CSL Behring

19 September 2023

FIMEA Report on HEMGENIX for Haemophilia B

BACKGROUND

- The Finnish Medicines Agency (Fimea) has completed an evaluation and released a report on the use of CSL Behring's HEMGENIX (etranacogene dezaparvovec) on 22 August to treat adults with severe and moderately severe haemophilia B.
- The evaluation is based on a comprehensive analysis of clinical data, focusing on a Phase 3 study named HOPE-B. In this pivotal trial, 54 patients received HEMGENIX gene therapy. Additionally, evidence was derived from a Phase 2b study (CT-AMT-061-01) involving three patients.
- The report reviews the clinical trials and cost-effectiveness of HEMGENIX compared to conventional FIX replacement therapies. The main findings are:
    - HEMGENIX is a one-time treatment that can increase FIX activity levels and reduce bleeding events for years.
    - In an indirect comparison, HEMGENIX was also compared to regular treatment (prophylaxis) with the widely used FIX replacement therapy, Alprolix. In the comparison, the annual bleeding rate was significantly reduced with HEMGENIX treatment, also compared to Alprolix.
    - According to the Agency, direct costs for HEMGENIX are substantial, amounting to EUR 2.8 million, which is more than ten times the annual patient costs of factor IX (FIX) substitution treatment (approximately EUR 216,000 per patient per year). While HEMGENIX has a high upfront cost it could save money in the long run by reducing the need for regular FIX replacement therapy.

COMMENTS TO THE REPORT BY CSL BEHRING

Fimea concluded that the biggest uncertainty factor in the cost-effectiveness analysis is the duration of the HEMGENIX treatment. For this reason, Fimea had proposed alternative scenarios to the marketing authorisation holder's baseline analysis by modifying the duration of the effect of treatment and the annual number of bleeding episodes.

1. Fimea suggests a decline in effect staring already from year 1.

CSL Behring response:

Durability curves should not start to decline already at year 1, since we have actual patient data that shows that this is in fact not the case.

A key driver of the cost-effectiveness results is the duration of the treatment effect of HEMGENIX. It is therefore appropriate to explore how sensitive the results are to alternative durability

assumptions. However, we think it is **important to focus on where the uncertainty lies. Therefore, the durability of the treatment effect is not to be in the region where data indeed demonstrate a sustained clinical effect**. For this reason, we do not agree on the strategy used by Fimea i.e., conducting the staircase analysis already from year one where existent durability data demonstrate sustained effect.

A staircase analysis may nevertheless constitute a reasonable way of exploring uncertainty around durability. However, this is provided if the staircase analysis starts when the uncertainty arises and not prior to this point in time. The point at which the uncertainty arises should in turn be informed by clinical data.

In the pivotal **HOPE-B trial**, participants treated with HEMGENIX sustained endogenous FIX activity levels with a mean endogenous FIX activity of 36.66 IU/dL (SD; min, max = ±18.96; 4.7, 99.2) at **24 months**. However, studies prove that the effects of recombinant AAV based gene therapy can be maintained over long periods of time. The durability of treatment effect was demonstrated over a **five-year follow-up** period in the **phase I/II study** achieved by AMT-060 (n=10) [A & B], the precursor of HEMGENIX which uses the same recombinant AAV5 capsid containing the identical gene-expression cassette but with a wild-type human FIX transgene (which differs from FIX Padua by two nucleotides). The most recently published follow-up of the earliest successful liver directed AAV based haemophilia B gene therapy trial demonstrated stable therapeutic expression of FIX up to **8 years follow up** [C]; currently these patients have been followed for up to **13.5 years and FIX levels remain stable** [D].

Based on the above studies, as a reasonable conservative assumption, HEMGENIX therapeutic effect can be assumed to have **long-term durability of more than 10 years with near normal and sustained FIX activity**. Therefore, it is not reasonable to model a decrease in durability already from year one.

In conclusion, **durability should not start to decline already at year 1**, since this does not align with what has been observed in clinical studies.

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2. <u>Fimea has used a 2.5 grading scale where each year 2.5 to 10.0% of the patients return permanently to regular FIX replacement therapy.</u>

In Fimea's scenarios, the significance of the duration of the treatment effect has been assessed using simple models in which a certain proportion of patients is transferred to regular FIX replacement therapy annually. A 2.5% grading between 2.5% and 10.0% had been selected for the modelling to demonstrate the significance of the duration of the treatment effect for the cost-effectiveness assessment.

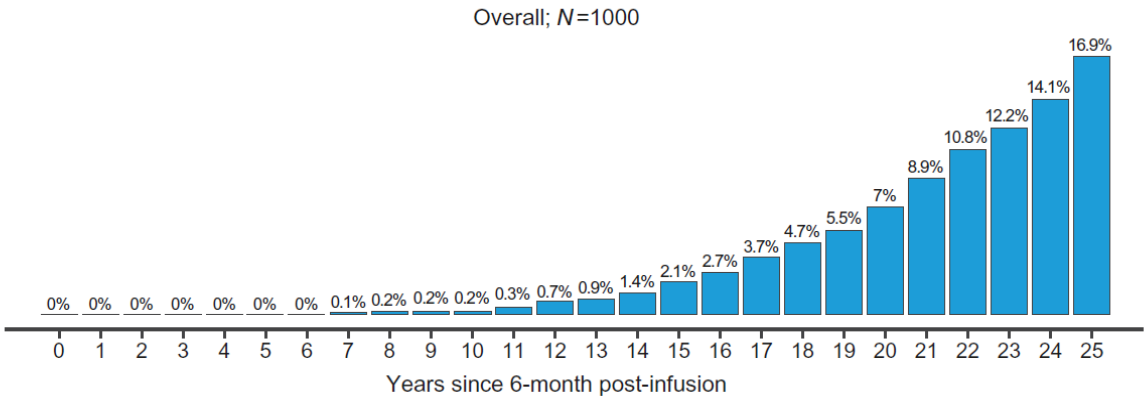
CSL Behring response:

CSL Behring does not agree with Fimea in the use of the staircase analysis (2.5-10.0%) and recommend instead to use the Bayesian statistical model prediction published in a peer-revied journal.

CSL Behring still believe that the curve, see Figure 1 below, from the **peer-reviewed publication by Shah et al.** [E] submitted in the dossier to Fimea **is the most relevant curve to use to predict**

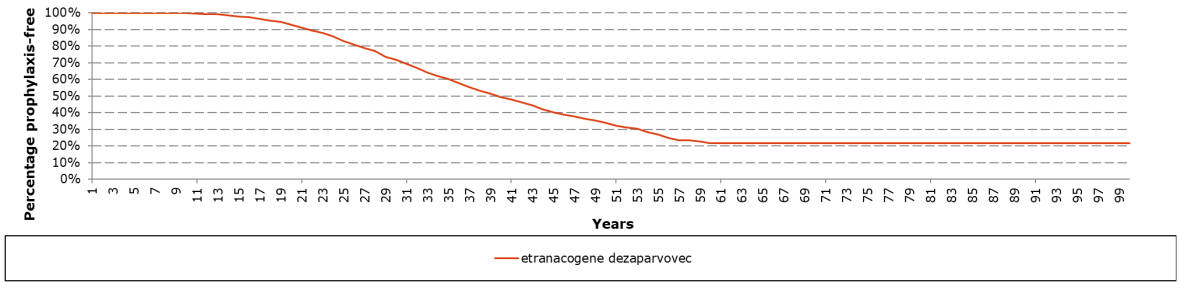
long term durability for HEMGENIX. The cost-effectiveness model, also submitted to Fimea, is based on this curve, see Figure 2 below. The Bayesian and Frequentist linear mixed models described in Shah et al [E] predicted that no more than 6/55 (10.91%) observed participants would have FIX activity levels <2% up to 25.5 years post-infusion. Bayesian model-based predictions of future participants suggest >80% would be free from prophylactic FIX replacement products 25.5 years post-infusion. **These predictions [E] are in line with existing clinical evidence.**

Figure 1: Bayesian statistical model prediction of the overall cumulative percentage of treated patients, who over time will return to FIX activity levels less than 2%.



Abbreviations: FIX, factor IX; N, number
Based on using currently available data from the phase IIb and phase III HEMGENIX studies.
Source: Shah et al. (2022)

Figure 2: HEMGENIX durability (FIX activity level). Durability curve used in cost-effectiveness model submitted to Fimea (based on Shah et al 2022).



In this case Fimea suggested a 2.5% grading between 2.5% and 10.0% for the modelling to demonstrate the significance of the duration of the treatment effect for the cost-effectiveness assessment.

The rate of decline in durability is significantly higher in the staircase analysis than that suggested by the Bayesian statistical modelling. Together this amounts to that the area under the durability curve (proportion of patients with FIX levels >2%) is significantly lower for the 2.5%, 5%, 7.5% and

10% staircase analysis than that suggested by the Bayesian statistical modelling approach; 30, 19, 13 and 9 compared to 40, a difference in total durability of -9, -21, -27 and -30 respectively. **It is not reasonable from clinical evidence to believe that for example 10% of patients will return to regular prophylactic treatment every year.** That means that if 10% return to regular FIX replacement therapy (prophylaxis) every year, then approximately 10 patients out of the 52 patients in HOPE-B should have returned to prophylaxis after two years, while in fact 0 patients in the HOPE-B trial had done so in reality. Accordingly, we consider this scenario highly unlikely and not compatible with observed data.

In conclusion, **CSL Behring recommends using the Bayesian statistical model prediction** instead of the 2.5-10.0% staircase analysis since the Bayesian statistical model prediction better aligns with existing clinical evidence.

In addition, Fimea has also examined scenarios in which the time horizon of the model has been significantly shortened compared to the marketing authorisation holder's baseline analysis.

3. Fimea has examined scenarios in which the time horizon of the model was significantly shortened compared to the marketing authorization holder's baseline analysis.

CSL Behring response:

CSL Behring does not agree to assess HEMGENIX with a shorter time horizon since the cost savings and increases on QoL then not are captured correctly.

CSL Behring´s standpoint is that **substitution therapy is a lifelong treatment with repeated intravenous infusions that can never be stopped, as long as the patient lives**; **accordingly, a life-long perspective is the only relevant perspective** that can be used for comparison with a once-off, single dose gene therapy treatment. Restricting the analysis to a short time horizon essentially ignores the long-term cost saving and treatment benefit opportunities of HEMGENIX.

We would also like to point out that a sample size in the HOPE-B study of >50 patients is not small, particularly in rare diseases. We believe such sample size provides relatively robust parameter estimates. The effects over the time horizons these analyses intend to assess are largely not relevant to the sample size (note this comment is also relevant to make for the other statements above).

Restricting time-horizon means that the analysis no longer is based on a cost-effectiveness assessment, which requires a life-time horizon, **meaning that neither potential cost savings nor increases in QoL are captured appropriately.**

The guide on good modelling practices from ISPOR reads “The time horizon of the model should be long enough to capture relevant differences in outcomes across strategies. A lifetime horizon may be required.” See [F] section II-3b.

According to the most recent guidelines from NICE “The time horizon for estimating clinical effectiveness and value for money should be long enough to reflect all important differences in costs or outcomes between the technologies being compared.... A lifetime time horizon is needed when alternative technologies lead to differences in survival or benefits that last for the remainder of a person's life.” See [G] section 4.2.22 and 4.2.23.

Furthermore, “For a lifetime time horizon, it is often necessary to extrapolate data beyond the duration of the clinical trials... analyses that compare several alternative scenarios reflecting different assumptions about future effects using different statistical models are desirable... Analyses that limit the time horizon to periods shorter than the expected effect of the technology do not usually provide the best estimates of benefits and costs.“ See [G] section 4.2.24.

In conclusion, CSL Behring believes that the restriction on time horizon is not an appropriate way of accounting for the uncertainty in the duration of the treatment effect. The consequence of using this approach to handle uncertainty is that neither potential cost savings nor increases in QoL are captured in a reasonable and adequate way. Therefore, our **recommendation is to use a lifelong perspective to predict durability.**

In addition, we would also comment on the fact that two patients in the HOPE-B trial were excluded from the modeling.

4. FIMEA repeatedly states that “patients who did not achieve the expected response to treatment have been removed from the modelling” or similar wordings.

CSL Behring response:

CSL Behring thinks the statement above by Fimea is misleading and arguably incorrect. The two patients were not removed because they did not “achieve the expected response” but because we consider them irrelevant in the comparison, see below.

There are two non-responder patients exposed to HEMGENIX that were excluded from the modelling. One of the patients did not achieve response to treatment after receiving 10% of the dose, the lack of response is indeed expected considering the dose. The second patient had an extremely high titer of neutralizing antibodies and as specified in the SmPC, we know that this may affect the response; in other words, the outcome is not entirely unexpected. We do not expect patients with this high antibody titer to be treated in clinical practice, except for exceptional cases and within studies.

In conclusion, **these two patients were excluded because we consider the patients not relevant in the modelling, not because they “did not achieve the expected response".**

CSL Behring

References:

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