Report by the Domain Taskforce Horizon Scanning,
Taskforce of the Beneluxa Initiative

Beneluxa
Initiative on Pharmaceutical Policy

Pharmaceutical Developments

on

Haemophilia

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Executive Summary

This report, written by the Taskforce Horizon Scanning of the Beneluxa Initiative, describes the current situation of Haemophilia and provides an overview of new pharmaceutical developments regarding this disease.

The current treatment options are listed, as well as the pharmaceutical costs in some of the Beneluxa countries.

The focus of this report are the pharmaceuticals with the potential to enter the market in the upcoming years. These are displayed in a detailed table.

The setup of the clinical trials, including the used biomarkers, are summarised. Also, the possible challenges, both on HTA level as on Health care level, are described.

With this report, the Beneluxa Initiative aims to timely inform policy makers, healthcare organizations, payers and the general public on upcoming new pharmaceuticals and possible challenges.

The authors declare that there is no conflict of interest

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PHARMACEUTICAL DEVELOPMENTS - HAEMOPHILIA

Report by the taskforce Horizon Scanning of the Beneluxa Initiative

About Beneluxa Horizon Scanning

Developments on new drugs often come in bursts. As soon as a new working mechanism or disease pathway is discovered, pharmaceutical companies seize the opportunity to develop new treatments for the relevant patients. The Horizon Scanning task force of Beneluxa scans these developments and summarises those which may have a significant impact on policy, to a short report. It describes the background of the respective indication, current treatment options and most importantly, new pharmaceuticals that are expected to enter the market in the coming years. The reports aim to inform policy makers, healthcare organizations, payers, and the general public in a timely way on upcoming new pharmaceuticals and possible challenges

This report is focusing on haemophilia.

Introduction

Even though the prevalence of Haemophilia is rather low it is associated with high aggregate costs and imposes a high financial burden on individuals and healthcare systems. Recently, several new pharmaceuticals reached the clinical phase of development with the possibility to provide new treatment options.

This report is based on information from clinical trials, academic papers and completed in Q4 of 2021.

Background on indication

Haemophilia A and B are rare X-linked bleeding disorders caused by mutations in the genes encoding coagulation factor VIII (FVIII) and factor IX (FIX).

The disease severity in haemophilia is classified according to the plasma level of FVIII or FIX activity.[1] The severe form is defined as a factor level <1% of normal, the moderate form as a factor level of 1-5%, and the mild form with a factor level >5 and <40%.[2] Patients with severe haemophilia frequently develop haemorrhages into joints, muscles, or soft tissues without any apparent cause. They can also suffer from life-threatening bleeding episodes such as intracranial haemorrhages. Persons with mild and moderate factor deficiency rarely experience spontaneous haemorrhages, and excessive bleeding mainly occurs following trauma or in association with invasive procedures.

[1] Berntorp E, Shapiro AD. "Modern haemophilia care", *Lancet* Apr 14;379(9824), pp. 1447–1456, 2012.

Incidence and Prevalence of disease

Haemophilia A (HA) is more common than haemophilia B (HB), with a prevalence of one in 5,000 male live births compared to one in 30,000, respectively.[2] Overall, the incidence of haemophilia in the general population is 1 in 10,000.[3]

While primarily a disease which affects men, women can also be sufferers. As it is an X-linked recessive disease, the carrier mothers' sons have a 50% risk of being affected and the mothers' daughters a 50% risk of being carriers.[4] These female carriers can pass on the mutation to male offspring, even though they do not develop symptoms themselves. Technically, a female can develop haemophilia if she is born to a female carrier and a man affected by haemophilia, but this is very rare.

As a result of the recent progress made in the field of haemophilia therapy, the life span of people with haemophilia has gradually become similar to that of males in the general population, at least in more developed countries.[5]

Estimated prevalence in 2019[6]

Total cases of Haemophilia

Country	Patient numbers	% of population
Austria	813	0.009%
Belgium	1267	0.01%
Ireland	915	0.018%
Luxembourg	N/A*	
Netherlands	1277	0.007%

***Luxembourg:** haemophilia A prevalence (per 100 000 males) in 2004 = 14.7[7]; haemophilia B prevalence (per 100 000 males) in 2000 = 0.47[8]

[2] Castaman G, Matino D., "Hemophilia A and B: molecular and clinical similarities and differences", *Haematologica*. 2019 Sep;104(9), pp. 1702-1709, 2019.
[3] Haemophilia: A disease of women as well. *South African journal of child health*, March; 10(1), pp. 29-32, 2016.
[4] Haemophilia: A disease of women as well. *South African journal of child health*, March; 10(1), pp. 29-32, 2016.
[5] Franchini M., "The modern treatment of haemophilia: a narrative review", *Blood Transfus* Apr;11(2), pp. 178-82, 2013.
[6] Report on the Annual Global Survey 2019 published by the World Federation of Haemophilia 2020.
[7] Jeffrey S. Stonebraker, "A study of variations in the reported haemophilia A, prevalence around the world", *Facts and figures* December 2010 No. 8.
[8] Jeffrey S.Stonebraker, "A study of variations in the reported haemophilia B prevalence around the world", *Facts and figures* August 2011 No. 10.

Age distribution: Haemophilia A&B[9]

Haemophilia A

Country	Patient numbers	0–4years	5–13yrs	14–18yrs	19–44yrs	45+yrs
Ireland	664	4%	18%	9%	37%	32%
Netherlands	1,115	5%	10%	7%	34%	43%
Austria	693	3%	9%	8%	42%	38%
Belgium	1,015	3%	10%	9%	35%	43%
Luxembourg	N/A	N/A	N/A	N/A	N/A	N/A

Haemophilia B

Country	Patient numbers	0–4years	5–13yrs	14–18yrs	19–44yrs	45+yrs
Ireland	251	4%	14%	11%	42%	29%
Netherlands	162	4%	9%	12%	35%	40%
Austria	138	1%	12%	57%	45%	36%
Belgium	243	2%	9%	7%	34%	48%
Luxembourg	N/A	N/A	N/A	N/A	N/A	N/A

Note: the discrepancy between the **total** Haemophilia figures for each country and the figure of **A type + B type combined** is that some cases were of an unknown type.

Economic burden

Although haemophilia affects only a small portion of the population, it is associated with high aggregate costs and imposes a high financial burden on individuals and healthcare systems. The majority of these costs are direct costs, which include antihaemophilic medication, clinician visits, hospitalizations, medical and surgical procedures, and laboratory tests. Indirect costs are those associated with reduced productivity and increased absenteeism caused by haemophilia, its treatment, resulting disability, and death.[10]

[9] Report on the Annual Global Survey 2019 published by the World Federation of Haemophilia 2020

[10] Chen SL.,"Economic costs of hemophilia and the impact of prophylactic treatment on patient management", *Am J Manag Care*. 2016 Apr;22(5 Suppl), pp. 126-33, 2016.

Currently there is no cure for haemophilia. Lifelong treatment is therefore required. The aim of treatment for haemophilia A and B is to prevent bleeding episodes from occurring. Prophylaxis is the standard of care for people with severe haemophilia and for some people with moderate haemophilia.[11]

Prophylaxis with clotting factor concentrates (CFCs) is referred to as regular replacement therapy; it stands in contrast to episodic replacement therapy (also known as on-demand therapy), which is defined as the administration of CFCs only at the time of a bleed.[15]

Depending on the type of haemophilia (A or B) and the severity of the disease, different treatment regimens are possible and can be categorized as follows:

- Factor Replacement Therapy (Clotting Factors Concentrates)
- By-passing agents
- Non-Factor replacement therapy
- Non-specific haemostatic treatments:

A study published in 2017, reported that the total annual cost (based on list prices) of severe haemophilia for the five countries for 2014 was estimated at EUR 1.55 billion, or just under EUR 200,000 per patient. The highest per-patient costs were in Germany (mean EUR 319,024) and the lowest were in the United Kingdom (mean EUR 129,365), with a study average of EUR 199,541. Drug expenditure constitutes 97.9% of direct costs.[12]

Expected positioning of new therapies

The treatment of haemophilia has mainly relied on factor replacement therapy, which restores haemostasis by replacing the missing coagulation factor. In recent years, novel alternative therapies for the treatment of haemophilia in patients with and without inhibitors have been developed.[13]

Haemophilia provides an attractive target for gene therapy studies, due to the monogenic nature of these disorders and easily measurable endpoints (factor levels and bleed rates). All successful, pre-clinical and clinical studies to date have utilized recombinant adeno-associated viral (AAV) vectors for factor VIII or IX hepatocyte transduction. [14]

Current treatment options

[11] Srivastava,I. et al., "WFH Guidelines for the Management of Hemophilia, 3rd edition", *Haemophilia* 26(Suppl 6), pp. 1–158, 2020.
[12] O'Hara, J., Hughes, D., Camp, C. *et al.*, "The cost of severe haemophilia in Europe: the CHESS study". *Orphanet J Rare Dis* 12, p. 106, 2017.
[13] Chowdary P. "Nonfactor Therapies: New Approaches to Prophylactic Treatment of Haemophilia", *Hamostaseologie* Aug;41(4), pp. 247-256, 2021
[14] Paul Batty, David Lillicrap, "Advances and challenges for hemophilia gene therapy **"***Human Molecular Genetics*, Volume 28, Issue R1, pp. R95–R101, 2019.

Factor replacing therapies consist of replacing the missing factor VIII or factor IX. Injected in the body they replace the natural clotting proteins missing in haemophilia patients.[15] There are two main types of CFCs: virally inactivated plasma-derived products made from plasma donated by human blood donors; and recombinant products manufactured using genetically engineered cells and recombinant technology. CFC FVIII are indicated for patients with haemophilia type A and CFC FIX for haemophilia type B.

Some CFC FVIII treatments distinguish themselves by the extended half-life (EHL). EHL products permit to reduce the treatment burden of prophylaxis by allowing longer intervals between injections (every 3 to 5 days). [15,16] Similarly, in CFC FIX products, one can distinguish standard-acting recombinant FIX (rFIX) vs long-acting rFIX. The latter providing improved pharmacokinetic parameters with extended half-life of rFIX, allowing less frequent dosing and the potential for better patient outcomes than standard-acting rFIX or plasma derived FIX (pdFIX) products.[17]

Factor replacing therapies can however lead to production of inhibitors preventing the replacement factor from working.[18] In these cases, patients can be treated with **"bypassing agents"** which are however less effective as factor replacement therapies. Bypassing agents are given by injection into a vein or into a into central venous access devices (CVADs).[19] These treatments can be given as prophylaxis (every 2-3 days) or on demand.

The first licensed **non-factor replacement therapy** for haemophilia A is emicizumab that mimics the cofactor activity of FVIII. It is administered subcutaneously once weekly, and in some cases once every 2 or 4 weeks.[15] Although bypassing agents have been shown to provide effective prophylaxis, emicizumab has been proven to be superior for bleed prevention in patients with persistent inhibitors.[19]

Finally, in mild to moderate forms of haemophilia **non-specific haemostatic treatments** can be indicated.

Treatments

- **Clotting Factor Concentrates FVIII:** octocog alfa turoctocog alfasimoctocog alfa; moroctocog alfa.
- *With Extended Half-Life (EHL):* rurioctocog alfa pegol*, lonoctocog alfa;* efmoroctocog alfa, damoctocog alfa pegol; susoctocog alfa, turoctocog alfa pegol, human coagulation factor VIII / human von willebrand factor
- **Treatments Clotting Factor Concentrates FIX:** nonacog alfa, coagulation factor ix, High-purity plasma-derived human factor IX concentrate, nonacog gamma.
- W*ith EHL*: eftrenonacog alfa, albutrepenonacog alfa, nonacog beta pegol

[15] Knobe, K., & Berntorp, E., "New treatments in hemophilia: insights for the clinician", *Therapeutic advances in hematology*, *3*(3), pp. 165–175, 2012.
[16] Hae Kyung Kim et al., "Cost of patients with hemophilia A treated with standard half-life or extended half-life FVIII in Spain", *Expert Review of Pharmacoeconomics & Outcomes Research*, 21(2), pp.315-320, 2021
[17] Castaman, G., " The benefits of prophylaxis in patients with hemophilia B"*, Expert Review of Hematology*, 11 (8), pp. 673-683, 2018.
[18] NHS England (2019). "Clinical Commissioning Policy: Emicizumab as prophylaxis in people with severe congenital haemophilia A without factor VIII inhibitors (all ages)". Available at: 1819-Emicizumab-as-prophylaxis-in-people-with-severe-congenital-haemophilia-A-without-factor-VIII-inhibitors.pdf (england.nhs.uk). Last accessed on 11/08/2021.
[20] Charles Nakar, Amy Shapiro, Hemophilia A with inhibitor: Immune tolerance induction (ITI) in the mirror of time, Transfusion and Apheresis Science,Volume 58, Issue 5, 2019, Pages 578-589.

- **Treatment By-passing agents:** human coagulation factor VIII (inhibitor bypassing fraction), eptacog alfa (activated), susoctocog alfa
- **Non-factor replacement therapy:** emicizumab
- **Non-specific haemostatic treatments:** Desmopressin, tranexamic acid

International Guidelines

Overview of leading international guidelines specific for subject.

- **WFH Guidelines for the Management of Hemophilia**, 3rd edition (2020). *Haemophilia* 26(Suppl 6),1–158. DOI: 10.1111/hae.14046.
- Tiede, A. et al. (2020). **International recommendations on the diagnosis and treatment of acquired hemophilia A**, *Haematologica* 105(7), 1791-1801. https://doi.org/10.3324/haematol.2019.230771
- National Hemophilia Foundation (US). **MASAC recommendations concerning products licensed for the treatment of haemophilia and other bleeding disorders** (Revised August 2020). Available at: https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-263-masac-recommendations-concerning-products-licensed-for-the-treatment-of-hemophilia-and-other-bleeding-disorders. Last accessed on 11/08/2021.

Current treatment costs

Cost per patient per year for different Beneluxa members:

Overview Treatments costs haemophilia - Beneluxa Countries

	Total cost(€)	Cost(€)/patient	Total costs	Cost(€)/patient	Total cost(€)	Cost(€)/patient	Total cost(€)	Cost(€)/patient
ATC Code and Name	NL	NL	LU	LU	AT	AT	BE	BE
B02BD02 coagulation factor VIII	57 766 149	N/A	3 236 898	N/A	26 277 253	N/A	69 492 643	N/A
B02BD04 coagulation factor IX	15 294 522	N/A	27 190	N/A	3 776 965	N/A	4 588 034	N/A
B02BX06 emicizumab	17 274 302	N/A	304 313	N/A	7 513 296	N/A	49 805 552	N/A

AT: Costs based on 2020 list prices (tax not included).Costs for medication within hospital treatments are not included.
LU: Costs based on 2020 list prices (tax incl.) not including hospital treatments. Costs B02BX06 based on 2021 data (available on 11/2021)
NL: GIP databank, 2020. Costs based on 2020 list prices of haemophilia products within the hospital (tax incl.) Costs B02BX06 based on 2020 data (available on 07/2020)
BE: Data based on 2019 prices (gross costs, retail + hospital) except for B02BX06 which is based on 2020 data (available on 07/2020)

IE: Since 2012 there is a centralised procurement process in Ireland for all products used to treat Haemophilia. These prices are protected by the terms of the procurement agreements. Ireland regrets that is unable to share the data on products or costings due to confidential and sensitive issues.

For confidentiality, reasons we cannot disclose detailed data per product. However, an analysis of the available, permitted data, highlights disparities regarding treatment options available or commonly used in the different countries.

Moreover, the data also points to important disparities in costs/patients for those products where the data was available. Commonalities are however also observed. As such within class B02BD02 (Haemophilia A indication) *octocog alfa*, *efmoroctocog alfa, moroctocog alfa* represent in most countries the biggest overall costs per product.

In *octocog alfa* this can be explained by a relatively high number of patients combined with relatively high costs/patient. For *efmoroctocog alfa* and *moroctocog alfa* this results from relatively high costs/patient. *Damoctocog alfa pegol* corresponds in this class to the highest costs/patient and *Factor VIII* to the lowest costs/patient.

In class-B02BD04 (Heamophilia B indication) *eftrenonacog alfa* stands out in overall costs and *albutrepenonacog alfa* in costs/patient. Finally, *emicizumab* (B02BX06) indicated in haemophilia A, recently entered most Beneluxa markets and presented a significant growth in budget impact especially when compared to the overall costs of class B02BD02.

New pharmaceuticals to enter the market between 2021 and 2025

INN	Mf.	Label	MoA	Trial / EMA numbers	PEs	PCD	Filed at EMA?	MA (est.)	Chance of MA	Cost pp/py (est.)	Other studies?
Dalcinonacog alfa	Catalyst Biosciences	Severe Haemophilia B (without inhibitors)	Peptide hydrolases; Recombinant proteins (Factor IX replacements)	NCT03995784 (phase 2)	The dose required to achieve steady-state FIX levels >12%	Study completed Apr. 2020	No	2023 (earliest estimate based on the fact that Phase 3 still has to be announced)	Uncertain	€€€€	None
Marzeptacog alfa	Catalyst Biosciences	Haemophilia A or B (with inhibitors)	Peptide hydrolases; Recombinant proteins (Factor VIIa replacements)	NCT04489537 (phase 3)	Bleeding episode treatment success	Jan. 2022	No	2023	Likely	€€€	Factor VII Deficiency, Glanzmann Thrombasthenia (phase 1|2)
Marstacimab	Pfizer	Severe Haemophilia A or B (with or without inhibitors)	Monoclonal antibodies (Lipoprotein-associated coagulation inhibitor)	NCT03938792 (phase 3)	Annualized bleeding rate (ABR) of treated bleeding events, Incidence and severity of thrombotic events, Incidence of anti-drug antibody [ADA], Incidence of clinically significant persistent neutralizing antibody [NAb], Incidence and severity of injection site reaction, Number of participants with clinically significant changes	Aug. 2023	No	2024	Likely	€€€	None

INN	Mf.	Label	MoA	Trial / EMA numbers	PEs	PCD	Filed at EMA?	MA (est.)	Chance of MA	Cost pp/py (est.)	Other studies?
					from baseline in physical exam, Incidence of clinically significant laboratory value abnormalities, Incidence of severe hypersensitivity and anaphylactic reactions, Incidence of adverse events and serious adverse events, Number of participants with clinically significant changes from baseline in vital signs, Incidence and severity of thromboticangiopathy, Incidence of intravascular coagulation / consumption coagulopathy						
Fidanacogene elaparvovec	Pfizer	Moderately Severe to Severe Haemophilia B (without inhibitors)	Gene therapy (Factor IX replacements; Gene transference)	NCT03861273 (phase 3) NCT03307980 (phase 2)	Annualized bleeding rate (ABR), Vector derived FIX:C level	Jun. 2024	No	2025	Likely	€€€€	None

INN	Mf.	Label	MoA	Trial / EMA numbers	PEs	PCD	Filed at EMA?	MA (est.)	Chance of MA	Cost pp/py (est.)	Other studies?
Giroctocogene fitelparvovec	Pfizer	Moderately Severe to Severe Haemophilia A (without inhibitors)	Gene therapy (Factor VIII replacements; Gene transference)	NCT04370054 (phase 3) NCT03061201 (phase 2)	Annualized bleeding rate (ABR)	Sep. 2022	No	2023	Likely	€€€€	None
Valoctocogene Roxaparvovec	BioMarin	(Severe) Haemophilia A (without inhibitors)	Gene therapy (Factor VIII replacements; Gene transference)	NCT03370913 NCT03392974 NCT04323098 (all in phase 3)	Change of the median FVIII activity	Sep. 2022	No	2023	Likely	€€€€	None
Etranacogene dezaparvovec	uniQure	Severe or Moderately Severe Haemophilia B (without inhibitors)	Gene therapy (Factor IX replacements; Gene transference)	NCT03569891 (phase 3) NCT03489291 (phase 2)	Factor IX activity levels	Mar. 2021	No	2022	Likely	€€€€	None
Trenonacog alfa	Medexus Pharma	Haemophilia B	Recombinant Factor IX	NCT03855280 (phase 3)	Annualized Bleed Rate	Aug. 2021	No	2021	Likely	€€€€	None
BT200	Medical University of Vienna	Haemophilia A, Von Willebrand diseases	anti-VWF aptamer	NCT04677803 (phase 2)	Increase in platelet count and/or FVIII activity	Sep. 2021	No	2021	Uncertain	€€€*	None

INN	Mf.	Label	MoA	Trial / EMA numbers	PEs	PCD	Filed at EMA?	MA (est.)	Chance of MA	Cost pp/py (est.)	Other studies?
Concizumab	Novo Nordisk A/S	Haemophilia A, B without inhibitors Haemophilia A, B with inhibitors	anti-TFPI antibody	NCT04082429 (phase 3) NCT04083781 (phase 3)	Number of treated spontaneous and traumatic bleeding episodes	Nov. 2021	No	2022	Likely	€€€*	NCT04921956 : compassionate use
Efanesoctocog alfa	Bioverativ (Sanofi)	Severe Haemophilia A Severe Haemophilia A (children)	Recombinant Factor VIII	NCT04161495 (phase 3) NCT04759131 (phase 3)	Annualized Bleed Rate Occurrence of inhibitor development	Jan. 2022	No	2022	Likely	€€€€	NCT04644575 : long-term safety and efficacy in haemophilia A NCT04770935 : Von Willebbrand diseases
Fitusiran	Genzyme (Sanofi)	Haemophilia A and B Haemophilia A and B (children) Severe Haemophilia A with inhibitors Severe Haemophilia A without inhibitors	Anti-thrombin RNAi	NCT03549871 (phase 3) NCT03974113 (phase 2/3) NCT03417102 (phase 3) NCT03417245 (phase 3)	Annualized Bleed Rate Percent change in plasma antithrombin activity levels Annualized Bleed Rate Annualized Bleed Rate	Nov. 2020	No	2021	Likely	€€€€	NCT03754790 : long-term safety and efficacy in haemophilia A or B, with or without inhibitors

INN	Mf.	Label	MoA	Trial / EMA numbers	PEs	PCD	Filed at EMA?	MA (est.)	Chance of MA	Cost pp/py (est.)	Other studies?
NNC0365-3769 A	Novo Nordisk A/S	Haemophilia A With or Without Factor VIII Inhibitor	Factor VIII mimetic human bispecific antibody	NCT04204408 (phase 2)	Treatment-Emergent Adverse Events	Jan. 2024	No	2024	Uncertain	€€€€	None
Eptacog beta	LFB USA	Congenital Haemophilia A/B Patients With Inhibitors to Factor VIII/IX Undergoing Elective Surgery/Other Invasive Procedures Haemophilia A or B patients with inhibitors to Factor VIII or IX (children)	Recombinant Factor VIIa	NCT02548143 (phase 3) NCT02448680 (phase 3)	Percentage of Surgical or Other Invasive Procedures Defined as "Good" or "Excellent" Response to LR769 Treatment Proportion of Successfully Treated Mild/Moderate Bleeding Episodes Per FDA Requirement. Proportion of Successfully Treated Bleeding Episodes (Mild/Moderate/Severe) Per EMA Definition	Jun. 2017	Yes	2022	Final outcome mid-2022	€€€€	None

***Best estimation, no suitable comparator found**

Summary of used abbrevations

€	<€1,000 per patient per annum
€€	€1,0000 to < €25,000 per patient per annum
€€€	€25,000 to <€100,000 per patient per annum
€€€€	≥ €100,000 per patient per annum

EMA=European Medicines Agency; Filed at EMA (Yes/No); INN=International Non-proprietary Name (Agreed upon name for the substance, potentially chemical name or 'drug' name) ; Label: Specific indication / place in treatment (i.e. for Alzheimer: Moderate AD, Mild AD, inherited AD, …); MA=marketing authorisation; Mf=manufacturer (Firm responsible for production/study sponsor); MoA=Mechanism of Action; PCD: Primary Completion Date (Estimated completion date of clinical trials, potential release date of intermediary/final results); PE: Primary Endpoint(s) (Endpoint as identified on clinicaltrials.gov or EMA); TBC=to be confirmed; Trial / EMA numbers: Trial number as registered on clinicaltrials.gov or as registered with EMA

Legend:

- INN: International non-proprietary name
  Agreed upon name for the substance, potentially chemical name, or 'drug' name
- Mf.: Manufacturer
  Firm responsible for production/study sponsor
- Label: Specific indication / place in treatment
  (i.e., for Alzheimer: Moderate AD, Mild AD, inherited AD, …)
- MoA: Mechanism of Action
- Trial / EMA numbers: Trial number as registered on clinicaltrials.gov or as registered with EMA
- PE: Primary Endpoint(s)
  Endpoint as identified on clinicaltrials.gov or EMA
- PCD: Primary Completion Date
  Estimated completion date of clinical trials, potential release date of intermediary/final results
- Filed at EMA
  Yes/No
- MA (est.): Market Authorisation: Estimated date of Market authorisation in case of it being granted
  Chance of MA (Likely/Uncertain): based on available information, Cost pp/py (est.) : Cost per patient per year € - €€€€, (<1 000/pp/py - >100 000/pp/py)
- Other studies: where the substance is being studied

General characteristics of new studies/pharmaceuticals

Setup of clinical trials

- Patient characteristics: More than half of the trials considered in this report concerns severe haemophiliac patients. Gene therapies are being developed but trials only include adults for now, due to the difficulty of active dividing hepatocytes in paediatric patients.[20] Other non-factor therapies (Fitusiran, Concizumab) claim the potential advantage to be used in Haemophilia A but also Haemophilia B and other inherited coagulation disorders, with or without inhibitors.[21]
- Biomarkers: Distinct biomarkers associated with gene therapies or specific antibodies are being developed, in addition to traditional endpoints such as bleeding events or factor activity levels (see below "Testing for biomarkers: cost and practicality implications").
  Novel outcome measures: There is no validated outcome to measure the impact and the success of a gene therapy that could potentially cure a congenital disease. This point is further discussed in the section below, "HTA challenges".

Main biomarkers used in clinical trials

- **For patients selection**
- CD4 count
- Platelet count
- Inhibitor titer Pre-existing AAV antibodies (gene therapies)
- Level of Factor VIII activity (Haemophilia A) Level of Factor IX activity (Haemophilia B)
- Liver function (in the context of hepatotoxicity in gene therapies)
- Vector shedding (gene therapies)
- ALT measurements for hepatotoxicity (gene therapies)
-
- **As outcome measure**
- Increase in platelet counts
- Change in FVIII and activity FIX activity levels
- Anti-drug antibody [ADA]
- Neutralizing antibody [NAb]
- Plasma anti-thrombin activity levels
- Relative changes in D-dimer
- Relative changes in prothrombin fragment 1 and 2
- Relative changes in fibrinogen

Possible challenges

[20] S. W. Pipe, "Delivering on the promise of gene therapy for haemophilia," Haemophilia, vol. 27, no. S3, pp. 114–121, 2021.
[21] P. M. Mannucci, "Hemophilia therapy: The future has begun," Haematologica, vol. 105, no. 3, pp. 545–553, 2020.

HTA challenges

- Gap between regulatory and HTA data requirements: There is no agreement within the haemophilia community, as to how outcomes should be measured within gene therapy RCTs, whether using clinical, patient reported or laboratory outcomes. More common outcomes between current therapies and gene therapies, and among gene therapies themselves, are needed to allow for direct comparisons (factor levels, QoL assessments scales)[22]; The project CoreHEM has been developing a core set of outcomes in this perspective.[23]
- In addition to RCTs, which remain the gold standard, real world evidence will be needed to characterise the impact of new drugs on long-term outcomes: long-term safety (cancer development, passing of the transcript to the next generation)[21] and efficacy studies (loss of gene expression, persistence of transfer, factor threshold defined as "success", interpatient variability) will be needed with gene therapies but data generation will be slow due to the low prevalence of the disease. [20]

Health system challenges

- Budgetary impact: Treatments such as gene therapies are expected to be highly priced upfront. [21].
- Mechanism of Action: Non-factor-replacement therapies (such as specific antibody therapies) are being developed for a subcutaneous administration with potential longer intervals. These products are thus expected to be higher priced but to lead to reduction in terms of patient management costs.[20] [21]
- Concerning gene therapy, limited administration in specific clinical centres, specialized training of staff (among others to follow and monitor the selection criteria in patients), monitoring of the performance of the medical teams, and the medical monitoring of the acute and intermediate-term adverse events require the most immediate attention. Long-term follow-up in clinical trials and registries is required and a coordinated approach by all stakeholders is necessary to ensure safe and effective administration. A complete package of care of gene therapy delivery will thus need to be developed.[20] [24] [25]
    - Testing for biomarkers: Cost and practicality implications?

Biomarkers for patients' selection: In clinical trials, gene therapy also requires a non-routine measurement of cellular and humoral immunity as well as the determination of the release of vector particles through body fluids.

[22] P. Batty and D. Lillicrap, "Advances and challenges for hemophilia gene therapy," *Hum. Mol. Genet*., vol. 28, no. R1, pp. R95–R101, 2019.
[23] G. F. Pierce and A. Iorio, "Past, present and future of haemophilia gene therapy: From vectors and transgenes to known and unknown outcomes," *Haemophilia*, vol. 24, no. March, pp. 60–67, 2018.
[24] N. Machin and M. V. Ragni, "Measuring success in hemophilia gene therapy using a factor level & outcomes yardstick," *Expert Rev. Hematol*., vol. 11, no. 2, pp. 83–86, 2018.
[25] W. Miesbach et al., "Delivery of AAV-based gene therapy through haemophilia centres—A need for re-evaluation of infrastructure and comprehensive care: A Joint publication of EAHAD and EHC," *Haemophilia*, no. July, pp. 1–7, 2021.
[29] Thomas, A.E. (2018), Biosimilars and haemophilia. Haemophilia, 24: 17-19.

One of the selection criteria for the majority of gene therapy platforms is the absence of already existing antibodies to AAV; none of these tests are standardized or utilise commonly used reagents, which makes inter- and intra-laboratory comparison of antibody levels or T-cell titres difficult.

However, it is not clear what tests need to be transposed from the clinical trials into service delivery and what can be dropped. [25]

- The question of biosimilars in haemophilia

The development of inhibitors to plasma protein therapies is a major adverse reaction in patients with haemophilia. Inhibitors remain an unpredictable risk, caused by genetic risk factors and treatment-related factors. There are thus great uncertainties about the development of inhibitors with biosimilar products. Given the costs of inhibitors treatment, the unknowns of biosimilars could offset the potential cost savings hoped for from biosimilars.

The relevant differences in immunogenicity between two products must then be addressed in clinical trials. However, many factor concentrates are available, and new products are on the horizon. Haemophilia being a rare disease, the patient population is limited with trials for new therapies competing for recruitment. The field of factor replacement therapy is constantly developing with next-generation products and “biobetters” replacing the older factor concentrates rather than development of biosimilar products for such concentrates[29].

Hence, there are currently no biosimilar medicines licensed for the treatment of haemophilia. As of January 2022, a biosimilar of the product NovoSeven (eptacog alfa) was under review by the EMA, supported by a multicentre, randomized, double-blinded, single dose, two-way cross-over Phase 3 study (NCT03935334).