

Product Snapshot

Pipeline

SB-525 (giroctocogene fitelparvovec)

Provided to you by FormularyDecisions

Last updated 06/16/2022

Prepared by Warren Smith, PharmD

Clinical Consultant Pharmacist

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 	

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 (giroctocogene 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

NCT / Study ID	Study description	Study population	Phase, study design, sample size	Status	Highlights
	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	<p>Factor VIII prophylaxis therapy post-study drug infusion</p> <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 $\leq 200 \text{ mm}^3$ and/or viral load $> 20 \text{ copies/mL}$ 			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	<p>Potential prior authorization criteria for consideration:</p> <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/NCT03061201 2. 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.html 4. Centers for Disease Control and Prevention. What is hemophilia? Accessed December 21, 2021. https://www.cdc.gov/ncbddd/hemophilia/facts.html 5. 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.14046 6. 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
------------------	---

**Request
additional
information**

10. Pasi KJ, Rangarajan S, Kim B, et al. Achievement of normal circulating Factor VIII activity following BMN 270 AAV5-FVIII gene transfer: interim, long-term efficacy and safety results from a phase 1/2 study in patients with severe hemophilia A [abstract #603]. Presented at: 2017 American Society of Hematology Annual Meeting; December 11, 2017; Atlanta, GA.
11. Pasi KJ, Rangarajan S, Georgiev P, et al. Targeting of antithrombin in hemophilia A or B with RNAi therapy. *New Engl J Med*. 2017;377:819-828.
12. Red Book Online® [online database]. Greenwood Village, CO: IBM Watson Health. Accessed June 16, 2022.
13. Hemophilia News Today. SB-525 for hemophilia A. Accessed March 12, 2020. <https://hemophilianewstoday.com/sb-525/>
14. Pfizer. Dose-ranging study of recombinant AAV2/6 human Factor 8 gene therapy SB-525 in subjects with severe hemophilia A. NLM identifier: NCT03061201. Accessed March 12, 2020. <https://clinicaltrials.gov/ct2/show/study/NCT03061201>
15. Pfizer. Six month lead-in study to evaluate prospective efficacy and safety data of current FIX prophylaxis replacement therapy in adult hemophilia B subjects (FIX:C≤2%) or current FVIII prophylaxis replacement therapy in adult hemophilia A subjects (FIX:C≤1%). NLM identifier: NCT03587116. Accessed March 12, 2020. <https://clinicaltrials.gov/ct2/show/NCT03587116>
16. Pfizer. Study to evaluate the efficacy and safety of PF-07055480/girotocogene fitelparvovec gene therapy in moderately severe to severe hemophilia A adults (AFFINE). NLM identifier: NCT04370054. Accessed December 21, 2021. <https://clinicaltrials.gov/ct2/show/NCT04370054>
17. Konkle BA, Stine K, Visweshwar N, et al. Initial results of the Alta study, a phase 1/2, open label, adaptive, dose-ranging study to assess the safety and tolerability of SB-525 gene therapy in adult subjects with hemophilia A. Lecture presented at: International Society on Thrombosis and Haemostasis; July 6, 2019; Melbourne, Australia.
18. Pfizer Inc. and Sangamo Therapeutics, Inc. Pfizer and Sangamo announce updated phase 1/2 results showing sustained bleeding control in highest dose cohort through two years following hemophilia A gene therapy. December 12, 2021. Accessed December 21, 2021. <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-sangamo-announce-updated-phase-12-results-1>

⇒ Please use the [eRequest Tool](#) to submit a request to the manufacturer.

⇒ Please contact us at clinicalpharmacy@umassmed.edu for questions about this Product Snapshot.