[18]
School dropout cost	Indirect	Patient/Society		55.00	
Other costs	–	–		100.00	

Abbreviations: CFC, clotting factor concentrates; HTC, Hemophilia Treatment Center; INR, Indian rupees.
[a]Costs considered for 50 kg person.

TABLE 3 Utility inputs.

	Utility value
Non-inhibitor patient with hemophilia without complication	.90
Non-inhibitor patient with major bleed	.10
Non-inhibitor patient with joint bleed	.40
Non-inhibitor patient with soft tissue bleed	.60
Non-inhibitor orthopedic complications/disablity	.25

non-inhibitor HA patients (or their caregivers for children) and 25 physicians treating haemophilia in major Indian cities. The interviews included seven patients on HDP, 21 patients on LDP and 62 patients on ODT. Treatment-related health state utility values were not included in the model, and no dis-utility (decrement in utility) was accounted for by adverse clinical events.

2.3 | Data analysis

The base-case analysis compared emicizumab prophylaxis with ODT, LDP, IDP and HDP with FVIII using the incremental cost-effectiveness ratio (ICER). Costs calculated in 2019 INR, future costs and benefits were discounted at 3.5% annually. The analysis considered perspectives from the Indian payer, patient and society. As no fixed willingness-to-pay (WTP) threshold existed, the cost-effectiveness threshold was based on the country's per-capita GDP following Health Technology Assessment guidelines.[23,24]

We used one-way sensitivity analysis (OWSA) to identify impactful parameters, varying each by 20%. Probabilistic sensitivity analysis (PSA) with 1000 Monte Carlo simulations provided a comprehensive view of result uncertainty. PSA used theoretical probability distributions for key factors (bleed probabilities, costs, utilities) and generated cost-effectiveness acceptability curves (CEAC) and scatter plots to show treatment cost-effectiveness at different thresholds.

3 | RESULTS

The base-case analysis showed that emicizumab prophylaxis was associated with 941 QALYs (.78/month), whereas ODT, LDP, IDP and HDP with FVIII were associated with 209 (.17/month), 410 (.34/month),410 (.34/month) and 574 QALYs (.48/month), respectively. Emicizumab provided greater QALYs compared with ODT, LDP, IDP and HDP (Table 4A–C). However, emicizumab was more costly, with a total estimated cost of INR 207,128,983 (INR 172,607/month) compared with INR 19,696,526 (INR 16,413/month) for ODT, INR 44,818,564 (INR 37,348/month) for LDP, INR 66,506,022 (INR 55,421/month) for IDP, and INR 196,885,053 (INR 164,070/month) for HDP, respectively. Emicizumab prophylaxis was shown to be a cost-effective strategy over HDP with FVIII (ICER/QALY INR 27,869).

Emicizumab prophylaxis was not shown to be a cost-effective option compared with ODT (ICER/QALY INR 255,876), IDP (ICER/QALY INR 264,592), and LDP with FVIII (ICER/QALY INR 305,398) at 1-time per capita GDP (INR 151,760 at current prices during 2019–2020[38]). However, except LDP these comparators could be considered a cost-effective treatment at 2-times or more per capita GDP.

Another base-case analysis comparing ODT as the main treatment showed that ODT was associated with an ICER/QALY of INR 124,960 for LDP, INR 232,836 for IDP, INR 485,523 for HDP and INR 255,876 for emicizumab prophylaxis, respectively. At a WTP of 1-time per capita GDP, ODT may not be a cost-effective treatment strategy against emicizumab and the FVIII prophylactic treatment regimens except LDP.

The results of OWSA of emicizumab prophylaxis compared with ODT, LDP with FVIII, IDP with FVIII and HDP with FVIII are presented in Figure 2A–D. In the Tornado diagrams comparing emicizumab prophylaxis with ODT, LDP, IDP and HDP. The cost of emicizumab was the parameter that has the highest impact on the ICER, with ICER/QALY value reaching up to INR 309,288 (vs. ODT), INR 379,014 (vs. LDP with FVIII), INR 338,208 (vs. IDP with FVIII) and INR 134,311 (vs. HDP with FVIII) at the upper bound of the cost (Figure 2A–D).

Figure 3A,B shows the results of Monte-Carlo simulations conducted for incremental cost per QALY gained and a scatter plot of incremental costs and incremental QALYs for each of the 1000 iterations of the PSA. The CEAC projects a 94.7% probability that the ICER falls below INR 450,000/QALY (three-times per capita GDP), 49.4% probability that the ICER falls below INR 300,000/QALY (two-timesper capita GDP), and 0% probability that the ICER falls below INR 150,000/QALY (one-time per capita GDP).

4 | DISCUSSION

This cost-utility analysis investigates the cost-effectiveness of emicizumab prophylaxis versus ODT, LDP, IDP and HDP with FVIII by evaluating long-term costs and health outcomes in patients with severe HA without inhibitors. The base-case analysis results indicated emicizumab prophylaxis to be a cost-effective option compared with HDP, with an ICER/QALY of INR 27,869. Compared with IDP, LDP and ODT, emicizumab was found to be a cost-effective option if the paying threshold is >1 per capita GDP with an ICER/QALY of INR 264,592, INR 305,398 and INR 255,876, respectively. The WHO also suggests a threshold below three times the national annual GDP per capita as highly cost-effective.[24] In OWSA, the cost of emicizumab appeared to be the parameter with the highest impact on ICER values and PSA results were consistent with base-case analysis. As per the authors knowledge, this is the first study reporting the economic value of emicizumab prophylaxis in the context of an Indian setting.

Markov model was chosen in our analysis as it is one of the most commonly used modelling techniques in the health-economic evaluation and health technology assessment.[25] Markov model is a state-transition model that has been shown to be useful for chronic diseases (i.e., diseases with longer time frames) or when disease

TABLE 4A Results of base-case analysis comparing emicizumab prophylaxis with other treatment options (100 years' time horizon).

Comparators	Total costs (in INR)	Total QALYs[a]	Total LY[a]	Incremental costs	Incremental QALYs[a]	Incremental LY[a]	ICER: incremental cost per QALY (in INR)	ICER: incremental cost per LY (in INR)
Prophylaxis with emicizumab	207,128,983	941	1048					
On demand therapy	19,696,526	209	459	187,432,458	733	589	255,876	318,076
LDP with factor VIII	44,818,564	410	619	162,310,419	531	429	305,398	378,681
HDP with factor VIII	196,885,053	574	750	10,243,930	368	298	27,869	34,383
Intermediate-dose prophylaxis	66,506,022	410	619	140,622,961	531	429	264,592	328,083

Abbreviations: FVIII, factor VIII; HDP, high-dose prophylaxis; ICER, incremental cost-effectiveness ratio; INR, Indian rupees; LDP, low-dose prophylaxis; LY, life-years; QALY, quality-adjusted life-years.
[a]Expressed in months.

TABLE 4B Results of emicizumab prophylaxis comparing with other treatment options (1 years' time horizon).

Comparators	Total costs (in INR)	Total QALYs[a]	Total LY[a]	Incremental costs	Incremental QALYs[a]	Incremental LY[a]	ICER: incremental cost per QALY (in INR)	ICER: incremental cost per LY (in INR)
Prophylaxis with emicizumab	207,128,9	9.41	10.48					
On demand therapy	19,696,5	2.09	4.59	187,432,4	7.33	5.89	255,876	318,076
LDP with factor VIII	44,818,5	4.10	6.19	162,310,4	5.31	4.29	305,398	378,681
HDP with factor VIII	196,885,0	5.74	7.50	10,243,9	3.68	2.98	27,869	34,383
Intermediate-dose prophylaxis	66,506,0	4.10	6.19	140,622,9	5.31	4.29	264,592	328,083

Abbreviations: FVIII, factor VIII; HDP, high-dose prophylaxis; ICER, incremental cost-effectiveness ratio; INR, Indian rupees; LDP, low-dose prophylaxis; LY, life-years; QALY, quality-adjusted life-years.
[a]Expressed in months.

TABLE 4C Results of emicizumab prophylaxis comparing with other treatment options (1 month time horizon).

Comparators	Total costs (in INR)	Total QALYs[a]	Total LY[a]	Incremental costs	Incremental QALYs[a]	Incremental LY[a]	ICER: incremental cost per QALY (in INR)	ICER: incremental cost per LY (in INR)
Prophylaxis with emicizumab	172,607.49	.78	.87					
On demand therapy	16,413.77	.17	.38	156,193.71	.61	.49	255,876	318,076
LDP with factor VIII	37,348.80	.34	.52	135,258.68	.44	.36	305,398	378,681
HDP with factor VIII	164,070.88	.48	.62	8,536.61	.31	.25	27,869	34,383
Intermediate-dose prophylaxis	55,421.69	.34	.52	117,185.80	.44	.36	264,592	328,083

Abbreviations: FVIII, factor VIII; HDP, High-dose prophylaxis; ICER, incremental cost-effectiveness ratio; INR, Indian rupees; LDP, low-dose prophylaxis; LY, life-years; QALY, quality-adjusted life-years.
[a]Expressed in months.

probabilities vary over time.[26] The use of Markov model for haemophilia disease is well-reported in the literature.[27]

Prior to our study, several other analyses from the United State (US), Italy, France and Korea have evaluated and reported the cost-effectiveness of emicizumab prophylaxis.[13–15,28,29] The Institute for Clinical and Economic Review group from the US conducted a cost-effectiveness analysis of emicizumab prophylaxis versus FVIII in HA patients without inhibitors of all ages eligible for prophylactic therapy using Markov model with a lifetime time horizon and 6 months cycle from the healthcare perspective. Results indicated emicizumab

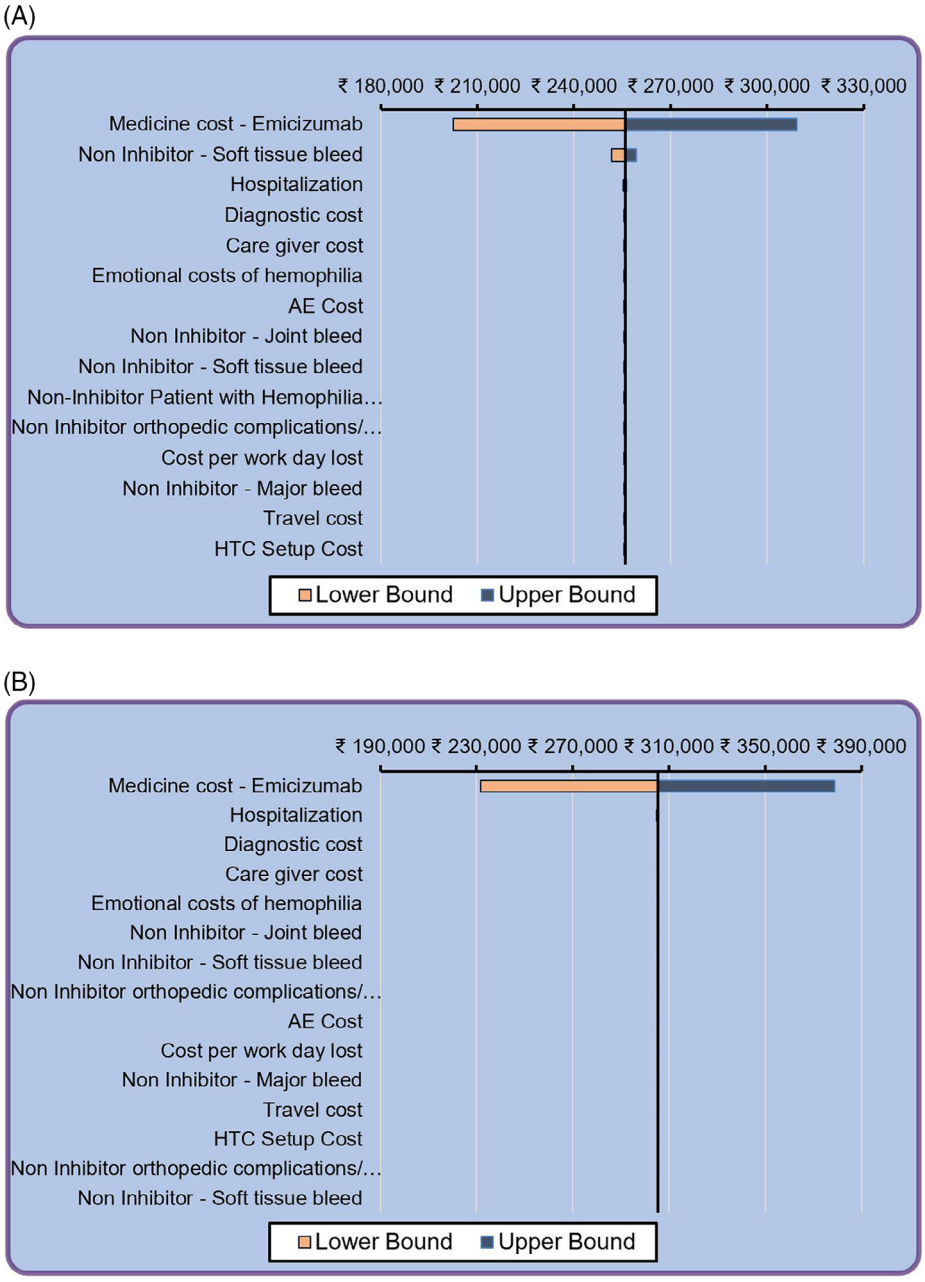

FIGURE 2 (A) Results of one-way sensitivity analysis of emicizumab prophylaxis versus on-demand therapy. AE, adverse event; HTC, haemophilia treatment center, in the middle of the diagram, there is typically a reference line that represents the baseline or expected treatment effectiveness when the parameter is at its current value. The horizontal axis of the sensitivity analysis displays bars that extend to the left and right, representing the impact of variations in the specific parameter on the effectiveness of the two treatment approaches. (B) Results of one-way sensitivity analysis of emicizumab prophylaxis versus low-dose prophylaxis with FVIII. AE, adverse event; HTC, haemophilia treatment center. (C) Results of one-way sensitivity analysis of emicizumab prophylaxis versus intermediate-dose prophylaxis with FVIII. AE, adverse event; HTC, haemophilia treatment center. (D) Results of one-way sensitivity analysis of emicizumab prophylaxis versus high-dose prophylaxis with FVIII. AE, adverse event; HTC, haemophilia treatment center.

a cost-saving strategy compared with FVIII prophylaxis.[28] Emicizumab prophylaxis was also shown to be the dominant treatment option over FVIII prophylaxis in another analysis from the US using a model cycle of 1 week.[13] Emicizumab models from Italy and South Korea used a lifetime horizon and 1 year model cycles, whereas the model from France used 5-year time horizon and a yearly cycle. In all these analyses, emicizumab was reported to be the cost-saving strategy compared to prophylaxis with BPAs in patients with HA. Our study aligns with previous findings, showing emicizumab prophylaxis as cost-saving versus FVIII. However, variations in populations, comparators, model details, and discounting rates exist among these studies.

Previous studies showed that 36.5% of students ($n = 148$) dropped out due to bleeding issues, with an average of 19.2 missed school days

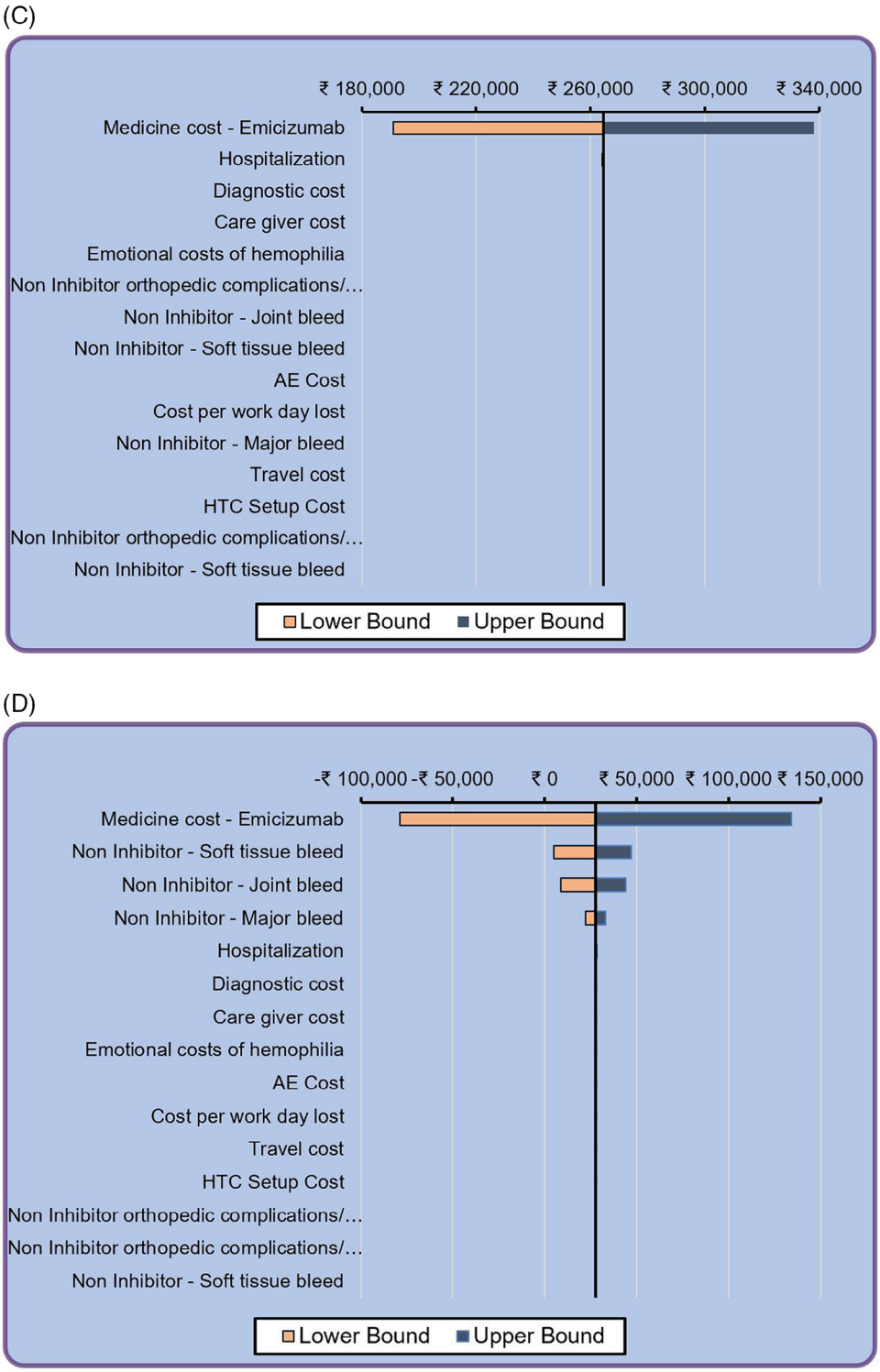

FIGURE 2 Continued

annually.[30] Additionally, 30% of HA patients develop neutralizing anti-FVIII antibodies, impacting treatment and QoL.[4,6] Emicizumab delayed inhibitor development by over 13 years compared to FVIII prophylaxis, leading to significant cost savings, especially for patients with inhibitors avoiding FVIII-bypassing agents prophylaxis.[31] The study emphasizes emicizumab positive impact, reducing school dropout rates, improving outcomes and offering cost savings for HA patients. Early prophylactic treatment is vital in preventing joint bleeds and haemophilic arthropathy in about 90% of PwHA.[32]

Data on the effectiveness of emicizumab from India are limited. LDP is the least costly of the types of prophylaxis with FVIII regimens, which makes it more accessible in resource-constrained countries, though

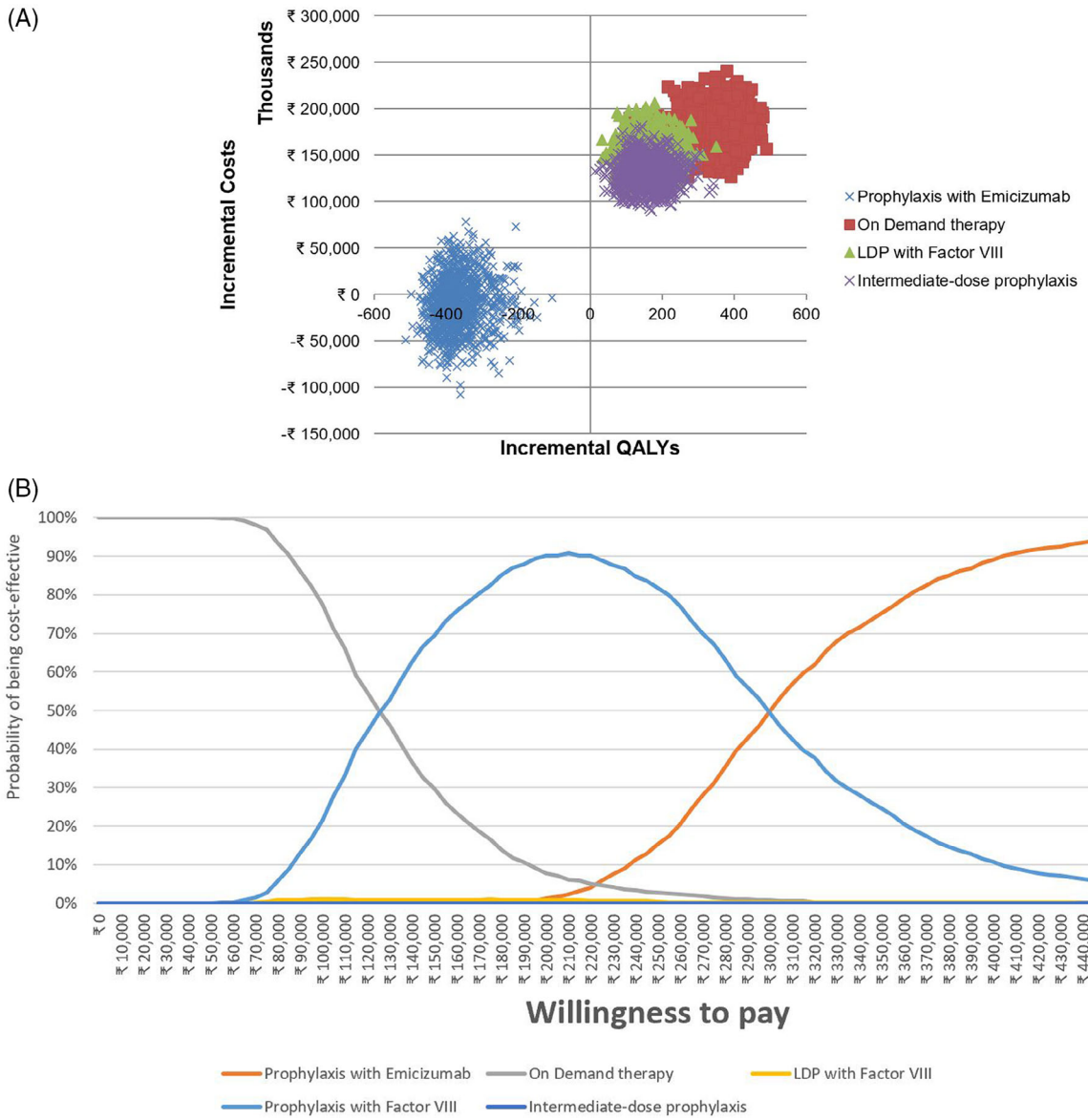

FIGURE 3 (A) Scatterplot curve for prophylaxis with emicizumab versus other comparators LDP, low-dose prophylaxis; QALY, quality-adjusted life-years A scatter plot is a graphical representation where each point on the plot corresponds to a specific intervention or treatment strategy. The *x*-axis typically represents costs, and the *y*-axis represents effectiveness (e.g., QALYs). Each point's position on the plot indicates the cost and effectiveness of the corresponding intervention. (B) Cost-effectiveness acceptability curve for prophylaxis with emicizumab versus other comparators LDP, low-dose prophylaxis, A CEAC is a graphical representation of the probability that a particular intervention is cost-effective at different willingness-to-pay (WTP) thresholds. It shows the probability that each intervention is cost-effective as the WTP threshold varies. If the CEAC curves for two or more interventions cross each other, it indicates that the preferred intervention changes based on the WTP threshold. The point where the curves cross can highlight the range of WTP values where one intervention becomes more cost-effective than the other.

the long-term effect on joint health is uncertain and may be poorer than those obtained with IDP or HDP regimens.[2–4] Although in the Indian context, the availability of IDP and HDP is extremely limited, with the majority of patients relying on ODT.[4] STASEY, a Phase IIIb, single-arm, open-label, multicentre study with 195 patients with HA (including 30 patients from India), showed that emicizumab prophylaxis was effective, with the majority of patients having zero treated bleeds during the study, and was well tolerated.[33] In a single-center study from India, emicizumab prophylaxis was given to four children with inhibitor-positive severe HA for a median of 34 weeks. Bleeding frequency decreased from 2 to 3.5 times per month to zero, and no significant adverse events were reported.[34] Although evidence on the effectiveness of emicizumab from an Indian setting is limited, emicizumab appears to be a promising agent for prophylaxis of patients with severe HA.[2–4]

Emicizumab, approved globally and in India, is a first-in-class prophylactic regimen for severe HA with several advantages over current treatments.[12] Clinical trials have demonstrated its efficacy and

safety, maintained low bleed rates, and reduced bleeding in target joints. Emicizumab unique 4-week half-life provides consistent and sustained therapeutic levels, offers flexible dosing options based on patient and physician preference.[9–11] Its subcutaneous administration allows for convenience and reduces the need for frequent healthcare visits. Emicizumab significantly reduced bleeds compared to prior FVIII prophylaxis in intra-patient comparisons. Emicizumab improved patient-reported outcomes, that is, reduction in pain, enhanced physical functioning and overall well-being, Better treatment adherence (98% vs. 89% for factor/bypass products) long-term joint health and less burden on the patient.[35] HAVEN trials showed significant reductions in bleeding rates and joint bleeds with emicizumab compared to factor VIII prophylaxis.[9,10] In the HAVEN-3 sub-group study, HJHS (Haemophilia Joint Health Score) improved after 48 weeks of emicizumab treatment, with sustained benefits throughout 96 weeks of prophylaxis.[36]

Notably, there was a significant reduction in bleeding into target joints during this period.[37] Callaghan et al. conducted a pooled analysis of HAVEN 1—4 trials, revealing that 94.1% reported no treated target joint bleeds.[37]

A previous study on severe haemophilia found that patients with joint-related complications had higher non-drug-related costs, including surgeries and outpatient care. Those with target joints had nearly three times higher bleeding-related hospital admission rates compared to those without target joints (.97 vs. .36).[38] The average non-drug-related direct costs per patient were EUR 5046 for patients with target joint complications, while patients without target joints incurred EUR 1684. Emicizumab consistently reduces both direct and indirect healthcare costs, resulting in significant savings.[38] It has the lowest costs among other therapies, reducing management expenses by up to 34% for adults and 43% for paediatric patients.[14,39] Additionally, the less frequent subcutaneous use decreases administration costs, leading to reduced healthcare expenses including visits, tests, hospitalizations and indirect costs.[14,39] A limitation of this study is not considering the complete healthcare resource utilization cost, like joint health deterioration. Medicine costs relied on tender prices, while hospitalization, emergency attendance and societal factors were specific to healthcare settings in Maharashtra or Kerala. Costs might vary in other settings, impacting analysis results.

5 | CONCLUSIONS

The study found that emicizumab prophylaxis is cost saving compared to HDP with FVIII. It could be considered a cost-effective option over ODT, LDP and IDP with FVIII for non-inhibitor PwHA in India (at WTP > 1 per capita GDP). In resource-limited countries like India, the use of **LDP** FVIII prophylaxis is questionable due to uncertainties about its long-term impact on joint health and the lack of long-term joint health protection. Emicizumab has shown persistent and low ABR when compared to LDP, IDP and ODT. This reduces the need for frequent infusions, improves adherence and significantly reduces non-drug-related expenses. Recent studies exploring low dose emicizumab strategies show almost comparable ABR and QoL grades. This underscores the need for further health utility research. Therefore, emicizumab prophylaxis promising humanistic, clinical and long-term economic outcomes make it a valuable option for treating PwHA in settings with limited resources.

CONFLICT OF INTEREST STATEMENT

The authors declared no interests that could be perceived as conflicts or biases, except for, P.C., who received speaker fees from Novo Nordisk India Limited.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available upon request. Please contact corresponding author for access to the data.

ETHICS STATEMENT

Ethical approval is not required for this study as it does not involve human subjects, animal experimentation or sensitive personal data. The research is conducted in accordance with established ethical standards and regulations.

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