NEW ENGLAND CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL

AN ICER PROGRAM

Emicizumab for Treatment of Hemophilia A in Patients with Inhibitors: Effectiveness and Value

Modeling Analysis Plan

November 20, 2017

Institute for Clinical and Economic Review

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Table of Contents

1. Overview

This document presents the analysis plan that details our modeling approach on methodology, and outcomes to be assessed for the economic evaluation of emicizumab in the prophylactic therapy of severe Hemophilia A patients with factor VIII inhibitors. Refer to the protocol for details on the systematic review of the clinical evidence on this topic.

2. Approach

The primary aim of this analysis will be to estimate the cost-effectiveness of emicizumab as prophylactic therapy for severe hemophilia A with inhibitors to factor VIII, using a Markov model. The model will compare emicizumab to two alternative strategies: (1) prophylaxis with bypassing agents and (2) no prophylaxis. For all three strategies, patients may be treated with bypassing agents when they bleed. Under the conditions of ICER's ultra-rare disease framework, we will consider dual 'base cases', which will reflect the health system and societal perspectives respectively. A societal perspective is included if the impact of the treatment on patient and caregiver productivity, education, disability and nursing home costs are substantial, and these costs are large relative to health care costs. If not assessed as a dual base case, this will be considered in a scenario analysis, if data allow. The analytic framework for this assessment is depicted in Figure 1 below. The model will be developed in Microsoft Excel.

3. Methods

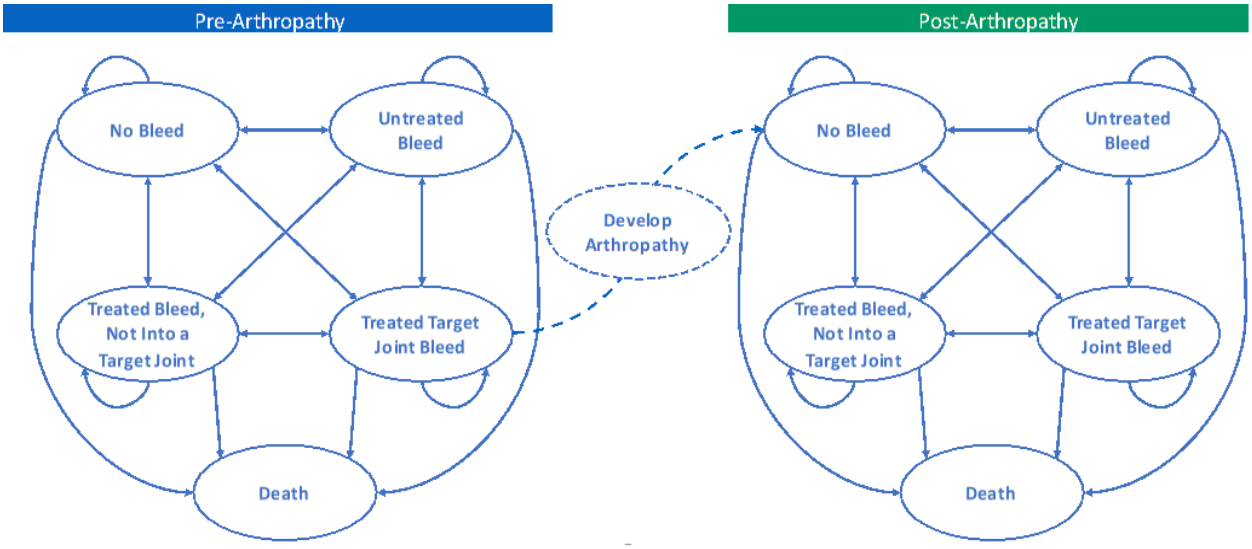
3.1 Model Structure

The Markov model structure tracks bleed events, development of arthropathy, and survival over time for a cohort of hemophilia A patients with inhibitors. Because arthropathy may have a pronounced impact on quality of life, resource utilization, and costs, including but not limited to the long-lasting impact of joint replacement surgery, we will separate pre-arthropathy and post-arthropathy patients into two sub-models within the overall model, so that a proportion of patients permanently transitions from the pre-arthropathy sub-model into the post-arthropathy sub-model in each model cycle. This allows us to circumvent the "memoryless" characteristic of Markov models regarding patient history, with patients having different sets of costs and utilities in each sub-model.

For each treatment regimen, a hypothetical patient population will begin the model in the pre-arthropathy "No Bleed" health state, where they remain until they die or suffer from a bleed event that transitions them to one of three Markov bleed states: "Untreated Bleed", "Treated Bleed Not

Into a Target Joint", or "Treated Target Joint Bleed" (target joint is defined as a single joint with three or more spontaneous bleeds into it within a consecutive 6-month period)[1] (Figure 1). If data allow, we will link the transition between pre- and post-arthropathy sub-models to the frequency of target joint bleeds; otherwise, we will apply a constant rate to all patients based on lifetime risk (73%) of arthropathy development (as depicted in Figure 1).[2] All hypothetical patients are modeled until they die from any health state in the model due to disease and non-disease-related causes.

Figure 1. Model Framework



3.2 Treatments

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The full list of interventions is as follows:

> **Interventions**. The intervention of interest will be subcutaneous injection of emicizumab for prophylaxis. Patients may be treated with bypassing agents (recombinant FVIIa (NovoSeven®; Novo Nordisk) or activated prothrombin complex concentrate (aPCC [FEIBA®; Shire]) during a bleeding episode while on prophylaxis with emicizumab.
>
> **Comparators.** We will compare prophylaxis with emicizumab to two alternatives: (1) prophylaxis with a bypassing agent, and (2) no prophylactic therapy. For each comparator, patients may be treated with bypassing agents when they bleed.

3.3 Target Populations

Consistent with the population of focus in the clinical trials of emicizumab, the population of interest in the model will be patients with severe hemophilia A with inhibitors to factor VIII who have either failed immune tolerance induction (ITI) or are not going to be treated with ITI. We will assume all patients are males (hemophilia A is X-chromosome linked, and the development of inhibitors in females is rare). We will evaluate adolescents and adults (age 12 years and older) as well as children (under 12 years).

Table 1. Patient Population Characteristics

Patient population	Median Age	Median Weight	Source
Age 12 years and older	37 years*	75 kg*	HAVEN 1[3]
Under 12 years	8.5 years	26.9 kg	HAVEN 2[4]

*Weighted average of arms A & B in the trial

3.4 Key Model Choices and Assumptions

- The model will utilize data from the HAVEN 1[3] (age 12 years and older) and HAVEN 2[4] (under 12 years) trials to derive effectiveness estimates for bleed event prevention for emicizumab prophylaxis and no prophylaxis.
- The model will utilize trial-derived effectiveness estimates for bleed event prevention for bypassing agent prophylaxis (aPCC and FVIIa combined).[5-8]
- Survival will be weighted by health state utilities estimated from the HAVEN 1 trial to model quality of life.[4] The trial elicited health-related quality of life using the 5-level version of the generic EuroQol 5-Dimension Self Report Questionnaire (EQ-5D-5L) visual analogue scale; index utility score at week 25; and the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) physical health subscale as well as total score at week 25 of follow-up. The generic EQ-5D-5L will be used for the base case analysis; the disease specific Haem-A-QoL in a sensitivity analysis. The model will also include separate utilities for different types of bleed events, and disutilities (if available in the published literature) for individual adverse events.
- The model will include all treatment costs associated with each individual regimen, including drug acquisition costs, drug administration costs (e.g. for subcutaneously or intravenously administered drugs), and supportive care costs (e.g. clinician visits and monitoring).
- Under the conditions of ICER's ultra-rare disease framework, we will consider dual base cases, which will reflect the health system and societal perspectives respectively. A societal perspective is included if the impact of the treatment on patient and caregiver productivity, education, disability and nursing home costs are substantial, and these costs are large relative to health care costs. If not assessed as a dual base case, this will be considered in a scenario analysis, if data allow. Outcomes will be estimated over a lifetime time horizon using weekly cycles to capture the potential lifetime impacts of short-term and ongoing morbidity and mortality. Costs and outcomes will be discounted at 3% per annum.[9]

Table 2. Key Model Assumptions and Rationales

Assumption	Rationale
A patient may transition to any bleed health state from another or to death during each one-week model cycle.	Trial data does not report transitions from one type of bleed to another. It is feasible that any type of bleed could follow another from week to week.
A patient may transition from the pre-arthropathy to the post-arthropathy model, but not vice versa.	Intra-articular bleeding (hemarthrosis) causes synovial hypertrophy and cartilage damage (arthropathy), manifesting as gradual but inexorable joint destruction.
Bleed event rates are equivalent in pre- and post-arthropathy.	Data on the relative occurrence of bleed events pre- and post-arthropathy are limited.
Joint-replacement surgery can only occur in the post-arthropathy model.	The development of joint arthropathy is a precondition for joint replacement surgery.
Treatment adherence will reflect the reported HAVEN 1 & 2 trials' discontinuation rates over the first 24 weeks.[3,4] We assume patients who discontinue prophylaxis will have the same bleed rates as the no prophylaxis population. Patients who remain on treatment beyond 24 weeks are assumed to be 100% adherent over their remaining lifetime in the base case analysis, but this will be varied in scenario analyses.	There is limited data on long-term use, however patients are at risk for bleed events, and thus require treatment, over their entire lifetime.
All patients are assumed to be male.	Hemophilia is an X-linked recessive disease affecting primarily males. Females with hemophilia A typically have less severe disease and are unlikely to develop inhibitors.
Patients on emicizumab will be awarded a one-time physician's office visit prior to prophylaxis initiation.	This one-time visit is assigned to educate patients on self-administration of emicizumab.
When patients reach the age of 12, their bleeding reduction with emicizumab becomes that of people age 12 and over (0.13)	Data on the persistence of the effect in those <12 years old vs.>12 years old is not available. A scenario analysis will explore the impact of assuming bleeding reduction persists at the childhood reduction level (0.01).
Pettersson score (0 = no arthropathy, maximum of 78) is assumed to be zero in the first model cycle in the base case analysis. We will model a range of starting Pettersson scores to assess less severe versus more severe patient populations.	The HAVEN 1 and 2 trials do not specify arthropathy-specific baseline patient characteristics. We will therefore report a range for increasing arthropathy scores at model entry, along with base case results.

3.5 Input Parameters

Clinical Inputs

We will utilize trial-derived estimates of annualized bleed rates to derive weekly transition probabilities for each bleed event health state. Since the HAVEN 2 trial of patients aged <12 years was a single arm study,[4] we may derive bleed event rates for patients <12 years based on the observed rate differences from the HAVEN 1 trial and bypassing agent trials; these estimates are yet to be determined (TBD). Modeled bleed events (see Figure 1) will be derived from trial-reported annualized bleed rates as follows:

- Untreated bleeds = All bleeds minus bypassing agent-treated bleeds
- Treated bleeds not into a target joint = Treated bleeds minus treated target joint bleeds
- Target joint bleed rates as reported by the trial publications

Table 3. Derivation of Transition Probabilities for Markov Model

Trial Outcomes: Age 12+ years	Reported Trial Result	Trial-Derived Outcomes for Model	Derived Annualized Bleed Rate	Conversion to Weekly Probability	1-year Cumulative Bleeds
All Bleeds		**Untreated Bleeds**			
ABR: No Prophylaxis[10]	28.3	No Prophylaxis	5.0	0.091	4.8
RR: Emicizumab Prophylaxis[10]	0.2	Emicizumab Prophylaxis	2.6	0.049	2.6
RR: BPA Prophylaxis	TBD	BPA Prophylaxis	TBD	TBD	TBD
BPA-Treated Bleeds		**Treated Bleeds, Not into a Target Joint**			
ABR: No Prophylaxis[10]	23.3	No Prophylaxis	20.3	0.322	16.8
RR: Emicizumab Prophylaxis	0.13	Emicizumab Prophylaxis	2.9	0.054	2.8
RR: BPA Prophylaxis[6]	0.28	BPA Prophylaxis	TBD	TBD	TBD
Treated Target Joint Bleeds		**Treated Target Joint Bleeds**			
ABR: No Prophylaxis[10]	3	No Prophylaxis	As reported	0.056	2.9
RR: Emicizumab Prophylaxis[10]	0.05	Emicizumab Prophylaxis	As reported	0.001	0.0
RR: BPA Prophylaxis	TBD	BPA Prophylaxis	TBD	TBD	TBD
Trial Outcomes: Age <12 years	**Reported Trial Result**	**Trial-Derived Outcomes for Model**	**Derived Annualized Bleed Rate**	**Conversion to Weekly Probability**	**1-year Cumulative Bleeds**
All Bleeds		**Untreated Bleeds**			
ABR: No Prophylaxis	TBD	No Prophylaxis	TBD	TBD	TBD
RR: Emicizumab Prophylaxis	TBD	Emicizumab Prophylaxis	TBD	TBD	TBD
RR: BPA Prophylaxis	TBD	BPA Prophylaxis	TBD	TBD	TBD
BPA-Treated Bleeds		**Treated Bleeds, Not into a Target Joint**			
ABR: No Prophylaxis[10]	23.3	No Prophylaxis	TBD	TBD	TBD
RR: Emicizumab Prophylaxis [4]	0.01	Emicizumab Prophylaxis	TBD	TBD	TBD

RR: BPA Prophylaxis	TBD	BPA Prophylaxis	TBD	TBD	TBD
Treated Target Joint Bleeds		**Treated Target Joint Bleeds**			
ABR: No Prophylaxis	TBD	No Prophylaxis	TBD	TBD	TBD
RR: Emicizumab Prophylaxis	TBD	Emicizumab Prophylaxis	TBD	TBD	TBD
RR: BPA Prophylaxis	TBD	BPA Prophylaxis	TBD	TBD	TBD

ABR = annualized bleed rate; RR = rate ratio for annualized bleed rates; BPA = bypassing agent; TBD = to be determined during clinical evidence review by research team.

Estimates for the development of arthropathy over time will be derived from the literature, or potentially extrapolated from the rate and cumulative number of target joint bleeds depending on the best literature data available. We will utilize the radiological Pettersson score to reflect the degree of arthropathy over time (minimum score 0 for joints without signs of arthropathy, to a maximum score of 78 points).[11,12] The Pettersson score is a validated radiological scoring system assessing the sum per patient of the total osteochondral changes in knees, elbows and ankles.[11] The reported relationship between target joint bleeds and the Pettersson score is a one point increase in the Pettersson score per 12.6 joint bleeds, on average (95% CI: 11.1 – 14.7).

In addition, the percentage of patients receiving orthopedic surgery will be based on the number of target joint bleeds that a patient incurs. We will utilize the approach by Fischer et al. and Earnshaw et al., in which patients who reach a Pettersson score of 28 (the threshold for clinically relevant damage) will be assumed to require orthopedic surgery.[13] As in Earnshaw et al., we will assume no joint replacement surgeries are performed after patients reached 80 years of age.[14] We will also model reduced quality of life with increasing Pettersson score, based on Fischer et al.[15]

Mortality will be based on the age-adjusted male U.S. population and the increased rate of death for hemophilia A patients with inhibitors, derived from a retrospective study of 7,386 males with severe hemophilia A over a 13-year period that reported a 70% increased odds of death for inhibitor patients.[16]

Drug utilization

The schedule of doses for each drug in each prophylaxis regimen as well as protocol dosage for the indication will be used to model drug utilization and associated costs.

Table 4. Treatment Regimen Recommended Dosage

	Emicizumab SC	Bypassing Agent: FVIIa	Bypassing Agent: aPCC
Brand name	Hemlibra®	NovoSeven®	FEIBA®
Manufacturer	Genentech	Novo Nordisk	Shire
Route of administration	Subcutaneous	Intravenous	Intravenous
Dosage Forms and Strengths[16,17]	Single-dose vials of 30mg/ml, 60mg/0.4ml,	Single-use vials of 1, 2, 5, or 8 mg	500, 1000, or 2500 units per vial

	105mg/0.7ml and 150mg/ml		
Prophylaxis Dosing [18,19,20,21]	3.0 mg/kg weekly for the first four weeks, followed by 1.5 mg/kg weekly	90 or 270 µg/kg	85 units/kg every other day
Bleed Event, On Demand Dosing[5,22]	NA	90 mcg/kg every 2 hours, adjustable based on severity of bleeding until hemostasis is achieved 90 mcg/kg every 3-6 hours after hemostasis is achieved for severe bleeds	50-100 units/kg every 6-12 hours until pain/disabilities and/or bleeding is resolved.

Drug Cost Inputs

We will use net prices derived from average sales price (ASP) for the bypassing agents while calculating treatment-related health care costs, since we currently do not have data on net price that includes discounts/rebates for these agents. For emicizumab, we will seek to identify anticipated discounts from WAC that will reflect a net price for the therapy. Hospital administered drugs will include mark-ups for a commercially insured population and no mark-up for Medicaid patients. Based on the regimen dosage specified above and available formulations for each drug, the model will utilize the lowest cost combination of tablets/vials for each regimen where appropriate.

Table 5. Drug Costs

	Emicizumab SC	Bypassing Agent: FVIIa	Bypassing Agent: aPCC
Cost Unit	1.5mg	1 mcg	1 IU
WAC per Unit	$148.8	$2.16[23]	$2.16[23]
ASP per Unit	N/A	$2.00[24]	$1.94[24]
ASP Discount from WAC	N/A	7%	10%

Healthcare Utilization Inputs

Additional healthcare utilization could occur with treatment administration and during therapy, including the initial office visit where patients are taught how to self-administer, hospitalizations for treatment of bleeds, and visits to hemophilia treatment centers. Costs for supportive care other than the treatment of a bleed event will be derived from published studies, and will include costs of ongoing care that are essential to the current paradigm of treatment.

Table 6. Healthcare Utilization and Cost Inputs

	Emicizumab Prophylaxis	No Prophylaxis	Bypassing Agent Prophylaxis	Source
Mean (95% CI) days hospitalized within 24 weeks during HAVEN 1	1.2 (0.0 to 3.0)	4.2 (0.0 to 8.8)	4.0 (0.0 to 8.4)[18]	Genentech[25] Shrestha et al[26]
Per-Bleed non-pharmacy costs (weekly) • Age 6-18 yrs • Age 19-44 yrs • Age >45 yrs	 $878 $4,551 $13,178	 $3,046 $4,439 $6,612	 $878 $4,551 $13,178	Shrestha et al[26]
Total non-pharmacy hemophilia-related costs (annual) • Age 6-18 yrs • Age 19-44 yrs • Age >45 yrs	 TBD~ TBD~ TBD~	 $53,408 $56,311 $37,980	 $15,864 $22,028 $45,311	Shrestha et al[26]
Hospitalization cost for major bleed event	$33,466			Earnshaw et al.[14] (inflated to 2017 $)
Arthropathy surgery cost	$45,286			Earnshaw et al.[14] (inflated to 2017 $)
Per visit cost to families to receive care^ at: • HTC • Local Clinic	 $161 ($0 - $850) $17 ($0 - $210)			Price et al.[27]
Time off work per visit: • HTC • Local Clinic	 1 day (0-3 days) 1 day (0-1 days)			Price et al.[27]

*HCPCS Code: 99213. Non-Facility Price; ~TBD by economic research team; ^Includes transportation, parking, accommodation, meals and childcare; THC: Hemophilia Treatment Center.

Health State Utilities

Health state utilities will be derived from manufacturer submitted data from the HAVEN 1 trial[3] and other literature sources,[28-30] applied to the relevant health states. We will use consistent health state utility values across treatments evaluated in the model. We will include disutilities (if available) for individual adverse events, lasting for one week and assessed in the first cycle of the model.

Table 7. Quality of Life Inputs

Parameter	Value
Utility: hemophilia A with inhibitors, no bleed	0.82[28]
Utility: hemophilia A with inhibitors, treated bleed not into a target joint	0.66[28]
Utility: hemophilia A with inhibitors, target joint bleed	0.54[29]
Utility: arthropathy by Pettersson Score (PS)[15] • PS 0-4 • PS 4-12 • PS 13-21 • PS 22-39 • PS 40-78	 0.83 0.81 0.77 0.74 0.72
Utility: orthopedic surgery	0.19[31]
Disutility: central venous access device	-0.02[30]

[#]Calculated as utility of 'hemophilia A patients with inhibitors, treated bleed not into a target joint' (0.66) minus disutility 'hemophilia A with inhibitors, target joint bleed' (-0.12).

Adverse Events

The model will include any common adverse events that occur in >5% of patients as observed in the key clinical trials and/or the drug's prescribing information, as well as any serious adverse events documented in the trials. Each adverse event will have an associated cost and disutility that will be applied for each patient experiencing such an event. Costs for adverse events will be based on resource utilization associated with appropriate adverse event treatments as reported in previous analyses and unit prices from the Centers for Medicare and Medicaid Services (CMS) list of Medicare Physician Fee Schedule for the fiscal year 2017.[32]

Table 8. Adverse Event Inputs

Adverse Event	Adverse Event Cost[33]	Emicizumab Prophylaxis[3]	No Prophylaxis[3]	BPA Prophylaxis
Injection Site Reaction	$4,473	24%	8%	TBD
Headache	$4,030	9%	8%	TBD
Fatigue	$4,062	9%	8%	TBD
Upper Respiratory Tract Infection	$5,075	21%	0%	TBD
Arthralgia	$4,046	6%	8%	TBD
Serious Adverse Events:				
Thrombotic microangiopathy	$13,335	3%		TBD
Skin necrosis	$7,667	3%		TBD
Thrombophlebitis superficial	$7,708	3%		TBD
Iron deficiency anemia	$7,267	3%		TBD
Hemarthrosis	$6,555		8%	TBD
Muscle hemorrhage	$6,906	3%		TBD

TBD during systematic review of literature.

3.6 Model Outcomes

Clinical outcomes will include the cumulative incidence of each bleed event, and we will report the absolute risk reduction in bleed events for the treatment comparisons. We will evaluate life expectancy, quality-adjusted life-expectancy, and health care costs for each treatment strategy, and calculate total costs, life-expectancy and quality-adjusted life years, and the incremental costs per life-year and per quality-adjusted life-year (QALY) gained of emicizumab versus each comparator. In addition, we will report costs per consequence avoided, e.g. cost per bleed averted and cost per inpatient hospital stay averted.

3.7 Analysis

Each model cycle will last one week to capture the costs and utilities related to the frequencies of bleed events for each regimen. Patient survival, quality-adjusted survival, and health care costs will be estimated for each model cycle and then summarized over 1-year, 5-year, 10-year, and lifetime time horizons for each treatment option. Differences in survival, quality-adjusted survival and costs between each treatment and comparator will be used to calculate incremental cost-effectiveness ratios.

Sensitivity Analyses

We will conduct one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Probabilistic sensitivity analyses will also be performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We will also perform threshold analyses for drug costs across a range of incremental cost-effectiveness ratios (from $50,000 to $500,000 per QALY).

Scenario Analyses

Multiple scenario analyses will be conducted to evaluate the impact of key model choices and assumptions on the robustness of the results and conclusions. As data allow, we will consider conducting scenario analyses that include:

- higher bleed rates in patients with arthropathy,
- patient Pettersson score (arthropathy severity) in first model cycle,
- proportion of patients unable to use aPCC on demand when treated with emicizumab,
- differential adherence rates for emicizumab versus prophylactic treatment with bypassing agents,
- when patients reach the age of 12, their bleeding reduction persists at the childhood reduction level,

- productivity losses of patients/caregivers,
- quality of life of caregivers.

Model Validation

We will use several approaches to validate the model. First, we will present our methodology and preliminary results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we will refine data inputs used in the model, as needed. Second, we will vary model input parameters to evaluate face validity of changes in results. We will perform model verification for model calculations using internal reviewers. Finally, we will compare results to other cost-effectiveness models in this therapy area.

References

1. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Definitions in hemophilia: communication from the SSC of the ISTH. *Journal of thrombosis and haemostasis : JTH.* 2014;12(11):1935-1939.
2. Aznar JA, Marco A, Jimenez-Yuste V, et al. Is on-demand treatment effective in patients with severe haemophilia? *Haemophilia : the official journal of the World Federation of Hemophilia.* 2012;18(5):738-742.
3. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. *The New England Journal of Medicine.* 2017.
4. Young G OJ, Liesner R, et al. HAVEN 2: Efficacy, safety and pharmacokinetics of once-weekly prophylactic emicizumab (ACE910) in pediatric patients (<12 years) with hemophilia A with inhibitors: interim analysis of single-arm, multicenter, open-label, phase 3 study. . *Interim Results oral presentation* July 9, 2017.
5. Konkle BA, Ebbesen LS, Erhardtsen E, et al. Randomized, prospective clinical trial of recombinant factor VIIa for secondary prophylaxis in hemophilia patients with inhibitors. *Journal of Thrombosis & Haemostasis.*5(9):1904-1913.
6. Antunes SV, Tangada S, Stasyshyn O, et al. Randomized comparison of prophylaxis and on-demand regimens with FEIBA NF in the treatment of haemophilia A and B with inhibitors. *Haemophilia : the official journal of the World Federation of Hemophilia.* 2014;20(1):65-72.
7. Antunes SV, Tangada S, Phillips J, et al. Comparison of historic on-demand versus prospective on-demand and prophylaxis bleeding episodes in hemophilia A and B patients with inhibitors treated with FEIBA NF. 2014;20:96.
8. Leissinger C, Gringeri A, Antmen B, et al. Anti-inhibitor coagulant complex prophylaxis in hemophilia with inhibitors. *The New England journal of medicine.* 2011;365(18):1684-1692.
9. Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG. *Cost-effectiveness in health and medicine.* Oxford University Press; 2016.
10. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. *New England Journal of Medicine.* 2017;377(9):809-818.
11. Pettersson H, Nilsson IM, Hedner U, Norehn K, Ahlberg A. Radiologic evaluation of prophylaxis in severe haemophilia. *Acta paediatrica Scandinavica.* 1981;70(4):565-570.
12. Fischer K, van Hout BA, van der Bom JG, Grobbee DE, van den Berg HM. Association between joint bleeds and Pettersson scores in severe haemophilia. *Acta radiologica (Stockholm, Sweden : 1987).* 2002;43(5):528-532.
13. Fischer K, Pouw ME, Lewandowski D, Janssen MP, van den Berg HM, van Hout BA. A modeling approach to evaluate long-term outcome of prophylactic and on demand treatment strategies for severe hemophilia A. *Haematologica.* 2011;96(5):738-743.
14. Earnshaw S, Graham C, McDade C, Spears J, Kessler C. Factor VIII alloantibody inhibitors: cost analysis of immune tolerance induction vs. prophylaxis and on-demand with bypass treatment. *Haemophilia : the official journal of the World Federation of Hemophilia.* 2015;21(3):310-319.
15. Fischer K, de Kleijn P, Negrier C, et al. The association of haemophilic arthropathy with Health-Related Quality of Life: a post hoc analysis. *Haemophilia : the official journal of the World Federation of Hemophilia.* 2016;22(6):833-840.
16. Walsh CE, Soucie JM, Miller CH. Impact of inhibitors on hemophilia A mortality in the United States. *American journal of hematology.* 2015;90(5):400-405.
17. Centers for Disease Control. *United States Life Tables, 2013.*

18. Young G, Shafer FE, Rojas P, Seremetis S. Single 270 microg kg(-1)-dose rFVIIa vs. standard 90 microg kg(-1)-dose rFVIIa and APCC for home treatment of joint bleeds in haemophilia patients with inhibitors: a randomized comparison. *Haemophilia : the official journal of the World Federation of Hemophilia.*14(2):287-294.
19. Genentech. *Hemlibra package insert.* 2017.
20. Novo Nordisk. *NovoSeven RT package insert.* 2017.
21. Shire. FEIBA package insert. . www.shirecontent.com/PI/PDFs/FEIBA_USA_ENG.pdf. . Accessed October 29, 2017.
22. Hoots WK, Ebbesen LS, Konkle BA, et al. Secondary prophylaxis with recombinant activated factor VII improves health-related quality of life of haemophilia patients with inhibitors.[Erratum appears in Haemophilia. 2008 May;14(3):670]. *Haemophilia : the official journal of the World Federation of Hemophilia.*14(3):466-475.
23. Redbook Online [online database]. *Truven Health Analytics* 2017(Greenwood Village, CO).
24. Center for Medicare and Medicaid Services. *Medicare Part B Drug Average Sales Price.* 2017.
25. Formal communication to ICER from Genentech. In.
26. Shrestha A, Eldar-Lissai A, Hou N, Lakdawalla DN, Batt K. Real-world resource use and costs of haemophilia A-related bleeding. *Haemophilia : the official journal of the World Federation of Hemophilia.* 2017;23(4):e267-e275.
27. Price VE, Hawes SA, Bouchard A, Vaughan A, Jarock C, Kuhle S. Unmeasured costs of haemophilia: the economic burden on families with children with haemophilia. *Haemophilia : the official journal of the World Federation of Hemophilia.* 2015;21(4):e294-299.
28. Neufeld EJ, Recht M, Sabio H, et al. Effect of acute bleeding on daily quality of life assessments in patients with congenital hemophilia with inhibitors and their families: observations from the dosing observational study in hemophilia. *Value in Health.* 2012;15(6):916-925.
29. Mazza G, O'Hara J, Carroll L, Camp C, Hoxer CS, Wilkinson L. The Impact of Haemophilia Complications on Health-Related Quality of Life for Adults with Severe Haemophilia. *Value in Health.* 2016;19(7):A593.
30. Naraine V, Risebrough N, Oh P, et al. Health-related quality-of-life treatments for severe haemophilia: utility measurements using the Standard Gamble technique. *Haemophilia : the official journal of the World Federation of Hemophilia.* 2002;8(2):112-120.
31. Colombo GL, Di Matteo S, Mancuso ME, Santagostino E. Cost–utility analysis of prophylaxis versus treatment on demand in severe hemophilia A. *ClinicoEconomics and Outcomes Research: CEOR.* 2011;3:55-61.
32. Centers for Medicare and Medicaid Services. *Physician Fee Schedule Search.*
33. Centers for Medicare and Medicaid Services. *2017 Final Rule and Correction Notice Tables. Tables 1A-1E and Table 5.* 2017.