Mitigating the Unmet Needs of Hemophilia Patients: A Case Study of the Development Strategy Behind a Novel siRNA Hemophilia Combination Medical Device.

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Mitigating the Unmet Needs of Hemophilia Patients: A Case Study of the Development Strategy Behind a Novel siRNA Hemophilia Combination Medical Device.

Kristin C. Fong

A Thesis in the Field of Biotechnology for the Degree of Master of Liberal Arts in Extension Studies

Harvard University
November 2017
Abstract

The purpose of this case study is to discuss the strategy behind the selection and development of a novel combination medical device to treat hemophilia patients in order to improve treatment for all segments of the hemophilia community leading to overall better patient outcomes. Replacement therapy of the necessary missing clotting factors is the current standard of care, but involves repeated prophylactic intravenous infusions. Fitusiran is a siRNA therapeutic designed to treat hemophilia patients by reducing expression of antithrombin (AT) in order to indirectly restore normal homeostasis. Its pharmacokinetic profile enables it to be dosed subcutaneously at monthly intervals, while maintaining a consistent level of plasma AT levels. Combined with a fixed low injection volume for all adolescent and adult patients, fitusiran is an ideal candidate to utilize an autoinjection device. Both of these features are expected to increase therapeutic adherence and improve patient health. To advance a combination device for approval, regulatory agencies require documentation of the device development process. The User Needs Assessment and consideration of regulatory standards on medical devices and human factors were used to develop the fitusiran device User Requirements document and inform the design of the device platform. Based on established dosing and viscosity criteria and human factors/user needs assessments, the SHL Molly device was selected for delivery of fitusiran. Although Alnylam has improved their understanding of the hemophilia patient population’s needs, there are still uncertainties about the selected Molly device’s compatibility with fitusiran. In addition, because Alnylam was continuing
to establish their siRNA platform while developing fitusiran, this led to certain inefficiencies in the process and necessitated an expedited approach to developing a device for fitusiran in order to position it for a successful launch. Through this device development process, Alnylam can utilize its learnings in device development for future programs.
Acknowledgments

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I am grateful to my parents for reassuring me when I thought I was lost in a sea of words. To Samantha and Skylar, thank you for being making me laugh when I needed it the most. And finally, to Desmond, for keeping me sane and making sure I well fed throughout this process.
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Hemophilia is a rare disease characterized by recurrent bleeding episodes, often occurring in joints and muscles. The ability of blood to clot normally is reduced in individuals with hemophilia due to a physical lack or functional defect in one or more coagulation proteins. The incidence of hemophilia is about 1 in 5000 live births in the United States alone and while the worldwide incidence is not well known, it is estimated that nearly 400,000 are living with the disorder (Hemophilia Federation of America, 2015; Zakieh & Siddiqui, 2017). A novel combination medical device is under development to improve upon current hemophilia therapies which require repeated intravenous infusions and lack long term efficacy. The goal of this work was to discuss the strategy behind the development of a combination medical device to treat hemophilia patients to increase the quality of life of patients while simultaneously improving on treatment adherence.

Hemophilia Disease Mechanism

When a blood vessel is injured or damaged in a normal individual, a process to control and ultimately halt bleeding is initiated; this is called hemostasis (Hoffman, 2003). Clotting factors, with the help of platelets, are proteins that are essential for inducing a blood clot (National Heart, Lung and Blood Institute, 2013). In response to blood vessel injury, platelets aggregate at the damaged site to form a primary platelet plug. In parallel, a series of chemical signals activate coagulation proteins onto platelet
surface and initiate thrombin generation. Thrombin is a serine protease which, when activated, plays a pivotal role in hemostasis converting fibrinogen to fibrin (Di Cera, 2008). Propagation of fibrin production stabilizes the clot as fibrin crosslinks to the platelets (Hoffman, 2003; Vine, 2009). Fibrin crosslinking is essential for effective hemostasis (European haemophilia consortium, n.d.; National Heart, Lung and Blood Institute, 2013). Individuals who are deficient in coagulation proteins will have reduced thrombin generation and thus reduce the body’s ability to promote fibrin generation to stop a bleed event.

There are two types of hemophilia: hemophilia A, characterized by the lack of adequate coagulation factor Factor VIII (FVIII), and hemophilia B, characterized by the lack of adequate factor IX (FIX) (National Heart, Lung and Blood Institute, 2013). Loss of function of either one of these clotting factors reduces thrombin generation. When thrombin generation is reduced, the loss of fibrin formation ultimately halts the fibrin mesh which stabilizes a clot. Figure 1 below shows a simplified mechanism of action when FVIII or FIX is lost and its effect on blood clot formation.
Both types of hemophilia are recessive X-linked monogenic disorders (National Heart, Lung and Blood Institute, 2013). Thus, clinical signs of hemophilia more commonly occur in males, who carry only one X chromosome (Srivastava, et al., 2013). Females, who have two X chromosomes, are typically asymptomatic and are considered carriers of the disease. Figure 1 depicts the inheritance pattern of hemophilia (Hemophilia Federation of America, 2015).

While hemophilia is generally considered an inherited disease, one-third of cases of hemophilia have no family history of the disorder (Hemophilia Federation of America, 2015). This population of hemophilia cases result from spontaneously acquired genetic mutations (Peyvandi, Garagiola, & Young, 2016). Genetic analysis of patients with hemophilia reveal that gene inversions in particular are associated with severe cases of the disease, and results in coagulation factor levels of less than 1IU/dL (i.e. less than 1% of normal) (Peyvandi, Garagiola, & Young, 2016). Point mutations such as missense, nonsense, and splice site mutations are the most common molecular defects in hemophilia patients, and correlate with moderate or mild forms of the disease. Additionally, large deletions and nonsense mutations are associated with patients who are more likely to generate an immune response, where antibodies are generated to protect
against foreign proteins, to factor replacement therapy, known as “inhibitors” (Peyvandi, Garagiola, & Young, 2016). These patients face particular challenges in managing their disease once they become resistant to replacement therapy.

Table 1. WFH Annual Global Survey Summary Demographics

<table>
<thead>
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<th>Demographic</th>
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<tr>
<td>Number of people identified with hemophilia (any type)</td>
<td>187,183</td>
</tr>
<tr>
<td>Number of people identified with hemophilia A</td>
<td>151,159</td>
</tr>
<tr>
<td>Number of people identified with hemophilia B</td>
<td>30,310</td>
</tr>
<tr>
<td>Number of people with hemophilia A with current clinically identified inhibitors</td>
<td>3,099</td>
</tr>
<tr>
<td>Number of people with hemophilia B with current clinically identified inhibitors</td>
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The primary phenotype of hemophilia is a tendency to bruise early or bleed spontaneously or after minimal trauma (Srivastava, et al., 2013). Diagnosis often occurs during early childhood, where initial spontaneous bleeding may occur in joints, muscles, and/or soft tissues such as mucus membranes in the mouth, gums, nose, and gastrointestinal tract (European haemophilia consortium, n.d.; Srivastava, et al., 2013). These symptoms continue as the child ages. Other hemophilia-related symptoms include: arthritis, muscle weakness, scar tissue formation in joints/on veins, heavy and painful menses, and/or fatigue (Srivastava, et al., 2013). Joint bleeds are the most common type of bleed event in hemophilia, resulting in joint pain and swelling (Srivastava, et al., 2013; World Federation of Hemophilia, 2014). Long term effects of repeated joint bleeds lead
to hemophilic arthritis where smooth cartilage is damaged, and the muscles around the joint are destabilized (Figure 3) (Srivastava, et al., 2013; World Federation of Hemophilia, 2014). Over time, continued damage to cartilage from joint bleeds ultimately leads to loss of underlying bone, pain and immobility as shown in Figure 4 (Rodriguez-Merchan, 2014; World Federation of Hemophilia, 2014). Furthermore, peripheral nerve damage secondary joint bleeds is common, and can lead to neuropathy of upper and lower limbs (Rodriguez-Merchan, 2014). Muscle bleeds, the second most frequent site of bleeding after joints, occur when capillaries in the muscle are injured (Rodriguez-Merchan, 2014; World Federation of Hemophilia, 2014). Swelling in the affected area can cause muscle spasms or numbness due to compression of nerves or arteries (Figure 5) (Rodriguez-Merchan, 2014; World Federation of Hemophilia, 2014). As with joint bleeds, frequent muscle bleeds can cause long term damage resulting in muscle weakness or paralysis due to nerve compression, muscle shortening, and fibrosis (Rodriguez-Merchan, 2014). These long term effects will restrict a person’s range of motion. Life-threatening bleeds can occur in intracranial joints, the soft tissues of the neck and throat, or the gastrointestinal space, and require immediate treatment to supplement the patient’s clotting factor levels and regain hemostasis (Kouides & Fogarty, 2010; Rodriguez-Merchan, 2014; Srivastava, et al., 2013).

Observational studies have been used to assess the impact of the disease and current therapies on health-related quality of life (HRQoL) of hemophilia patients. HRQoL is used as a measurement of a patient’s personal perspective on their physical and mental health in combination with their own clinical indicators of the disease (Oladapo, et al., 2015). HRQoL scores have been related to treatment adherence levels in adolescents (Garcia Dasi, et al., 2015). Higher HRQoL scores have correlated with less chronic pain among adolescents and young adults with hemophilia (McLaughlin, et al., 2014). Other studies reveal a lower HRQoL in the hemophilia patient population compared to the general population with the lowest scores in those with severe forms of disease (Figure 6) (Oladapo, et al., 2015). Patients who are “inhibitors”, e.g. those who develop an immune response that makes them refractory to therapy, are reported to have further reduced quality of life as compared to non-inhibitor hemophilia patients (Figure 7) (Morfini, et al., 2007).
Figure 6. Health-related quality of life (HRQol) score in hemophilia patients. This graph depicts a decreased HRQol score in severe (teal) and mild/moderation (maroon) hemophilia patients compared to the general population without hemophilia (blue). Adapted from “Health-related quality of life assessment in haemophilia patients on prophylaxis therapy: a systematic review of results from prospective clinical trials” by A O Oladapo, et al, 2015, Haemophilia 344-358. Copyright 2015 John Wiley & Sons Ltd.

Figure 7. Percent of reported problems in hemophilia patients. Patients report mobility and paint/discomfort are reported as highest problem in an EQ-SD questionnaire (Group A=Inhibitors, aged 14-35yrs, Group B= Inhibitors, aged 36-65yrs, Group C= Non-inhibitors, aged 14-35). From “European study on orthopaedic status of haemophilia patients with inhibitors” by M Morfini, et al, 2007, Haemophilia, 13 (5),p611. Copyright 2007 by World Federation of Hemophilia.
Historically, treatments for hemophilia have relied on the replacement of missing or non-functional clotting factors to promote thrombin function in patients, restore the ability to maintain homeostasis, and prevent pathologic bleeding events (National Heart, Lung and Blood Institute, 2013). The first reported treatments for hemophilia consisted of blood transfusions in 1840 (Farr, 1981; Schramm, 2014). By the 1960s, hemophilia therapy evolved to intravenous infusions of fresh frozen plasma (FFP), however this treatment was also not ideal due to the large volumes of infusion required to stop bleeding episodes (Ingram, 1976; Kasper, 2012). In 1965, a new method of cryoprecipitating plasma to isolate and concentrate clotting factors was invented (Dallman & Pool, 1968; Schramm, 2014). The method consisted of rapidly freezing plasma followed by slowly thawing frozen FPP at a low temperature (Dallman & Pool, 1968). The cryoprecipitate contained plasma proteins rich with FVIII clotting factor and fibrinogen, which allowed for smaller intravenous infusion volumes of concentrated FVIII (Dallman & Pool, 1968). This advancement allowed the treatment of bleeding events in an outpatient setting (Ingram, 1976; Kasper, 2012). By the late 1960s, pooled plasma could be processed to form separate preparations of FVIII and FIX for treatment tailored to the subtype of hemophilia (Dallman & Pool, 1968). In addition, the implementation of lyophilization (drying) allowed a breakthrough for at-home treatments by enabling accurate amounts of concentrated FVIII or FIX to be measured and packaged, which meant that patients were now able to self-infuse in the comfort of their home (Kasper, 2012; Schramm, 2014). However, by the 1980s, evidence showed that blood-borne viruses, such as HIV and hepatitis, could be transmitted through human blood, plasma, and plasma-derived products (Schramm, 2014). Manufacturers of plasma-
derived factors responded by introducing pasteurization and heat treatment to deactivate pathogens (Schramm, 2014). Furthermore, improvements in blood donor screening with the implementation of HIV and HCV antibody testing in 1985 and 1990, respectively, improved the overall safety of blood-derived products (Schramm, 2014). Despite the presence of these measures in manufacturing and testing, the safety of plasma-derived products continued to be a concern in the hemophilia community (Mannucci, 2008). In the mid-80s, the need for plasma-derived factors and the risk of contracting a blood-borne virus was eliminated with another breakthrough in the generation of in vitro systems for generating high concentrations of recombinant FVIII and FIX (Mannucci, 2008). Recombinant factors, rFVIII and rFIX, were licensed as therapeutics for the treatment of hemophilia A and B in 1992 and 1997, respectively (Kumar, Dunn, & Carcao, 2016; Mannucci, 2008).

There are several protocols of clotting factor administration, known as replacement therapy that may be tailored to patient need (Srivastava, et al., 2013; National Heart, Lung and Blood Institute, 2013). The three main types consist of: (i) Episodic (on-demand), (ii) continuous prophylaxis, and (iii) intermittent prophylaxis (World Federation of Hemophilia, 2014). Episodic treatment is given, as needed, at the time of a bleeding event to stop the ongoing bleed (National Heart, Lung and Blood Institute, 2013; World Federation of Hemophilia, 2014). Continuous therapy defined as consistent regular treatments (weekly or twice weekly) to prevent bleed events (Srivastava, et al., 2013). Intermittent, or periodic, prophylaxis infusions are given for no more than 45 weeks, total, in a year to prevent bleeds (Srivastava, et al., 2013). In the 1960s, Nilsson et al. hypothesized that continuous prophylactic treatment given
regularly to early diagnosed patients would prevent recurrent hemarthrosis (bleeding in
the joint space) and subsequent joint damage. Studies from various European and North
American groups in late 1990s to mid-2000s, including a 25-year cohort study of 60
patients (Nilsson, Berntorp, Lofgvist, & Pettersson, 1992), showed that prophylactic
treatment was superior to on-demand therapy for reducing overall bleed events (Kumar,
Dunn, & Carcao, 2016; Nilsson, Berntorp, Lofgvist, & Pettersson, 1992). Following the
study by Nilsson et al, in 1995 the World Federation of Haemophilia and the United
Kingdom Haemophilia Centre Doctors’ Organization recommended starting prophylaxis
therapy early, ideally before the second joint bleed, to reduce risk of spontaneous bleeds
and joint damage (Kumar, Dunn, & Carcao, 2016). Prophylaxis therapy is now the
standard of care for treating children with severe hemophilia (Kumar, Dunn, & Carcao,
2016; World Federation of Hemophilia, 2014). All three types of replacement therapies
aim to prevent bleeding events, joint destruction, and preserve of musculoskeletal
function in patients with hemophilia (Srivastava, et al., 2013). Adherence to treatment via
consistent prophylaxis can improve to a patient’s long-term overall health. When patients
do not adhere to treatment, long term complications such as permanent joint or muscle
damage occur.

Replacement therapy must be injected directly into the bloodstream (i.e.
intravenously) in order to be able to activate the blood clotting cascade. The supplies
necessary for a patient to infuse themselves intravenously are the following (Srivastava,
et al., 2013; World Federation of Hemophilia, 2014): Sharps container, disposable wipes,
alcohol wipe, bandage, cotton balls, tape, tourniquet, butterfly needle, syringe, transfer
needle/filter needle, factor concentrate, latex gloves, and diluent (sterile water) supplied with the concentrate.

Infusion therapy occurs via repeated peripheral vein access or the use of surgically implanted catheters. For peripheral vein infusions, as depicted in Figure 8 a butterfly needle is typically utilized to inject factor into the blood stream. Treatment with butterfly needles can be completed quickly by the patient or their caregiver if veins are large and easy to find, but may be more challenging in some patients, especially children (Srivastava, et al., 2013). In such cases, caregivers may administer replacement factor with a catheter as an alternative to butterfly needle administration. There are two types of infusion by way of catheter: Port-a-catheter, a surgically implanted subcutaneous (under the skin) device connected to a central vein; or a peripherally inserted central catheter (PICC), which is inserted into a vein and partly stays outside the body. Under-the-skin port-a-catheter devices can be accessed repeatedly for years; however, to access the port, sterile technique must be used to prevent infections. Other complications include clot formation within the catheter. The use of PICC devices for infusions requires no needle sticks because it is partially outside the body, in contrast to port-a-catheters. However, these types of catheters last only a few weeks or months compared to years with a port.
Figure 8. How to intravenously infuse replacement therapy. This figure illustrates the number of steps required to infuse with a butterfly needle. From Hemophilia in Pictures by World Federation of Hemophilia, 2014 (https://www.wfh.org/en/page.aspx?pid=1297). Copyright 2004 by World Federation of Hemophilia.

Although patients can lead relatively normal lives with timely administration of clotting factors, there are several drawbacks to factor replacement therapy. First, while prophylaxis aims to minimize joint bleeds, this type of treatment may not completely prevent bleeds and the accumulation of joint damage over time (Young, 2012). Replacement therapy (episodic, continuous prophylaxis, or intermittent prophylaxis) involves repeated intravenous infusions and typically includes use of central venous catheters, which are often uncomfortable for patients, caregivers, babies, children, and especially those who undergo once- or twice-weekly administrations (Journeycake, Quinn, Miller, Zajac, & Buchanan, 2001; Srivastava, et al., 2013). Hemophilia caregivers are often the patient’s parents, and may feel burdened over the physical symptoms of the disease and the stress of managing infusions to their child. A study by Cutter, et al on hemophilia and education and work in the United States reported a negative impact on
employment for hemophilia caregivers, and nearly a third of caregivers voluntarily left the workforce to care for their children with hemophilia (Cutter, et al., 2017).

Many patients and caregivers of patients with hemophilia administer their factor at home without medical supervision. Although home infusions may increase their quality of life due to fewer medical facility visits, it is associated with the challenge of appropriately storing supplies and clotting factor, and keeping track of their inventory to prevent expiration or degradation of factor (Hemophilia of Georgia, n.d.; von der Lippe, Frich, Harris, & Solbrække, 2017). Storage at the correct temperature in particular is important in order to sustain factor viability and functionality (Hemophilia of Georgia, n.d.). Preparing factor is time consuming and involves reconstitution of factor, mixing, venipuncture, and infusions. According to a qualitative study reporting on patient experiences of bleed events, the time it took to prepare and inject a typical IV infusion of factor was an average of 15 minutes and was up to 30 minutes (Flood, et al., 2014). Additionally, even after bleeding has stopped, patients reported feeling lingering symptoms resulting from the bleed such as bruising, soreness, swelling and stiffness (Flood, et al., 2014). The location of the bleed and patient factors also affect recovery. For example adults may take up to 3 days to recover from a joint bleed episode whereas adolescents may recover in a few hours (Flood, et al., 2014). This difference in recovery time may also be affected by the time to administration of treatment where adolescents were able to infuse factor at school in a nurse’s office, whereas adults typically waited until the end of their scheduled workday to treat their bleed at home (Flood, et al., 2014).

A serious complication that may occur with replacement therapy is the potential for development of antibodies, an immune response, against the infused clotting factor.
(Gomez, et al., 2014; National Heart, Lung and Blood Institute, 2013). Development of antibodies in response to the “foreign” clotting factor could lead to its increased clearance, preventing the functionality of the clotting factor and thereby eliminating its therapeutic benefit on the patient. Patients who develop an immune response to replacement therapy can no longer utilize infusions as a method of treatment and are commonly referred to as “inhibitors” (Srivastava, et al., 2013). Population studies reveal that 20 to 30 percent of people with hemophilia A and at 2-5 percent of those with hemophilia B are inhibitor patients (National Heart, Lung and Blood Institute, 2013; World Federation of Hemophilia, 2015). Thus there are approximately 3000 hemophilia A and over 100 hemophilia B clinically identified inhibitors worldwide, as shown in Table 1 (World Federation of Hemophilia, 2015). There is a high unmet need for inhibitor patients who cannot use replacement therapy, as they may have more than 15-25 bleeding events per year leading to more than five in-hospital days per year (Srivastava, et al., 2013; World Federation of Hemophilia, 2014). Furthermore, inhibitor patients are more likely to die of a bleed-related death compared to non-inhibitors (Walsh, Soucie, Miller, & United States Hemophilia Treatment Center Network, 2015). Replacement therapies such as anti-inhibitor coagulation concentrate and recombinant factor offers a preventative means to stop bleeding events, by supplementing a missing entity. It is not a cure and therefore replacement therapy is a burden to patients who utilize it weekly as a means for survival (Chen, 2016).

Status of Hemophilia Market

There are now numerous hemophilia A and B therapies approved for market from several pharmaceutical companies, making this disease market highly competitive from a
business standpoint. Since the standard of hemophilia care has shifted from episodic
treatment towards early age prophylactic factor infusions, hemophilia management has
evolved to include in-home prophylactic regimens which have improved the quality of
life and life expectancy in hemophilia patients (Kumar, Dunn, & Carcao, 2016).
Particularly with adolescents and young adults, those who adhered to prophylaxis had
lower odds of having chronic pain and a better quality of life compared to those who
were the least adherent to treatment (McLaughlin, et al., 2014).

The major classes of hemophilia treatment available or in development today are
described in Table 3. Some of these therapeutics include factors with extended half-lives
(i.e. albumin fusion, PEGylation, Fc-domain fusion) to reduce the number of infusions
patients require for treating hemophilia A (Table 4) or B (Table 5). Although continuous
adherence to prophylaxis can improve the quality of life of patients, Replacement therapy
does not ease the requirement for IV infusions that patients must administer themselves
or that caregivers must administer to children.

While there is currently no hemophilia therapy that includes a monthly dosing
regimen, there is a company developing hemophilia therapies with characteristics
superior to the current standard of care. Emicizumab, developed by Chugai
Pharmaceutical Co, Ltd with Roche and Genentech, was designed as a cofactor, a helper
molecule, to bring factor IXa (FIXa) and factor X (FX) together to activate the
coagulation cascade to treat hemophilia A, similar to clotting factor, factor VIIIa FVIIIa’s
mechanism of action (Figure 9) (Shima, et al., 2016). Emicizumab, a bispecific
monoclonal antibody, can be administered weekly with a single subcutaneous injection.
In a Phase III clinical trial, weekly administration of Emicizumab for 12 weeks showed
robust decrease in bleeding rates of hemophilia A patients and inhibitor patients, with no anti-drug antibody development (Shima, et al., 2016). The median bleeding rates in the lowest dose cohort, 0.3mg/kg, decreased from 32.5 to 4.4% (Shima, et al., 2016).

Figure 9. Emicizumab mechanism of action. A depiction of factorVIIa (A) and emicizumab (B) promoting factor X (FX) and factor IXa (FIXa) to promote factorXa (FXa) activation. Adapted from “Factor VIII Memetic Function of Humanized Bispecific Antibody in Hemophilia A,” by M. Shima, et al, 2016, N Engl J Med, p. S5. Copyright 2016 by the Massachusettts Medical Society.

There also continues to be an unmet need for the inhibitor patient population who are prone to medical emergencies. In order to revolutionize hemophilia treatment, new therapeutics must offer solutions to the current replacement therapy drawbacks. For instance, the development of an alternative route of administration would alleviate the restriction and uncomfortable nature of intravenous catheters. In addition, new therapeutics should offer less frequent administrations of therapy to reduce the high treatment burden of a patient and their caregivers who need to schedule their life around replacement therapy. Caregivers who spend more than 8 hours infusing their children report a greater burden of how their child with hemophilia is perceived, their own
emotional stress, and financial stress (von Mackensen, Wisniewski, Urgo, & Boggio, 2015). Less frequent factor administrations would likely also improve patient compliance with treatment which would reduce the high economic costs of hospitalizations, outpatient visits, and treatment (Chen, 2016), which are estimated nationally to be $60 million annually in emergency departments (Zakieh & Siddiqui, 2017). Most importantly, new hemophilia therapies should have a reduced “inhibitor” effect on patients or complete resistance to antibody development.

Emerging siRNA Hemophilia Therapeutic

Small interfering RNA (siRNA) is a gene silencing method that falls in the larger category of RNA interference (RNAi) (de Fougerolles & Vornlocher, 2007; Sehgal, et al., 2015). RNAi is a natural pathway of gene silencing in organisms to regulate gene expression (Fire, et al., 1997; de Fougerolles & Vornlocher, 2007). siRNAs are short chemically modified ribonucleic acids with gene sequences complementary to cellular mRNAs and have been shown to disrupt the translation, or synthesis, of specific proteins by targeting the protein’s mRNA (de Fougerolles & Vornlocher, 2007). siRNAs can be conjugated to a sugar ligand, N-Acetylgalactosamine (GalNAc), which can efficiently bind to asialoglycoprotein receptor (ASGPR), a cell surface receptor expressed primarily on hepatocytes (Nair, et al., 2014; Sehgal, et al., 2015). In general, once an siRNA is delivered to hepatocytes and internalized into the cytoplasm via GalNAc-ASGPR binding, the siRNA is loaded into a RNA-induced silencing complex (RISC). Through complementary binding of the targeting mRNA sequence, RISC cleaves the mRNA leading to the eventual silencing or decreased in expression of the targeting protein of
interest. This mechanism is depicted in Figure 10. Utilizing GalNAc to mediate delivery of an siRNA to hepatocytes enables the treatment of any liver-related genetic disease.


Alnylam Pharmaceuticals is currently developing a siRNA-based therapeutic as an alternative method of treatment for hemophilia A and B. The siRNA therapeutic is named ALN-AT3 and is also known as “fitusiran”. Fitusiran started as part of the company’s 5x15 therapeutic product strategy launched in January 2011 and is now part of the company’s 2020 pipeline progression goal. Alnylam’s 5x15 company goal was to establish and bring five RNAi therapeutic programs addressing rare genetically defined diseases with major unmet medical need to clinical trials by 2015 (Alnylam
As part of their 5x15 goal, Alnylam aimed to identify and measure clinically meaningful biomarkers for each Phase I human proof of concept clinical trial in order to assess therapeutic activity in the clinic. It was through this goal that antithrombin (AT) was identified as a targeting biomarker to treat hemophilia.

Fitusiran was designed to reestablish hemostasis by inhibiting AT synthesis. The therapeutic hypothesis of using fitusiran as a therapy for hemophilia and other rare bleeding disorders is that these bleeding disorders have ineffective clot formation due to insufficient thrombin generation (Sehgal, et al., 2015). AT is a protein expressed only in the liver and acts as a natural anticoagulant and is the major endogenous inhibitor of thrombin. As depicted in Figure 1, when AT expression is downregulated, thrombin generation can occur through a coagulation cascade which converts prothrombin to thrombin (Sehgal, et al., 2015). Thrombin, the final enzyme in the clotting pathway, then acts to convert fibrinogen to fibrin, forming a clot and thereby halting a bleeding event. Therefore, by utilizing RNAi, fitusiran can reestablish hemostasis by lowering AT expression to promote thrombin generation.

Fitusiran was developed while Alnylam was establishing their siRNA delivery platform and originally started as a siRNA packaged in a lipid nanoparticle (LNP). Fitusiran has since transformed from an LNP-derivative to a “tri-GalNAc” conjugated siRNA to its current and final form, containing a single GalNAc. At the time of Alnylam’s 5x15 announcement, the company’s siRNA platform relied on lipid nanoparticle (LNP) mediated siRNA delivery to its therapeutic target in the liver. LNP containing siRNA is endocytosed into the hepatocyte where siRNA is released into the cytoplasm through a series of pH dependent changes. LNP delivery ultimately required
the need for IV infusion to deliver siRNA therapeutic to patients, in addition to, weight-based therapeutic dosing. Preclinically, LNP delivered siRNA had shown to result in potent, dose-dependent silencing of a targeted protein. Below is a figure depicting preclinical results of Alnylam’s initial LNP-siRNA formulation delivered intravenously targeting antithrombin, their therapeutic target for hemophilia A and B (Figure 11).

Figure 11. Preclinical analysis of relative AT mRNA. Relative antithrombin (AT) mRNA 24 hours post-intravenous dose, 10mL/kg of siAT3, in wild-type mice. From “RNAi-Mediated Inhibition of a Natural Anticoagulant for the Treatment of Hemophilia” by Alnylam Pharmaceuticals, 2012 (http://www.alnylam.com/web/assets/ALNY-OTS-Hemophilia-Oct2012.pdf) Copyright 2012 by Alnylam.

These preclinical results showed targeted, dose-dependent, RNAi-mediated silencing in vivo with an LNP-siRNA 24 hours post dose. While fitusiran progressed preclinically, Alnylam’s siRNA platform was moving away from LNP mediated delivery and thus, away from IV administration. Alnylam went on to develop a targeted delivery approach to hepatocytes in the liver. It was found that specific chemical modifications on an siRNA could enhance its stability in circulation while improving on safety and potency profiles. In addition, an siRNA conjugated to trivalent GalNAc ligand was
discovered to have high binding affinity to ASGPR on hepatocytes. The enhanced stability and utilization of ASPGR as a targeted delivery mechanism allowed for single fixed-dose subcutaneous administration for any liver target in Alnylam’s platform. As shown in Figure 12, one of fitusiran’s early siRNA-GalNAc iterations was shown to suppress antithrombin protein levels down to nearly 100% for up to 25 days after a single subcutaneous dose in wild type mice (Alnylam Pharmaceuticals, 2012). GalNAc’s unique binding relationship with ASGPR steered Alnylam’s siRNA platform away from LNP packaged siRNAs to siRNA-GalNAc conjugates. Thus, possibility of single subcutaneous dose delivery through an injection device had materialized, despite Alnylam not having any expertise in the area of device development.

Figure 12. Preclinical results of ALN-AT3. Plots display dose-dependent lowering of relative AT mRNA, activity, and antigen (left panel) and durable knockdown of AT (right panel) in wild type mice after a single subcutaneous dose of ALN-AT3. From “RNAi-Mediated Inhibition of a Natural Anticoagulant for the Treatment of Hemophilia” by Alnylam Pharmaceuticals, 2012 (http://www.alnylam.com/web/assets/ALNY-OTS-Hemophilia-Oct2012.pdf) Copyright 2012 by Alnylam.

Alnyalm’s preclinical analysis of AT knockdown through subcutaneous administration of fitusiran translated into humans in a Phase I clinical trial where hemophilia A or B patients were subcutaneously dosed weekly or monthly with fitusiran.
The safety and efficacy of fitusiran was evaluated in the Phase I study. Plasma AT and thrombin generation (TG) were evaluated to understand the effect of fitusiran in patients as a clinical endpoint. In the Phase I study, dose-dependent decreases in AT protein was observed in fitusiran’s siRNA-GalNAc design (Figure 13) (Pasi, et al., 2017).

Additionally, patients had a mean thrombin generation increase of 289% relative to baseline and a decrease in AT levels/production greater than 75% (Figure 14) (Pasi, et al., 2017). Median annual bleed rates (ABR) of all phase I study patients (n=41), showed evidence of therapeutic activity in the clinic (Figure 15) (Pasi, et al., 2017).

Figure 13. Relative AT levels in a Phase I clinical trial. This plot depicts a dose-dependent decrease in relative AT from a weekly to monthly fitusiran dosing regimen in Parts A, B, and C. From “Targeting of Antithrombin in Hemophilia A or B with RNAi Therapy,” by K Pasi, et al., 2017 The New England Journal of Medicine. pS15. Copyright 2017 by Massachusetts Medical Society.

Figure 15. Median annual bleed rates (ABRs) in a Phase I clinical trial. Mean ABRs of patients with (black) and without (gray) inhibitors dosed with fitusiran are decreased. From “Interim Data from fitusiran Phase I Trial” by Alnylam Pharmaceuticals, 2016 (http://www.alnylam.com/capella/presentations/interim-data-from-fitusiran-ph-1-trial/) Copyright 2016 by Alnylam.
siRNA Combination Medical Device

In order to address the unmet needs of the hemophilia patient population and improve upon treatment adherence to promote patients’ short and long term health, a fitusiran-autoinjection device was planned for development. Consistent prophylaxis can promote a patient’s long-term overall health (Srivastava, et al., 2013). When patients do not adhere to treatment, complications such as permanent joint or muscle damage occur, causing limited range of motion. Therefore, developing a device to increase therapeutic adherence with a long acting, temperature stable siRNA could greatly increase quality of life of hemophilia patients. Alnylam does not currently have an autoinjection device on the market, making this the company’s first trek towards device development while continuing to advance fitusiran to pivotal clinical studies in parallel.

Autoinjection devices have already been successfully in several clinical applications. For example, Mylan, a company specializing in generic pharmaceuticals has been widely successful with their popular branded autoinjection combination device, EpiPen, to deliver epinephrine in a safe and effective manner to prevent anaphylaxis as a result of an allergic reaction (Mylan, 2016). A single-use autoinjector device would replace the burden of intravenous infusions and the burden of storing large quantities of replacement factor(s) and supplies. This type of device would be considered a combination medical device, as it would be a combination of drug and delivery device (U.S. Department of Health and Human Services, n.d.), and would be the first of its kind to incorporate siRNA technology.

There are seven major phases in the life span of a medical device, according to the World Health Organization’s Medical Device Regulations publication: Conception and
development, manufacture, packaging and labelling, advertising, sale, use, and disposal (World Health Organization, 2003). For the purposes of this case study, I will be focusing on Phase 1 “conception and development”.

Part of the development work that must go into designing a drug delivery product relies on company involvement and engagement with regulators. In the case of fitusiran, regulatory involvement is based heavily off of Alnylam’s development timeline for fitusiran and the company’s plans for device commercialization. Combination products such as autoinjection devices containing drug product typically involves more than one type of regulatory submission in order to market and distribute the final product (SHL Group, 2012). Combination products must go through regulatory requirements associated with each part of the device prior to launch to ensure that the product is fully evaluated for maximum benefit with minimum risk to the targeted patient population (U.S. Food and Drug Administration, 2016; World Health Organization, 2003). To drive fitusiran’s launch, Alnylam’s regulatory and development team for fitusiran has been communicating early and frequently with regulators from the FDA, EU, and other countries to understand the requirements necessary to define the intended use of the device, indication of use, targeted patient market, and correct regulatory pathway for such an approval. FDA regulatory submissions for combination devices must include safety studies in the context of its intended users, the intended use, and the intended use environment to assess any potential harm that the device may cause (U.S. Food and Drug Administration, 2016).

In all phases of device development, risk management is required to ensure patient safety. ISO 14971, an international organization for standardization (ISO)
standard which applies to risk management of medical devices by the manufacturer. The ISO is an independent, non-government organization where common standards are created to support innovation and provide solutions between nations (International Organization for Standardization, 2007). These standards developed by the ISO are utilized for the creation of goods and services to ensure their safety and reliability (International Organization for Standardization, 2007). These can range from manufactured goods/technology, food safety, agriculture and healthcare (International Organization for Standardization, 2007). ISO 14971 establishes a format and suggests tools, such as “fault trees”, to identify hazards associated with medical devices, to estimate and evaluate associate risks, to mitigate and control risks, and finally, to monitor the effectiveness of the controls (Lincoln, 2009). Within ISO 14971 includes eight processes that were designed to address device failures (ISO, 2012; Lincoln, 2009):

1. Risk management planning
2. Risk analysis
3. Risk evaluation
4. Risk controls
5. Overall residual risk acceptability
6. Risk management report
7. Risk management file
8. Production and post-production information

Good documentation of risk management under ISO 14971:2007 throughout the development process is a key element in the road to approval as it shows regulatory agencies that the manufacturer is actively working to improve on and ensure the safety of
their product by identifying potential scenarios in which the patient could be harmed by the product (i.e. a patient injects too much drug). In addition, risk management files will also include explanations of risks associated with the product to all members of the development team up to company management (Lincoln, 2009). During the development of fitusiran’s autoinjection device, Alnylam will be utilizing a risk management process with SHL Group, a company specializing in design and manufacturing of devices like autoinjectors, throughout the course of its lifecycle. Risk management will be particularly important during manufacturing of each device component where Alnylam will need to manage CGMP quality. CGMP is referred to as “current good manufacturing practices” which has been established by the FDA under regulation 21CFR part 820 (U.S. Food and Drug Administration, 2016). 21CFR part 820 includes requirements which govern the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installing, and servicing of all finished devices intended for human use (U.S. Food and Drug Administration, 2016). Each part of the device, whether it be produced or assembled in the same facility, different facilities or outsourced, must come from a compliant quality system. Alnylam will work with SHL Group, who have cGMP quality systems in place to fulfill the manufacturing needs of producing a device that will fit best with fitusiran and ensure the safety of each device component.

A major challenge that Alnylam faces while developing a hemophilia device is to create a beneficial product for a patient population who may or may not have used an injection device or be familiar and comfortable with siRNA therapy. To understand the hemophilia patient population’s unmet needs and their expectations of what a subcutaneous injection device to treat hemophilia may look like, user needs assessments
will be utilized. As another challenge, Alnylam will be developing a device for the first time, and will therefore be in unfamiliar development territory. The purpose of this case study is to describe how Alnylam will develop a strategy to launch fitusiran (ALN-AT3) in the United States and worldwide as a combination device for the hemophilia patient population. By targeting AT3 with RNAi technology and utilizing subcutaneous delivery, Alnylam aims to mitigate the unmet needs for this rare disease patient population.
Chapter II.
Research Methods

How Alnylam plans to develop a combination medical device with fitusiran are outlined within this section. Hemophilia patients were interviewed in focus groups in order to understand the unmet needs in the patient population and understand what a hemophilia therapeutic device should feature.

User Needs Assessment

The user needs assessment was conducted by UL Wiklund, a third-party organization specializing in human factor analysis, to gather user requirements for the development of an injection device to deliver hemophilia treatment. UL Wiklund and Alnylam developed a series of questions for hemophilia patients and caregivers of hemophiliacs (i.e. parents of children with hemophilia) to identify day-to-day experiences with hemophilia, symptoms relating to hemophilia and its impact on health, and perspectives of current and future treatments. These questions were meant to gain an understanding of hemophilia patients’ lives to develop the design of fitusiran’s autoinjection device. UL Wiklund conducted individual phone interviews with hemophilia patients and caregivers and in a second assessment, conducted a focus group consisting of hemophilia patients and caregivers. The purpose of the interview was described to the participant, after which the participant had the opportunity to consent to
the research. Below are a subset of interview questions which were asked to patients or their caregivers.

Questions involving day-to-day experiences with hemophilia

1. Please describe how hemophilia affects your day-to-day life.
2. What are some challenges of living with hemophilia?
3. Have you had to make any compromises or sacrifices due to your hemophilia?

Questions involving hemophilia symptoms and impact on health

1. How have these symptoms affected your life?
2. Have you ever missed work or school due to your hemophilia?
3. Has hemophilia caused you to have any difficulties with cognitive tasks, such as applying short- and long-term memory, staying focused, or reading?
4. If so, how has this affected your life?
5. What modifications do you make to minimize the effects of this impairment?
6. What modifications could be made to minimize the effects of this impairment?

Questions involving hemophilia treatments

1. Briefly describe your treatment regimen (e.g. treatment method, frequency of treatment, whether they use on-demand treatments and/or prophylaxis).
   a. [If applicable – Prophylaxis treatment] Probe to understand whether participants has a strict or intermittent prophylaxis regimen.
b. [If applicable – Infusions] Probe to understand whether they infuse at home independently or with support of caregiver.

c. [If applicable – Infusions] Probe to understand when they started infusions and how they learned to do infusions.

2. What do you like about this treatment method?

3. What do you dislike about this treatment method?

4. What would be your ideal treatment regimen?

Questions involving training, learning aids, and troubleshooting

1. What is the best way for someone to learn to use an injection device? What type of training/information would you need to feel comfortable using an injection device?

2. Have you ever encountered a problem or difficulty administering your treatment? If yes, please describe the issue and how you resolved it.

3. Have you ever asked someone for help administering your treatment? If yes, what type of help and whom did you ask?

Questions involving future of hemophilia treatment

1. What trends do you see in the treatment of hemophilia?

2. What advice do you have for a company developing a home-use injection device for treating hemophilia?
Development of User Requirements

The User Requirements is a document meant to inform the design of a drug delivery platform for fitusiran. UL Wiklund will develop the user requirements based on the following inputs:

- User profile of hemophilia patients
- Findings from User Needs assessments (phone interviews with hemophilia patients/caregivers and focus groups with hemophilia patients/caregivers)
- AAMI HE75:2009 – Human factors engineering – design of medical devices
- ISO 11040-8:2016 – Prefilled syringes – Part 8: Requirements and test methods for finished prefilled syringes
- ISO 15223-1:2012 – Part 1: Medical devices – Symbols to be used with medical device labels, labelling and information to be supplied
- FDA’s Safely Using Sharps (Needles and Syringes) at Home, at Work and on Travel
- UL Wiklund’s professional judgment and experience

Device Design Assessment

Following a user needs assessment, the device design or device type (e.g. autoinjection, syringe injection, multidose injection device) can be created based off the user needs responses. A device assessment by Cooper Perkins would focus on investigating traditional and/or emerging subcutaneous injection device platforms to identify how a delivery device would fit into the hemophilia market. Cooper Perkins assessed 30 suppliers, about 40 different subcutaneous needle-based device types. The
evaluation was driven by dose volume, viscosity capacity, maturity of device, dose volume configurability, and human factors/use needs evaluation. The initial supplier list was further narrowed by analysis of supplier device offerings, breadth of portfolio and responsiveness/suitability as a partner with Alnylam. Emphasis was placed on clinical efficacy and safety of commercial device, user experience (i.e. ergonomics increasing compliance and success), and appropriate match between supplier with Alnylam’s needs.

Cooper Perkins conducted an additional analysis of how pharmaceutical companies were currently addressing multiple fixed-dosing using a combination device. The devices which companies were using for multiple fixed dosing were compared by their device type (i.e. autoinjector or pre-filled syringe), deliverable dose volume, and formulation (i.e. varied drug concentration or same). This analysis was presented to Alnylam as a way to understand how other companies were utilizing combination devices for multiple fixed dosing of their biologics.

Failure Mode and Effects Analysis (FMEA)

To identify potential failures or harms and hazards of the fitusiran device, a FMEA table would be utilized in accordance to ISO 14971.
Chapter III.

Results

This section will outline the results from the focus group interviews and outline how the Alnylam came to select a combination medical device for fitusiran.

User Needs Assessment

UL Wiklund conducted user needs assessments to understand and support the development of user requirements for an autoinjection device that will administer RNAi therapy to hemophilia patients. The findings described below are analysis from patient phone interviews and a Hemophilia Focus Group. To recruit patients for the user needs assessment, UL Wiklund engaged with Rare Patient Voice, a third party recruiting firm to recruit a group of up to hemophilia patients and caregivers. In the first study, a total of 17 60-minute phone interviews were conducted. Of the 17 participants, there were 13 patients and 4 caregivers. The phone interview was hosted from UL Wiklund’s office and a participant joined the call remotely. Each participant was interviewed by a Managing Human Factors Specialist and Senior Human Factors Specialist. A Human Factors Assistant and 2 Human Factors Specialists served as data analysts for the interviews. Table 6 summarizes key demographic information regarding the patients who were interviewed over the phone.

The Focus Group user assessment consisted of 12 interviews which were conducted from two separate focus groups at market research facilities in Chicago and
Boston, each lasting 2 hours. The 12 focus group participants included 5 adult patients, 4 adolescent patients and 2 caregivers of 2 adolescent patient participants, and one caregiver of a patient who did not participate in the focus group. UL Wiklund staff audio-recorded phone interviews and video and audio-recorded each focus group. A Managing Human Factors Specialist administered the focus group and 2 Human Factors Specialists served as data analysts. The participants in each focus group were first introduced to each other and the focus group staff. The purpose of the focus group was summarized to the participants and then posed the interview questions. Following each interview and focus group, UL Wiklund consolidated and analyzed qualitative data and documented its findings. Alnylam used the assessment to guide the development of the fitusiran combination device. Table 7 summarizes the key demographic information regarding the patients who participated in the hemophilia focus group.

Results of surveys

The following section will summarize findings from UL Wiklund’s interview and focus group assessments. The results of each survey was separated into the following categories which will be discussed individually below: Day-to-day experiences in hemophilia, symptoms and impairments, current treatment regimen, impressions of subcutaneous injections, training and learning aids, and conclusions.

**Day-to-day experiences with hemophilia.** The primary reported symptom of hemophilia in both focus groups were repeat bleeds, reduced range of motion and arthritis caused by joint bleeds. The respondents in the phone interviews cited that the physical effects of hemophilia caused significant impact to their daily lives. The focus group reported
chronic pain as the primary physical symptom of hemophilia affecting their daily activities.

Patients and caregivers cited various limitations and challenges to patients’ day-to-day lives. In both the focus group and individual phone interviews, respondents cited significant physical activity limitations due to high risk of injury. Participants explained that people with hemophilia cannot take part in the same physical activities as their peers and as a result feel depressed, frustrated, sad, and disappointed. Some respondents explained that they have independently limited their own activities, realizing the implication of injury (i.e. a bleed event), which leaves the patient feeling left out of social activities (i.e. sports, roller-skating birthday parties). The focus group respondents indicated that they do participate in sports when they have administered treatment more frequently, as they have increased confidence that they are protected against bleeds. Additionally, focus group respondents explained how many of them feel frustrated that non-hemophiliacs have limited knowledge of hemophilia. They express that non-hemophiliacs can therefore can become overly concerned about minor injuries (i.e. small bruises). In contrast, the same respondents have experienced laypeople questioning the seriousness of their condition by asking if missed time at school or work is necessary. In some cases, patients perceived that even healthcare professionals were unaware of some aspects of the disease. For example, one respondent in the focus group, a caregiver with twin daughters who have hemophilia, described that their doctors had limited knowledge of females with hemophilia or were not aware that females could have the condition. She describes that her daughter’s physicians prescribed a birth control drug to prevent her
daughters from menstruating because they were unsure of how menstruation affects female hemophiliacs

Caregiver respondents in the phone user assessment describe strain on their social and family life due to caring for their child with hemophilia. Their social lives are reportedly affected by a constant feeling of fear that their child could be at risk during events involving physical activity. This impacts their mental health as they experience anxiety and depression when the wellbeing of their child is impacted. They report that their family life is negatively affected due to the disproportionate time spent caring for the child with hemophilia compared to other members of their families (i.e. siblings). This is echoed in the focus group assessment where participants reported feeling resented or felt resented by a sibling due to having hemophilia from the disproportionate attention from their parents. However, focus group participates responded that they felt jealous of their healthy siblings’ ability to play contact sports during adolescence. Patients have described feeling alone, outcast, and different than others from a young age.

Time spent managing hemophilia for participants in the phone interview assessment is described as “time consuming”. Both patients and caregivers explained that time spent administering treatment, visiting doctors, or resting hemophilia-related injuries is substantial. This, as reported in the phone interview assessment, negatively affects their careers from reduced job performance or time spent away from work, leading to increased financial burden already exacerbated by treatment cost. Patients also reveal that bleeds or symptoms resulting from bleeds resulted in absences of work or school of duration ranging from one day up to a couple months.
Symptom and impairments. Participants report the following symptoms in Table 8 from each user assessment. Both phone interview and focus group assessments reported chronic dexterity impairments due to hand or finger bleeds that lead to swelling, stiffness, pain, reduced grip strength, limited range of motion and difficulty in performing daily tasks such as writing or typing. However, some participants from the phone interview explained that they are unsure if the dexterity impairment is due to hemophilia or other medical conditions (i.e. carpal tunnel syndrome or rheumatoid arthritis). All participants from both user assessments indicate that dexterity impairments would not limit them handling an injection device like an autoinjector. Participants from the focus group noted that a one-handed delivery device would be valued especially when experiencing a hand bleed.

Other impairments noted in the phone interview assessment were cognitive, fatigue-related, and visual. Cognitive impairments were rarely reported, and included feeling drowsy or unable to focus on anything else during a bleed. Additionally, one participant felt that he had poor memory compared to his peers, but was unsure if this was due to his hemophilia or his concurrent hepatitis. Participants who reported fatigue-related impairment describe feeling fatigued due to joint pain causing poor sleep, regardless of how many hours of sleep they have. Several respondents, which included patients and a caregiver, explained that dealing with hemophilia (i.e. treatment or being cautious to prevent a bleed) is tiring. Lastly, one participant reported visual impairment, blurry vision, due to a head bleed which was resolved after regular infusion treatment.

Current treatment regimen. The summary of treatment regimens from the phone interview assessment is shown in Table 9. The treatment regimen summary from the
focus group assessment is shown in Table 10. Both user assessments include responses from both patients and caregivers.

Respondents from the phone interview and focus group assessments identified both benefits and disadvantages of treatment by way of IV infusion. The majority of patients and caregivers acknowledged that it was convenient and more time efficient to administer treatment in the comfort of their home rather than traveling to an emergency room or a medical clinic where they need be admitted to in order to be infused by a medical professional. Most participants reported being able to complete their infusions in 5-15 minutes, an acceptable duration of time. Nonetheless, even participants who completed infusion in 5 minutes indicated they would prefer a quicker treatment. Another benefit to IV infusions that participants identified was that the volume of medication needed to infuse was low, thus infusion could be completed quickly. Some participants commented that their IV medication had a long duration of action, or half-life, which required less frequent infusions compared to medications with a shorter half-life (i.e. once every other week infusion compared to two-three times each week). In addition, when asked what was liked about their or their child’s IV treatment, participants provided feedback on how they value the safety of their medication, knowing that their recombinant factor does not contain donated human plasma or albumin and, therefore, cannot transmit any blood borne viruses. A caregiver respondent in the phone interview assessment explained that she valued her child having an IV infusion access port so that treating her child was fast, easy, and reliable compared to accessing a vein manually each time.
Disadvantages of IV treatment that respondents reported were related to the technical aspects of its administration. Some participants felt that reconstituting their medication involved too many steps prior to administering their treatment. Some participants in the Focus Group required extra time to prep their treatment because they use a numbing cream, and must wait for it to take effect prior to infusing. Other participants felt that discarding residual medication left in the vial or needle after infusion was wasteful. Other disadvantages mentioned of their IV treatment were:

- Dislike of handling needles and the pain and anxiety that is associated with them.
- Accessing a vein can be challenging and there are occasional “misses”, thus requiring reinserting the needle and causing additional discomfort.
- Infusion needle can fall out (i.e. while multi-tasking), requiring them to reinsert the needle.
- Difficulty with starting an infusion due to scar tissue build up at the site of infusion or IV infusion port.
- Frequency of treatment administration.
- Needing to plan their day or week around their infusions which can occur daily or a few times a week.

There was a general consensus that a monthly treatment would be ideal considering infusing a few times a week is time consuming. Even a weekly treatment would be an improvement according to respondents.

**Impressions of subcutaneous injections.** When participants were asked what they envision an injection device to look like for treating hemophilia, a majority of them described the epinephrine auto-injector, Epi-Pen as an approachable device. They
described some key features that an injection device should have to ensure its ease of use and use-safety:

- Contain a small, protected and/or retracted needle before and after injection.
- Availability in varying doses to accommodate for appropriate dose based on their age, weight, and hemophilia severity.
- Pre-measured dose.
- Portability to enable quick and easy dose delivery.
- An available back-up dose/device should the first attempt be unsuccessful to do device malfunction or expiration of medication.
- Automatic medication shipment and delivery of next scheduled dose.

Participants expressed excitement and interest in a subcutaneous injection delivery device for treating hemophilia. However, several participants from both assessments explained that they would likely continue with IV infusions even with a subcutaneous injection device in the market because they did not want to change their current routine. Some participants responded that they would be hesitant to try a new medication after successfully using the same factor for years. Others reported that they would switch treatments if the device was simpler to use relative to their current infusion method. Most participants in the focus group were wary of treatment that was not factor and all respondents from each assessment noted that the new type of medication that is not factor would need to be more effective than current treatments in order to them to switch medication. Caregivers noted that a subcutaneous injection device may be more suitable for families or patients who have not yet invested the time and effort to learn IV infusion administration. Teaching and familiarizing their child with IV infusions was
perceived as time consuming and exhausting, and the caregivers who felt that way would be hesitant to introduce a new treatment regimen. However, a couple of participants in the focus group noted that they were willing to try the new medication that is not factor if it had clinical and usability advantages over their current treatment.

Participants were asked what the perceived benefits and disadvantages were of using a subcutaneous injection device as compared to a typical IV infusion method. Respondents from both assessments specifically cited lower complexity, less scar tissue, and less intimidation as advantages. Participants felt that using a subcutaneous injection device would be simpler overall than an IV infusion. Additionally, a lower complexity device was described as being less stressful and would allow for quicker treatment because there was no need to access a vein. Children would also have the capability of learning to deliver their own treatment independently rather than receiving caregiver assistance. Participants in the phone interview noted that they expected using a subcutaneous injection device would lower the rate of infection at the site of their IV infusion port, which can easily be contaminated by bacteria. The majority of participants from both user assessments did not foresee any drawbacks to using a subcutaneous injection device to treat hemophilia, however, many cited uncertainty regarding efficacy and safety. Some were unsure if a subcutaneously administered medication would be as effective as IV administration. Others were concerned about a potential immune response (i.e. allergic reaction) to a new medication. Some participants expected a subcutaneous injection device would be equally as painful as an IV infusion and worried about developing painful and visible bruises at the site of injection.
All participants believed that if prescribed an injection device, they would be able to self-administer the injections independently and would not need to rely on a caregiver or health care professional to administer treatment. Several participants in the focus group reported that they felt they could easily teach a layperson how to administer a subcutaneous injection with an injection device due to its simplicity, in contrast to, delivering IV infusions which were noted to be more complex and less intuitive.

When participants were asked what their ideal treatment regimen would look like, they mentioned the following characteristics:

- Fewer treatments
- Decreased treatment administration time (i.e. one minute rather than several minutes).
- A treatment not administrated through IV injection.
- Room temperature stable.
- Relatively small/discreet (i.e. the treatment would preserve the user’s privacy when administering a treatment or carrying the device).
- Great efficacy and duration of medication (i.e. a medication that maintains a consistent, high factor level through the next treatment.
- No assembly of device components.
- A device that requires no training due to its simplicity and intuitiveness.

**Training and learning aids.** To learn how to use a new subcutaneous injection device, most participants from each user assessment reported that they would prefer to learn the technique from a healthcare professional. Many participants from the phone interview noted that they learned their IV fusions as children at summer camps designed
specifically for children with hemophilia. At the camp, a healthcare professional (i.e. a nurse) would demonstrate the infusion technique in a step-by-step manner and had the children later practice infusing on rubber arms, balls, or other models. Other participants learned IV infusion from a home healthcare nurse, who provided training over the course of several visits. Some learned IV infusions by visiting the office of their healthcare provider. All participants valued personal and hands-on training from a healthcare professional because they could understand the steps necessary to infuse, they could observe an infusion administered by a trained professional, and they felt safe attempting their first infusion because a trainer was there to provide support and encouragement.

Most participants believed that a single training session would be sufficient to learn how to administer treatment through a subcutaneous injection device, whereas others recommended multiple sessions. Participants specifically recommended a healthcare professional to demonstrate, step-by-step, how to use the device, followed by allowing the patient to first practice on a model. The patient would then be allowed to administer an injection to himself or herself with supervision of the healthcare professional. All participants explained that the device should include instructions on how to use the device. These instructions should include a step-by-step guide with text and graphics. A few participants in the focus group suggested that an instructional video on how to use the device properly would be valuable to review proper technique.
Development of User Requirements

User requirements were developed for a subcutaneous injection device for the hemophilia patient population. The following section lists the requirements for the following aspects of the device: device design, medication delivery, training, learning aids, warnings, packaging, and storage. The following requirements listed are only a portion of the full user requirement document.

Device Design

1. The device shall feature no sharp edges or pinch points.
2. The device shall clearly distinguish the needle’s location.
3. The device should not require any assembly to increase device portability and to decrease opportunities for incorrect assembly.
4. The device shall be discreet in appearance to limit attracting unwanted attention from others.
5. The device’s body shape shall enable the user to grip the device securely with the right or left hand.
6. The device’s body’s texture shall provide a sturdy grip.
7. The device’s length shall not exceed 20.32cm to ensure portability.
8. The device’s body shall enable the user to visually inspect the medication.
9. The device’s body should feature abbreviated on-device instructions.
10. Safety-related on-device text-instructions should be accompanied by graphics of the same information to accommodate individuals with low literacy skills.
11. Safety-related, on-device instructions shall be positioned in a conspicuous location. The device should not have a visible needle to accommodate users, caregivers, and onlookers with needle phobia.

12. The needle shall not be separable from the device’s body.

13. The needle shall have a length to enable users to only inject subcutaneously (assuming a 45° - 90° insertion angle).

14. The needle and device shall have a precise fit, preventing the medication from leaking and the needle from moving during an injection.

15. The device shall have a needle protection mechanism (hereafter referred to as the “needle guard”).

16. The needle guard shall prevent users from encountering a needle stick injury before and after injection.

17. The needle guard shall prevent

Medication Delivery

1. The device shall enable the user to administer a dose of medication.

2. The device shall not require the user to manually measure the dose of medication.

3. The device shall enable the user to administer medication without relying on the user to locate and access a vein.

4. The device shall not require the user to reconstitute medication.

5. The user shall be able to deliver the medication into a more than one location on their body.

6. The device shall enable the user to administer medication using only one hand.
7. The device should enable the user to administer medication in a non-sterile environment (e.g., car, home, school) safely.

8. The injection duration (i.e., time to deliver the medication, from needle insertion to removal) shall be equal to or less than five minutes.

9. The device shall provide auditory, tactile, and/or visual feedback when it has delivered the full dose of medication.

10. The device shall enable the user to set up the device, administer an injection, and dispose of the device in less than 5 minutes.

11. The user shall have access to a backup device for use if the first device fails.

Training

1. Patient users should receive a one-on-one training on the device’s use from a healthcare professional.

2. Healthcare professionals who train patients on the device’s use should receive information on training best practices from the manufacturer.

3. Training shall include a demonstration and an opportunity for the patient to perform a “return demonstration.”

4. Training shall include information on proper preparation, medication delivery, and disposal, as well as troubleshooting and safety precautions.

Learning Aids

1. Instructions for use (IFU) shall be included in the device’s packaging.

2. The IFU shall include (but is not limited to) the following content:

   a. Manufacturer’s name and address.
b. Description of the package’s contents.

c. Device’s and medication’s indications and contraindications for use.

d. Medication name and/or the active ingredient.

e. Medication dose amount and/or concentration.

f. Description of how the medication works.

g. Indication of additional materials or supplies needed for device use.

h. If the device is single-use, a single use indication, compliant with the ISO 15223-1:2012 standard, to indicate that the device is for single use only.

i. Instructions for correct storage and/or handling conditions.

j. Warnings and/or precautions to take before device use.

k. Instruction directing the user to read the IFU before using the device.

l. Step-by-step instructions for preparing for an injection, administering an injection, and disposing of materials.

m. Instructions to inspect the medication before use and to not use the medication if:

   i. The expiration date on the device or packaging has passed.

   ii. The device is damaged.

   iii. The medication is cloudy, hazy, frozen, discolored, or contains particulates.
n. Troubleshooting information.

3. The IFU shall present steps in a hierarchical manner, clearly differentiating general steps from sub-steps.

4. The IFU shall include graphics alongside text instructions.

5. Where appropriate, the graphics shall depict the useful contextual information for proper task execution (e.g., motion arrows shall be used to communicate specific motions).

6. A training or how-to video should be available to the user.

7. A telephone hotline should be available for the user to ask questions regarding device use.

Warnings

1. All prohibitory text (i.e., “DO NOT” statements) shall be formatted in bold text and feature uppercase capitalization.

2. All safety messages shall include a warning symbol at the start of the safety message.

3. Safety messages regarding risks of different severities shall be color-coded in the following way:

4. Danger (if hazardous situation is not avoided, it will result in death or serious injury): red.

5. Warning (If hazardous situation is not avoided, it could result in death or serious injury): orange.

6. Caution (if hazardous situation is not avoided, it could result in minor or moderate injury): yellow.
7. Safety messages shall be written in a consistent negative construction (e.g., DO NOT tilt the device while removing).

8. Safety messages shall state explicit actions or conditions the user shall abide by to protect against potential risks or harms.

9. Safety messages should describe the potential harm that could arise from violating the safety recommendation.

Packaging

1. Users with dexterity impairments shall be able to open the packaging.

2. A limited number of instructional materials and device accessories shall accompany the device to prevent the user from feeling overwhelmed upon opening the device packaging.

3. Packaging shall maintain the sterility of the device.

4. Packaging shall protect the device from the stresses and hazards generated by manufacturing, shipping, and storage environments.

5. The packaging label shall at least contain:
   a. Manufacturer’s name and address.
   b. A description of the packaging’s contents.
   c. The word “STERILE”.
   d. The batch code in alphanumeric characters or machine-readable code (e.g., barcode), preceded by the word “LOT” or the serial number.
   e. An indication of the use-by-date, formatted as YYYY-MM-DD or YYYY-MM.
f. Instructions for correct storage and/or handling conditions; e.g., conditions related to temperature, direct sunlight, etc.

g. If the device is single use, a SINGLE USE indication, compliant with the ISO 15223-1:2012 standard, to indicate that the device is single use only.

Storage

1. The device shall not require refrigeration to ensure medication efficacy to increase portability, reduce medication waste, and decrease the likelihood the user administers ineffective medication.

Device Design Assessment

Based off user needs criteria, which includes Alnylam’s considerations and patient interests, Cooper Perkins presented 7 devices from 2 different manufacturers to Alnylam with specific selection criteria: dosing accuracy at small volumes, user experience to patient population and/or their caregivers (i.e. number of steps to inject, ergonomics), development time, development cost (i.e. total of customization, validation, and commercialization), device cost per injection, and business risk (i.e. supplier stability, distribution) (Table 2). These 7 devices are all manufactured by either the SHL Group or UniLife, and they consisted of a selective dose injector, prefilled syringes, or single dose autoinjectors. These devices were compared to a syringe and vial, typically how current hemophilia therapeutics are packaged. Each selection criteria was given a score ranging from -3 (poor) to +3 (excellent). The scores were totaled to give a final number and compared to a syringe & vial score.
### Table 2. Device Selection Criteria and Considerations

<table>
<thead>
<tr>
<th>Selection Criteria</th>
<th>Considerations</th>
</tr>
</thead>
</table>
| Dosing Accuracy    | Ability of device to house volume of dose  
                    | Success of administration by diligent user |
| User Experience    | Number of steps to administer a dose  
                    | Difficulty in administering dose (cognitively and physically)  
                    | Ergonomics |
| Development Time   | Timeframe of customization, design validation and clinical build of device |
| Development Cost   | Cost of engineering, tooling, and equipment |
| Device Cost        | Cost of device per dose/injection |
| Business Risk      | Supplier stability  
                    | Primary containment supply chain  
                    | Distribution of device |

Additionally, the Cooper Perkins survey presented several avenues by which Alnylam could address multiple fixed dosing using devices based off how other companies currently address this need. There are multiple ways in which pharmaceutical companies are addressing multiple fixed dosing of a biologic with a combination device:

In the case of Otrexup, a biologic used to treat arthritis by Antares Pharma, it has been approved as a single dose autoinjector which is manufactured in multiple dose strengths, from 7.5mg up to 25mg. An example of a company utilizing a variable dose autoinjector is Endo Pharmaceuticals with Sumavel DosePro, a biologic to treat migraines. Sumavel DosePro, another approved biologic in a combination device format, can deliver a single fixed volume dose at two different concentrations. Abbive, the maker of Humira, utilizes both single-use prefilled syringes produced in various dose volumes in addition to an autoinjection device with a single dose size.

Based on the selection criteria, Cooper Perkins concluded that the autoinjection device named “Molly” by SHL Group (Figure 16) containing a prefilled syringe or
cartridge inside the device, scored the highest in their user experience analysis. To address multiple dosing, the fitusiran could be packaged in multiple single-use Molly devices.

Figure 16. Molly device. The Molly is an autoinjection device which houses a 1mL syringe and plunger and includes a safety cap (purple). Taken from SHL Medical Products, SHL Group. 2015 (http://www.shl-group.com/product/molly-auto-injector). Copyright 2015 by SHL Group.

The Molly device is a compact autoinjector featuring a standard 1mL syringe housed in a compartment. In addition, it includes safety features such as a permanent hidden needle and a needle shield (SHL Group, 2015). SHL Group indicates that the Molly device features a “two-step” use: Remove cap and press against the skin. SHL describes the Molly device’s simplistic and minimal design allow quick and inexpensive customization.

Failure Mode and Effects Analysis (FMEA)

Failure Mode and Effects Analysis (FMEA) is a risk management technique that is part of risk management. Part of Alnylam’s Risk Management will be to utilize FMEA to understand the potential failures that could occur with the SHL Molly device. The FMEA table would include the following parameters per hazard:

- Steps of effect
- Hazard
• Harm
• Severity (score of 1-5, 5 being most severe)
• Occurrence
• Probability of hazard (Severity score x occurrence)
• Risk mitigation
• Design change
• New instructions

The FMEA table would include risk analysis for the end user (i.e. a hemophilia patient or a hemophilia caregiver), the design of the device, in addition to, potential risks from the manufacturing of the device components, assembly, to the drug itself. In order to mitigate potential design or manufacturing risks, Alnylam will need to collaborate with device suppliers to understand what those risks could be. Table 11 is an example of a potential harm a patient could encounter with an autoinjection device if the patient does not/improperly clean the injection site prior to administration. The severity score of mild to severe infection and mild to severe allergic reaction ranges from 2 to 5 and 2 to 4, respectively. The FMEA table suggests that in order to mitigate the hazard, the company would provide an alcohol wipe to be included with the sellable unit, in addition to, provide clear “Instructions For Use” (IFU) on cleaning the injection site.
Chapter IV.

Discussion and Next Steps

Hemophilia is a rare disease where the ability of blood to clot normally is reduced in individuals due to the lack of or defective clotting factors. Loss of function of Factor VIII (FVIII) in hemophilia A, or Factor IX in hemophilia B, reduces thrombin generation, a protein necessary to generate fibrin that stabilizes a developing clot (US Dept. of Health and Human Services, n.d.). Although there are a variety of approved hemophilia therapeutics (Table 3), there still remains an unmet need for more convenient and longer lasting treatment for patients. The user needs assessment conducted by UL Wiklund confirmed the need for a better therapeutic for hemophilia patients to ease the physical and mental burden of the disease on themselves and their caregivers. Alnylam Pharmaceuticals aims to address these needs with a new class of therapeutic, a siRNA, named fitusiran. Fitusiran targets the protein antithrombin (AT) and downregulates its expression by silencing its RNA. By reducing the levels of this inhibitor of the coagulation cascade, the therapeutic hypothesis is that this drug will promote increased thrombin generation and fibrin formation and thus reestablish normal hemostasis (Figure 1). A major benefit of fitusiran is that it could be administered subcutaneously, potentially once a month or less, and could be easily administered by the patient at home. There is currently no approved hemophilia therapeutic with these characteristics. Other benefits of fitusiran compared to the current standard of care include improved temperature stability of therapeutic, better therapeutic half-life, decreased likelihood of immunogenicity, or likelihood of developing resistance against therapeutic. With a large
number of hemophilia therapies currently in market, Alnylam seeks to develop a strategy
to differentiate fitusiran from the rest of the hemophilia therapeutic market while also
improving the patient experience of treatment to increase the quality of life of patients.
Thus, an injection delivery device for fitusiran was brought into development. This is
Alnylam’s first foray into developing medical devices. With a combination device such
as an autoinjector, a patient would no longer need to self – IV infuse, making treatment
less intrusive on their and their caregiver’s lives. The simplicity of using a combination
device also increases the compliance to treatment over the long term. Participants from
the UL Wiklund user assessment agreed that a device that is easier and faster to use
compared to their current method of administration (i.e. IV infusions) would address
many current unmet needs of hemophilia patients.

Findings from the user assessments are valuable in developing the User
Requirements to inform design specifications for how the Molly device can be further
customized, how fitusiran will be delivered (i.e. how long the injection duration will be),
how patients should be trained to use the device, what types of learning aids should be
included with the device packaging, device warnings, and how the device should be
stored. Following further Molly device customization to fit fitusiran, the fitusiran-Molly
device would be further tested in Human Factor (HF) studies to evaluate the user
interface of the product (e.g. product appearance, identification markings, container
closure, packaging configuration, labeling, and nomenclature), in addition to, its safety
for its intended users, for the intended uses, and for the intended use environment (Food
and Drug Administration, 2016). FDA regulatory submissions for combination devices
must include Human Factor (HF) studies, also known as Formative and Validation
studies. The Formative Study is intended to verify the design of the device is intended to work as it was intended to (Food and Drug Administration, 2016). The Validation Study serves to confirm that the device functions as it should (Food and Drug Administration, 2016). Multiple Formative studies may be performed if there are aspects of the device that need improvement. The FEMA table used to identify failures in a device would be further utilized here. These studies are meant to test and evaluate use-related risk analysis associated with the combination product (Food and Drug Administration, 2016; World Health Organization, 2003).

Conclusions

Although progress towards the goal of developing a fitusiran device has been made, the product development timelines have been relatively inefficient because Alnylam was attempting to develop a device while concurrently making modifications to the drug formulation and delivery platform. During fitusiran’s drug development lifecycle, Alnylam’s platform was evolving from LNP-siRNA delivery system, requiring weight based dosing, to several iterations of GalNAc-siRNA conjugation. Weight-based dosing would have entailed a delivery device with variable dose capabilities such as a multi-dose dial syringe, which was described in Cooper Perkin’s initial landscape survey of device possibilities in the hemophilia disease area. After Alnylam improved their GalNAc-siRNA delivery with a “tri-GalNac” design, a single low dosing volume was capable and Alnylam did not have to rely on weight based dosing. This meant that Alnylam could design a device with fixed dosing and have a better understanding of how they could incorporate this to the needs of hemophilia patients. With Cooper Perkins, the Molly device (figure 16) scored the highest in user experience, was thus selected as the
best fit device for hemophilia patients as a combination autoinjection device, offering low volume monthly dosing of treatment instead of prophylactic IV infusion treatment. While the fitusiran-Molly device continues its development path at Alnylam, there are ways in which this path would have been more efficient.

A typical device development life cycle of a drug begins with a vial & syringe, followed by development and approval of a pre-filled syringe (PFS) of the drug, and lastly, development and approval of an injection device (i.e. autoinjection device). It is typical of companies who use vial & syringe as their method of delivery of some therapeutics to move on to PFS because economically, less drug material is used for PFS compared to vials. Vials require “dead volume” to ensure enough material is capable of being dispensed by a typical syringe. When moving towards combination injection devices such as a PFS, measuring drug compatibility with each device material (i.e. syringe plunger, syringe container, silicone coating in syringe chamber) is necessary to ensure the integrity of the drug substance does not change when in contact with the device materials. Importantly, these tests identify if the drug product remains safe and stable for administration to a patient using the device. These types of material validation tests are typically included in a document called the Design History File, which is submitted to regulatory agencies when applying for device approval. Many of the device materials in PFS are also found in more complex combination devices such as autoinjection devices and therefore would not need to be re-tested as long as the tests have been well documented and validated.

When testing for device compatibility with drug product, break loose extrusion (BLE) force tests are typically conducted during device development prior to final device
selection. BLE force testing is meant to identify changes in force necessary to push a syringe plunger to allow for extrusion of material from the chamber. BLE testing is typically conducted with syringes filled with drug material or drug diluent in various environments (i.e. different temperature and relative humidity levels) where the syringe integrity could change.

These tests mentioned above are typically tested with a variety of other device products prior to selection of the final device. In device product development, choosing a final device in parallel with development of your drug can be risky. In the case of Alnylam’s fitusiran combination injection device development process, the company will need to work with SHL group to run validation studies to identify drug product to device material compatibility and BLE testing. Should there be fitusiran incompatibility with any component of the Molly device during the Validation tests, Alnylam would likely proceed with development of a PFS or simply switch to another injection device, therefore delaying the launch of fitusiran as an injection device. It is best practice in device development to understand the compatibility of drug product to device components. With this understanding, Alnylam can proceed towards a smoother development path for future programs.

Overall, to improve the lives of hemophilia patients, a more convenient therapy is needed for this disease population other than Replacement therapy. A patient must intravenously infuse Replacement therapy via continuous prophylaxis (i.e. treatment adherence) to maintain short and long term joint and muscle health. In order to ease the burden of these infusions while maintaining quality of life, fitusiran, a siRNA to treat hemophilia, is in development by Alnylam Pharmaceuticals as an autoinjection device.
Fitusiran is room temperature stable and can be dosed monthly as a low volume, subcutaneous injection. As a company with no prior experience in developing combination medical devices, Alnylam was striving to expedite their device development strategy to ensure a successful launch. Thus far, the fitusiran device’s User Requirements has been developed and the Molly device has been chosen as the delivery vehicle. Discrepancies in specific device material to drug compatibility tests may set the fitusiran device launch back, however, going back to conduct those analyses will ensure a safe and efficacious product for hemophilia patients.
Table 3. Major Classes of Hemophilia Therapy

<table>
<thead>
<tr>
<th>Treatment typea</th>
<th>Treatment descriptiona</th>
<th>No. approved for marketingb</th>
<th>No. of agents in development and stage of developmentc</th>
</tr>
</thead>
</table>
| Plasma-derived factor replacement    | • 1st generation hemophilia treatment  
• Purified clotting factor from donated human plasma                                  | 8                          |                                                       |
| Recombinant factor replacement       | • Manufactured clotting factor (low infection risk compared to plasma-derived)  
• Primary approach to hemophilia treatment  
• Risk of developing immune response to factor (inhibitors)                        | 15                         |                                                       |
| Bypassing factors                    | • Downstream clotting factors that promote coagulation which work independently of FVIII and FIX  
• Effective in both types of hemophilia regardless of inhibitor status                | 2                          | 2, Pre-Registration                                   |
| Long acting factor VIIa             | • Manufactured FVIIa clotting proteins that include chemical or protein modifications to enhance half-life (PEGylation, Fc-fusions, Albumin-fusions, XTEN, Polysialic acid polymers, single chain modifications) | 0                          |                                                       |
| Long acting recombinant factors | • Manufactured clotting proteins that include chemical or protein modifications to enhance half-life | 5 | 1, Phase I 1, Phase II 3, Phase III |
| Anti-TFPI antibodies | • Promote inhibition of tissue factor pathway inhibitor (TFPI) to facilitate hemostasis | 0 | 1, Pre-Registration 1, Phase I 2, Phase III |
| Bi-specific antibodies | • Manufactured antibody containing 2 antigen binding sites  • Mimics clotting factor activity by binding to its targets without replacing missing factor  • Potential to treat inhibitors | 0 | 3, Phase I |
| Gene therapy | • Replacement and expression of defective clotting factor-encoding gene  • One-time dose potential | 0 | 1, Phase III |

Note: This table describes the various classes of hemophilia therapies available now or in development. The number of approved therapeutics in the United States and the number of products in development and their state of development are shown. aNational Heart, Lung, and Blood Institute (2013), bNational Hemophilia Foundation Medical and Scientific Advisory Council (2017), cThe identification of the number of products in development and their stage of development was performed in ClinicalTrial.gov. The main search strategy used combinations of keywords such as hemophilia AND not yet recruiting OR recruiting OR enrolling by invitation OR active, not recruiting OR early Phase 1 OR Phase 1 OR Phase 2 OR Phase 3. Searches were conducted by manuscript author and were collated for the purpose of this table.
Table 4. Licensed FVIII Products to Treat Hemophilia A

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Manufacturer/Distributor</th>
<th>In-vitro manufacturing</th>
<th>Bioengineering/Chemical Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advate</td>
<td>Baxter/Baxalta</td>
<td>CHO</td>
<td>None</td>
</tr>
<tr>
<td>ADYNOVATE</td>
<td>Baxalta</td>
<td>CHO</td>
<td>PEGylation</td>
</tr>
<tr>
<td>AFSTYLA</td>
<td>CSL Behring</td>
<td>CHO</td>
<td>Single chain rFVIII</td>
</tr>
<tr>
<td>ELOCTATE</td>
<td>Biogen</td>
<td>HEK</td>
<td>B-domain Deleted, IgG-1 Fc-domain Fusion Protein</td>
</tr>
<tr>
<td>Kogenate FS/Helixate FS</td>
<td>Bayer (Helixate FS is distributed by CSL Behring)</td>
<td>BHK</td>
<td>None</td>
</tr>
<tr>
<td>Kovaltry</td>
<td>Bayer</td>
<td>BHK</td>
<td>None</td>
</tr>
<tr>
<td>NovoEight</td>
<td>Novo Nordisk</td>
<td>CHO</td>
<td>B-domain truncate</td>
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<tr>
<td>Nuwiq</td>
<td>Octapharma</td>
<td>HEK</td>
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<tr>
<td>Recombinate</td>
<td>Baxter/Baxalta</td>
<td>CHO</td>
<td>None</td>
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<tr>
<td>Xyntha</td>
<td>Pfizer</td>
<td>CHO</td>
<td>B-domain deleted</td>
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<tr>
<td>Hemofil M</td>
<td>Baxter/Baxalta</td>
<td>N/A, Immunoaffinity-purified from human plasma</td>
<td>None</td>
</tr>
<tr>
<td>Monoclate-P</td>
<td>CSL Behring</td>
<td>N/A, Immunoaffinity-purified from human plasma</td>
<td>None</td>
</tr>
</tbody>
</table>

Note: Products which are currently licensed for hemophilia treat A in the United States are shown above. Some products are manufactured in an in-vitro cell system using cell types: BHK, CHO, or HEK. Other products are purified from human plasma (immunoaffinity-purified). Products may be enhanced with bioengineered or chemical modifications. Adapted from National Hemophilia Foundation Medical and Scientific Advisory Council, (2017)
Table 5. Licensed FIX Products to Treat Hemophilia B

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Manufacturer/Distributor</th>
<th>In-vitro manufacturing</th>
<th>Bioengineering</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPROLIX</td>
<td>Biogen</td>
<td>HEK</td>
<td>IgG-1 Fc-Domain Fusion Protein</td>
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<tr>
<td>BeneFix</td>
<td>Pfizer</td>
<td>CHO</td>
<td>None</td>
</tr>
<tr>
<td>IDELVION</td>
<td>CSL Behring</td>
<td>CHO</td>
<td>Albumin Fusion Protein</td>
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<td>Ixinity</td>
<td>Emergent Biosolutions</td>
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<td>None</td>
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<tr>
<td>Rixubis</td>
<td>Baxter/Baxalta</td>
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<td>None</td>
</tr>
<tr>
<td>AlphaNine SD</td>
<td>Grifols</td>
<td>N/A, Immunoaffinity-purified from human plasma</td>
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<td>Mononine</td>
<td>CSL Behring</td>
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</tbody>
</table>

Note: Products which are currently licensed for hemophilia treat B in the United States are shown above. Some products are manufactured in an in-vitro cell system using cell types: CHO, or HEK. Other products are purified from human plasma (immunoaffinity-purified). Products may be enhanced with bioengineered or chemical modifications. Adapted from National Hemophilia Foundation Medical and Scientific Advisory Council, (2017)
### Table 6. Phone Interview Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>Patient Mean</td>
<td>33.2</td>
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<tr>
<td>Patient Range</td>
<td>16-58</td>
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<tr>
<td>Caregiver’s patient mean</td>
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<td>Caregiver’s patient Range</td>
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<tr>
<td><strong>Patient Gender</strong></td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
<td>1</td>
</tr>
<tr>
<td><strong>Caregiver Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
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<tr>
<td><strong>Respondent Type</strong></td>
<td></td>
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<tr>
<td>Patient</td>
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<tr>
<td>Caregiver</td>
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<tr>
<td><strong>Hemophilia Type</strong></td>
<td></td>
</tr>
<tr>
<td>A</td>
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</tr>
<tr>
<td>B</td>
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<tr>
<td><strong>Severity</strong></td>
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<tr>
<td>Severe</td>
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<tr>
<td><strong>Length of Treatment (years)</strong></td>
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<tr>
<td>Patient Mean</td>
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<td>Patient Range</td>
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<tr>
<td>Caregiver’s Patient Mean</td>
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<tr>
<td>Caregiver’s Patient Range</td>
<td>4.4-13.3</td>
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<tr>
<td><strong>Medications</strong></td>
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<td>Amicar</td>
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<td>Xyntha</td>
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<td>Rixubus</td>
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</tr>
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<td>Kogenate FS</td>
<td>1</td>
</tr>
<tr>
<td>Ixinity</td>
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<td>Pyrophylux</td>
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</tr>
<tr>
<td>AlphaN/Ate</td>
<td>1</td>
</tr>
<tr>
<td><strong>Treatment Regimen</strong></td>
<td></td>
</tr>
<tr>
<td>Prophylactic</td>
<td>11</td>
</tr>
<tr>
<td>Intermitant prophylactic</td>
<td>4</td>
</tr>
<tr>
<td>On-demand</td>
<td>2</td>
</tr>
<tr>
<td><strong>Inhibitor Developed</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
</tr>
<tr>
<td>No</td>
<td>13</td>
</tr>
</tbody>
</table>

Note: The demographics of the phone interview respondents in the user assessment conducted by UL Wiklund are shown in this table. The respondents are either hemophilia patients or a caregiver of a hemophiliac. The numerical values indicate age or the number of respondents who corresponded with the listed data description.
Note: The demographics of the hemophilia focus group respondents in the user assessment conducted by UL Wiklund are shown in this table. The respondents are either hemophilia patients or a caregiver of a hemophiliac. The numerical values indicate age or the number of respondents who corresponded with the listed data description.
Table 8. Reported Symptoms of Hemophilia

<table>
<thead>
<tr>
<th>Symptoms reported in Phone Interview</th>
<th>Symptoms reported in both user assessments</th>
<th>Symptoms reported in Focus Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint hyperextension</td>
<td>Joint bleeding, including ankles, knees, hips, shoulders, and elbows</td>
<td>Muscle weakness</td>
</tr>
<tr>
<td></td>
<td>Limited range of motion (i.e. reduced flexion or extension, complete immobility)</td>
<td>Muscle/soft tissue bleeding</td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
<td>Prolonged wound bleeds</td>
</tr>
<tr>
<td></td>
<td>Swelling, especially around the joints</td>
<td>Internal bleeding due to internal hematoma</td>
</tr>
<tr>
<td></td>
<td>Bruising</td>
<td>Heavy and painful menses</td>
</tr>
<tr>
<td></td>
<td>Nose bleeds</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Scar tissue (in joints, on veins)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: This table describes the physical symptoms of hemophilia reported by respondents in the UL Wiklund user needs assessment (phone interview and focus group). The phone interview and focus group respondents cited similar symptoms as reported in the table.

Table 9. Treatment Regimen of Phone Interview Participants

<table>
<thead>
<tr>
<th>Treatment type</th>
<th>Medication</th>
<th>Treatment frequency</th>
<th>Delivery Method</th>
<th>Treatment location</th>
<th>Administrator of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis</td>
<td>Helixate</td>
<td>Every other day</td>
<td>IV</td>
<td>Home</td>
<td>Patient self-administers</td>
</tr>
<tr>
<td>On-demand</td>
<td>Benefix</td>
<td>One treatment every several months</td>
<td>IV</td>
<td>Hemophilia treatment center</td>
<td>HCP infuses the patient</td>
</tr>
<tr>
<td>On-demand, some preventative</td>
<td>Kogenate FS</td>
<td>Three times each week</td>
<td>IV</td>
<td>Home</td>
<td>Patient self-administers</td>
</tr>
<tr>
<td>On-demand</td>
<td>Advate</td>
<td>Every other week</td>
<td>IV</td>
<td>Home</td>
<td>Patient self-administers</td>
</tr>
<tr>
<td>On-demand</td>
<td>Advate</td>
<td>One treatment every several months</td>
<td>IV</td>
<td>Home</td>
<td>Wife infuses the patient</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Recombinate</td>
<td>Three times each week</td>
<td>IV</td>
<td>Home</td>
<td>Patient self-administers</td>
</tr>
<tr>
<td>Prophylaxis, plus on-demand</td>
<td>Xyntha</td>
<td>Every other day</td>
<td>IV</td>
<td>Home</td>
<td>Patient self-infuses</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------</td>
<td>----------------</td>
<td>----</td>
<td>------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Prophylaxis, plus on-demand</td>
<td>Advate</td>
<td>Three times each week</td>
<td>IV via Mediport</td>
<td>Home</td>
<td>Parent infuses the patient</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Benefix and Amicar</td>
<td>Every other day</td>
<td>IV</td>
<td>Home</td>
<td>The patient, his parents, and his siblings all take turns infusing</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Alphanate</td>
<td>Every day</td>
<td>IV via Mediport</td>
<td>Home</td>
<td>Parent infuses the patient</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Eloctate</td>
<td>Two times each week</td>
<td>IV</td>
<td>Home</td>
<td>Patient self-infuses</td>
</tr>
<tr>
<td>On-demand</td>
<td>Benefix</td>
<td>Once each year</td>
<td>IV</td>
<td>Home</td>
<td>Patient attempts to self-infuse, but goes to urgent care if cannot self-infuse</td>
</tr>
<tr>
<td>Prophylaxis, plus on-demand</td>
<td>Eloctate</td>
<td>Two times each week</td>
<td>IV</td>
<td>Home</td>
<td>Patient self-infuses</td>
</tr>
<tr>
<td>Prophylaxis, plus on-demand</td>
<td>Benefix and Amicar</td>
<td>Two times each week</td>
<td>IV</td>
<td>Home</td>
<td>Patient self-infuses</td>
</tr>
<tr>
<td>On-demand</td>
<td>Ruxubus</td>
<td>Once every other month</td>
<td>IV</td>
<td>Home</td>
<td>Patient self-infuses</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Sulfoxaprim SS</td>
<td>Every day or every other day</td>
<td>IV</td>
<td>Health office at high school or at home</td>
<td>Patient self-infuses</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Ixinity</td>
<td>Two times each week</td>
<td>IV</td>
<td>Mostly home, sometimes in other locations such as on a plane or at a friend’s house</td>
<td>Patient self-infuses</td>
</tr>
</tbody>
</table>
Participant is a football player and infuses every day during football season. Otherwise, infusions occur every other day.

Note: Each row corresponds to one phone interview participant’s response in the UL Wiklund user assessment. A participant in the phone interview is either a hemophilia patient or a caregiver of a hemophiliac.
Table 10. Treatment Regimen of Focus Group Participants

<table>
<thead>
<tr>
<th>Type of hemophilia</th>
<th>Severity of hemophilia</th>
<th>Treatment type</th>
<th>Medication</th>
<th>Treatment frequency</th>
<th>Delivery Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Severe</td>
<td>Prophylaxis</td>
<td>Advate</td>
<td>Three times each week</td>
<td>IV</td>
</tr>
<tr>
<td>B</td>
<td>Severe</td>
<td>Prophylaxis</td>
<td>Benefix</td>
<td>Three times each week</td>
<td>IV</td>
</tr>
<tr>
<td>A</td>
<td>Mild</td>
<td>On-demand</td>
<td>Novo8</td>
<td>Two – three times ever</td>
<td>IV</td>
</tr>
<tr>
<td>A</td>
<td>Severe</td>
<td>Prophylaxis</td>
<td>Advate</td>
<td>Every other day</td>
<td>IV</td>
</tr>
<tr>
<td>B</td>
<td>Severe</td>
<td>Prophylaxis</td>
<td>Idelvion</td>
<td>Once each week</td>
<td>IV</td>
</tr>
<tr>
<td>B</td>
<td>Severe</td>
<td>Prophylaxis</td>
<td>Mono9, Benefix</td>
<td>Once each week</td>
<td>IV</td>
</tr>
<tr>
<td>A</td>
<td>Severe</td>
<td>Prophylaxis</td>
<td>Advate</td>
<td>Two – three times each week</td>
<td>IV</td>
</tr>
<tr>
<td>A</td>
<td>Severe</td>
<td>On-demand</td>
<td>Advate</td>
<td>Once every other week</td>
<td>IV</td>
</tr>
<tr>
<td>A</td>
<td>Moderate</td>
<td>Prophylaxis</td>
<td>Advate</td>
<td>Two – three times each week</td>
<td>IV</td>
</tr>
<tr>
<td>A²</td>
<td>Severe</td>
<td>Prophylaxis</td>
<td>Advate</td>
<td>Two – three times each week</td>
<td>IV</td>
</tr>
</tbody>
</table>

² This patient did not participate in the focus group. Her mother joined as a caregiver participant.

Note Each row corresponds to one phone interview participant’s response in the UL Wiklund user assessment. A participant in the phone interview is either a hemophilia patient or a caregiver of a hemophiliac patient.
<table>
<thead>
<tr>
<th>Steps of Effect</th>
<th>Potential Failure</th>
<th>Hazard</th>
<th>Potential Harm From Hazard</th>
<th>Severity (1-5)</th>
<th>Potential Causes of Failure Mode</th>
<th>Occurrence (1-5)</th>
<th>Risk Mitigation</th>
<th>Planned Risk Control Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clean injection site</td>
<td>User does not/improperly cleans injection site</td>
<td>Contamination</td>
<td>Mild (subcutaneous injection)</td>
<td>2</td>
<td>Inadequate IFU labeling</td>
<td>3</td>
<td>MED</td>
<td>Alcohol wipe to be included with sellable unit. Provide instructions on cleaning injection site.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mild allergic reaction</td>
<td>2</td>
<td>Inadequate IFU labeling</td>
<td>2</td>
<td>MED</td>
<td>Alcohol wipe to be included with sellable unit. Provide instructions on cleaning injection site.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe allergic reaction</td>
<td>4</td>
<td>Inadequate IFU labeling</td>
<td>2</td>
<td>HIGH</td>
<td>Alcohol wipe to be included with sellable unit. Provide instructions on cleaning injection site.</td>
</tr>
<tr>
<td>Step of Effect</td>
<td>Severity Score</td>
<td>Occurrence Score</td>
<td>Risk Priority Number</td>
<td>IFU Labeling</td>
<td>Harm Mitigation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>---------------</td>
<td>------------------</td>
<td>----------------------</td>
<td>--------------</td>
<td>-----------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe injection site reaction</td>
<td>5</td>
<td>2</td>
<td>HIGH</td>
<td>Inadequate IFU labeling</td>
<td>Alcohol wipe to be included with sellable unit. Provide instructions on cleaning injection site.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe infection</td>
<td>4</td>
<td>2</td>
<td>HIGH</td>
<td>Inadequate IFU labeling</td>
<td>Alcohol wipe to be included with sellable unit. Provide instructions on cleaning injection site.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: This is an example of a FMEA table describing a potential hazard in which a patient using an autoinjection device could encounter. The “Step of Effect” is the procedure in which the patient is expected to do and the potential of failure of the step is listed in the next column. The severity of the harm ranges from a score of 1 to 5 (1, as the least severe and 5 as the most severe). The occurrence score, ranging from 1 - 5, is based off the probability of the harm occurring (1, as the least probable and 5, as the most probable). IFU = Instructions For Use.
References


from Prospective Clinical Trials. *Haemophilia, 21*(5), e344-e358. doi:10.1111/hae.12759


