METHODS

**Study eligibility criteria**

* Patients with severe hemophilia A (Factor VIII levels <1% or <2%) who could be previously treated or untreated
* Minimum of 24 weeks of follow up
* Included at least one of the efficacy outcomes
* Excluded:
  + Observational Studies
  + Patients with acquired hemophilia
  + Follow-up period shorter than 24 weeks
  + Study population included mild and moderate patients (>2% Factor VIII levels)
  + Reported only surgical prophylaxis
  + Study population includes only patients with inhibitors
* Published before January 1, 2020
* FDA approved dosage regimens of the eligible medications, as recommended to be included by the BCBS plans.

**Eligible Medications**

Advate (Recombinant factor VIII)

Adynovate (Recombinant, PEGylated factor VIII)

Afstyla (Recombinant, single chain, factor VIII)

Eloctate (Recombinant, Fc Fusion Protein, factor VIII)

Kogenate FS (Recombinant, factor VIII)

Kovaltry (Recombinant, factor VIII)

NovoEight (Recombinant, B-domain truncated, factor VIII)

Nuwiq (Recombinant, B-domain deleted, factor VIII)

Recombinate (Recombinant, factor VIII)

Xyntha (Recombinant, B-domain deleted, factor VIII)

Hemofil M (Human Plasma-derived immunoaffinity purified, factor VIII)

Koate-DVI (antihemophilic factor, human, factor VIII)

Jivi (recombinant, PEGylated-aucl, factor VIII)

Esperoct (recombinant, glycopegylated-exei, factor VIII)

Hemlibra (emicizumab-kxwh).

**Efficacy Outcomes**

1. Proportion of patients with no reported bleeds
2. Number of bleeding events per person/per month (Calculated from Mean Annualized Bleeding Rate)

**Safety Outcomes**

The incidence of development of inhibitors was too small to detect a difference, with most studies reporting zero, therefore, was not included.

**Study Comparator and Meta-analysis**

* Hemophilia A studies generally compare prophylaxis with on-demand treatment using the same medication or are single-arm studies.
* We matched prophylaxis arms from different studies to simulate head-to-head trials based on covariates (age, follow-up period and other study population characteristics (% severe hemophilia, % previously treated, % with inhibitors) in order to conduct a network meta-analysis. We did the same between on-demand arms.
* Kogenate FS was chosen as the reference comparator based on it’s market share as well as it being the oldest drug with the relevant data available (Reference: IPD Analytics)