

Product Snapshot

Pipeline

SB-525 (giroctocogene fitelparvovec)

Provided to you by FormularyDecisions

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Product Overview

Manufacturer	Pfizer Inc. and Sangamo Therapeutics, Inc.
Status	<ul style="list-style-type: none">• No PDUFA date at this time• Fast Track status: 5/16/2017; Orphan Drug designation: 5/3/2017; Regenerative Medicine Advanced Therapy designation: 7/5/2019
Proposed indication	Hemophilia A
Therapeutic class	Gene therapy
Mechanism of action	<ul style="list-style-type: none">• SB-525 comprises a recombinant AAV6 encoding the complementary deoxyribonucleic acid for B domain deleted human Factor VIII to optimize both the vector manufacturing yield and liver-specific Factor VIII protein expression¹<ul style="list-style-type: none">○ The SB-525 transcriptional cassette incorporates multi-factorial modifications to the liver-specific promoter module, Factor VIII transgene, synthetic polyadenylation signal, and vector backbone sequence• SB-525 aids in the correction of the disease-causing mutation in the endogenous copy of the Factor VIII gene

Formulation	Solution for injection																
Dose and administration	<ul style="list-style-type: none"> • Dosing: 9e11 vg/kg to 3e13 vg/kg have been studied¹ • Route of administration: IV infusion¹ • Setting of administration: Not yet determined 																
Epidemiology of disease	<ul style="list-style-type: none"> • Incidence: In 2015, about 1/5,000 to 1/6,000 people (approximately 400 babies) in the US were born with hemophilia A (based on 2015 NORD data and 2016 CDC data)^{2,3} • Prevalence: In 2016, there was an estimated 20,000 people in the US with hemophilia (based on 2016 CDC data); however, the exact number of people living with hemophilia A in the US is unknown³ 																
Relevant ICD-10-CM code	D66 (hereditary Factor VIII deficiency)																
Distinguishing factors of product	<ul style="list-style-type: none"> • Unique MOA: Designed to deliver a copy of the Factor VIII gene to a patient's liver cell to induce Factor VIII expression and thus raise Factor VIII levels¹ • Study results have shown that SB-525 can safely induce durable clotting Factor VIII activity in patients with severe hemophilia A as demonstrated in the phase 1/2 Alta clinical trial¹ 																
Relevant disease background and treatment guidelines	<ul style="list-style-type: none"> • Hemophilia is a hereditary bleeding disorder characterized by an underlying defect in the ability to generate adequate levels of thrombin needed for effective clotting, such as a deficiency in coagulation FVIII (hemophilia A) or coagulation FIX (hemophilia B)⁴ • Prophylaxis is the standard of care for people with severe hemophilia and for some with moderate hemophilia⁵ • Prophylaxis with CFCs is always recommended over episodic therapy and should be individualized, taking into account patient bleeding phenotype, joint status, individual pharmacokinetics, and patient preference⁵ • Management of acute bleeding necessitates CFC replacement therapy and should be carried out in consultation with a hemophilia treatment center and staff experienced in inhibitor treatment⁵ • <u>World Federation of Hemophilia: Guidelines for the Management of Hemophilia (3rd Edition, August 2020)</u>⁵ 																
Competitive landscape	<ul style="list-style-type: none"> • FDA-approved agents for the treatment of hemophilia A include HEMLIBRA® (emicizumab-kxwh), NOVOEIGHT® (antihemophilic factor, recombinant), and XYNTHA® (antihemophilic factor [recombinant]); this list is not all-inclusive⁶⁻⁸ • Investigational agents <table border="1"> <tr> <td></td> <td>BMN-270^{9,10} (valoctocogene roxaparvovec)</td> <td>SAR-439774¹¹ (fitusiran)</td> </tr> <tr> <td>Manufacturer</td> <td>BioMarin Pharmaceutical Inc</td> <td>Sanofi</td> </tr> <tr> <td>Mechanism of action</td> <td>Gene therapy</td> <td>siRNA</td> </tr> <tr> <td>Phase of development</td> <td>BLA resubmission expected Q2 2022</td> <td>3</td> </tr> <tr> <td>PDUFA</td> <td>Unknown</td> <td>Unknown</td> </tr> </table>			BMN-270 ^{9,10} (valoctocogene roxaparvovec)	SAR-439774 ¹¹ (fitusiran)	Manufacturer	BioMarin Pharmaceutical Inc	Sanofi	Mechanism of action	Gene therapy	siRNA	Phase of development	BLA resubmission expected Q2 2022	3	PDUFA	Unknown	Unknown
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PDUFA	Unknown	Unknown															

Key: AAV6 – adeno-associated virus serotype 6 vector; BLA – Biologics License Application; CDC – Centers for Disease Control and Prevention; CFC – clotting factor concentrate; FVIII – Factor VIII; IV – intravenous; MOA – mechanism of action; NORD – National Organization for Rare Disorders; PDUFA – Prescription Drug User Fee Act; siRNA – small interfering ribonucleic acid.

Key Comparators

	SB-525 (griectocogene fitelparvovec) ¹	NOVOEIGHT (antihemophilic factor, recombinant) ⁶	XYNTHA (antihemophilic factor [recombinant]) ⁷	HEMLIBRA (emicizumab-kxwh) ⁸
Manufacturer	Pfizer Inc. and Sangamo Therapeutics, Inc.	Novo Nordisk Inc.	Wyeth Pharmaceuticals	Genentech, Inc.
Indications	Proposed indication: Severe hemophilia A	Adults and children with hemophilia A for: On-demand treatment and control of bleeding episodes Perioperative management Routine prophylaxis to reduce frequency of bleeding episodes	Adults and children with hemophilia A for: Control and prevention of bleeding episodes and for perioperative management	Adults and children with hemophilia A for: Routine prophylaxis to prevent or reduce frequency of bleeding episodes
Dosing	Route: IV injection Dosages studied ranged from 9e11 vg/kg to 3e13 vg/kg	IV injection Dosage required (IU) = body weight (kg) x desired Factor VIII increase (IU/dL or % normal) x 0.5 (IU/kg per IU/dL) Frequency determined by type of bleeding episode and recommendation of treating physician	Route: IV injection Dose: Required units = body weight (kg) x desired Factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL) Frequency of administration is determined by type of bleeding episode and recommendation of treating physician	3 mg/kg SC once weekly for the first 4 weeks, followed by one of the following: 1.5 mg/kg once weekly 3 mg/kg once every 2 weeks 6 mg/kg once every 4 weeks
Available or anticipated pricing¹²	TBD	AWP: \$2.40 WAC: \$2.00 (1 IU)	AWP: \$1.91 WAC: \$1.59 (1 IU)	AWP: \$18,948.01 WAC: \$15,790.01 150 mg/mL (1 mL SOL)

Key: AWP – average wholesale price; SC – subcutaneous; SOL – solution; TBD – to be determined; WAC – wholesale acquisition cost.

Clinical Trials

High-level overview:

- The SB-525 clinical development program consists of an open-label, adaptive, and dose-ranging phase 1/2 study for hemophilia A, an open-label, lead-in study for hemophilia A and B, and a phase 3 pivotal AFFINE trial evaluating SB-525 in adult male participants with moderately severe or severe hemophilia A¹³⁻¹⁶
- Initial results of the Alta study demonstrate that SB-525 has the potential to be a predictable and reliable treatment that may bring clinical benefit to patients with hemophilia A
 - SB-525 was generally well tolerated and demonstrated a dose-dependent increase in Factor VIII activity levels

NCT / Study ID	Study description	Study population	Phase, study design, sample size	Status	Highlights
NCT03061201 ¹⁴ ALTA	Open-label, adaptive, dose-ranging study assessing the safety and tolerability of SB-	<ul style="list-style-type: none"> Inclusion: Males aged ≥18 years diagnosed with severe hemophilia A treated or exposed to Factor VIII 	Phase 1/2, OL N=11 (actual)	<ul style="list-style-type: none"> Active, not recruiting Estimated study completion date: July 23, 2024 	<ul style="list-style-type: none"> All patients (N=4) treated with the SB-525 dose of 3e13 vg/kg did not experience any

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	525 in patients with severe hemophilia A	<p>concentrates or cryoprecipitate for at least 150 EDs; ≥12 bleeding episodes if receiving on-demand therapy over preceding 12 months</p> <ul style="list-style-type: none"> Exclusion: Presence of neutralizing antibodies; evidence of any bleeding disorder in addition to hemophilia A; markers of hepatic inflammation or acute kidney injury 		<ul style="list-style-type: none"> Initial results presented in 2019¹⁷ 	<p>spontaneous bleeding episodes ≥3 weeks post-treatment and did not require Factor VIII replacement therapy following initial prophylactic period post-SB-525 administration¹⁷</p> <ul style="list-style-type: none"> SB-525 showed dose-dependent increases in Factor VIII activity levels across all dose cohorts evaluated¹⁷ SB-525 was generally well tolerated, with treatment-related significant AEs of hypotension (grade 3, N=1) and fever (grade 2, N=3) only occurring in patients on the 3e13 vg/kg dose, which resolved with treatment within 24 hours¹⁷ At 104 weeks, 5 patients in the highest dose 3e13 vg/kg cohort had mean Factor VIII activity of 25.4% via chromogenic clotting assay¹⁸ The mean ABR through 1 year post-infusion was 0 and was 1.4 through the total duration of follow-up as of the October 1, 2021 cutoff date; all bleeding events occurred after 69 weeks post-infusion¹⁸

NCT / Study ID	Study description	Study population	Phase, study design, sample size	Status	Highlights
NCT03587116 ¹⁵	Open-label, multicenter, lead-in study to assess the efficacy and safety of SB-525 in patients with hemophilia A or B	<ul style="list-style-type: none"> • Inclusion: Males aged ≥18 and <65 years diagnosed with severe hemophilia A or B; previous experience with Factor IX or VIII therapy; no known hypersensitivity to Factor IX or VIII replacement product • Exclusion: Anti-AAV-Spark100 neutralizing antibody titer above or equal to 1:1 in hemophilia B patients or Anti-SB-525 capsid AAV6 neutralizing antibody titer (above or equal to lowest detectable titer) in hemophilia A patients; diagnosis of hepatitis B or C; currently on antiviral therapy for hepatitis B or C; pre-existing diagnoses of portal hypertension, splenomegaly, or hepatic encephalopathy; diagnosis of HIV; history of chronic infection; previously on fidanacogene elaparvec, SB-525, or any AAV gene-based therapy; planned procedure requiring Factor IX or VIII surgical prophylactic factor treatment in next 24 hours 	Phase 3, OL, MC N=250 (estimated)	<ul style="list-style-type: none"> • Recruiting • Estimated study completion date: May 14, 2023 	<ul style="list-style-type: none"> • Primary endpoints include ABR and incidence of serious AEs • Events of special interest include inhibitor against Factor IX or VIII, thrombotic events, and Factor IX or VIII hypersensitivity reactions
NCT04370054 ^{16,18} AFFINE	Open-label, multicenter, pivotal study to evaluate the efficacy and safety of giroctocogene fitelparvec in adult male participants with moderately severe or severe hemophilia A for	<ul style="list-style-type: none"> • Inclusion: Males who have been followed on routine Factor VIII prophylaxis therapy during the lead-in study and have ≥150 documented EDs to a Factor VIII protein product; moderately severe to severe hemophilia A; suspension of 	Phase 3, OL, MC N=63 (estimated)	<ul style="list-style-type: none"> • Active, not recruiting • Estimated study completion date: September 16, 2027 	<ul style="list-style-type: none"> • Primary endpoint is the ABR¹⁶ • Events of special interest include Factor VIII activity levels, annualized infusion rate, annualized Factor VIII consumption, change in

NCT / Study ID	Study description	Study population	Phase, study design, sample size	Status	Highlights
	the study duration of 5 years	Factor VIII prophylaxis therapy post-study drug infusion <ul style="list-style-type: none"> Exclusion: Anti-AAV6 neutralizing antibodies; history of inhibitor to Factor VIII; laboratory values at screening visit that are abnormal or outside acceptable study limits; significant and/or unstable liver disease, biliary disease, or significant liver fibrosis; planned surgical procedure requiring Factor VIII prophylactic factor treatment 12 months from screening visit; active hepatitis B or C; serological evidence of HIV-1 or HIV-2 with CD4+ cell count ≤ 200 mm³ and/or viral load >20 copies/mL 			joint health, patient-reported outcome instruments, and incidence and severity of AEs ¹⁶

Key: AAV – adeno-associated viral; AAV6 – adeno-associated virus serotype 6 vector; ABR – annual bleeding rate; AE – adverse event; CD4+ – cluster of differentiation 4 positive; ED – exposure day; MC – multicenter; N – sample size; NCT / Study ID – National Clinical Trial / study identifier; OL – open-label.

P&T Considerations

Factors affecting uptake	<ul style="list-style-type: none">• Giroctocogene fitelparvovec would be the first or second gene therapy FDA approved for hemophilia A, depending on the regulatory path for valoctocogene roxaparvovec• No information on drug cost is available
Formulary criteria	Potential prior authorization criteria for consideration: <ul style="list-style-type: none">• Diagnosis of severe hemophilia A• Aged ≥12 years• Male gender• Prescriber is a hematologist• Previous trial of factor concentrates or bypassing agents• No previous receipt of gene therapy for hemophilia A• Appropriate dosing
Contracting	Payers may consider entering into a value-based outcome agreement with the manufacturer; possible outcomes may include ABR over a set number of months or years

Key: ABR – annual bleeding rate; FDA – Food and Drug Administration.

References

Citations	<ol style="list-style-type: none">1. Sangamo Therapeutics. A phase 1/2, open-label, adaptive, dose-ranging study to assess the safety and tolerability of SB-525 (recombinant AAV2/6 human Factor 8 gene therapy) in adult subjects with severe hemophilia A. NLM identifier: NCT03061201. Accessed December 23, 2019. https://clinicaltrials.gov/ct2/show/study/NCT030612012. Rare Disease Database. Hemophilia A. Accessed December 23, 2019. https://rarediseases.org/rare-diseases/hemophilia-a/3. Centers for Disease Control and Prevention. Data and statistics on hemophilia. June 21, 2019. Accessed December 23, 2019. http://www.cdc.gov/ncbddd/hemophilia/data.html4. Centers for Disease Control and Prevention. What is hemophilia? Accessed December 21, 2021. https://www.cdc.gov/ncbddd/hemophilia/facts.html5. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia, 3rd edition [published correction appears in <i>Haemophilia</i>. 2021 Jul;27(4):699]. <i>Haemophilia</i>. 2020;26 Suppl 6:1-158. doi:10.1111/hae.140466. Novoeight prescribing information. Plainsboro, NJ: Novo Nordisk Inc.; 2020.7. Xyntha prescribing information. Philadelphia, PA: Wyeth Pharmaceuticals LLC; 2021.8. Hemlibra prescribing information. South San Francisco, CA: Genentech, Inc; 2022.9. BioMarin Pharmaceutical Inc. BioMarin announces second quarter 2021 financial results and corporate updates. July 28, 2021. Accessed May 5, 2022. https://investors.biopharm.com/2021-07-28-BioMarin-Announces-Second-Quarter-2021-Financial-Results-and-Corporate-Updates
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