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HEALTH TECHNOLOGY BRIEFING OCTOBER 2021

Fidanacogene elaparvovec for haemophilia B

NIHRIO ID	11967	**NICE ID**	9770
Developer/Company	Pfizer Limited, Spark Therapeutics Inc,	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Fidanacogene elaparvovec in development for the treatment of moderately severe or severe haemophilia B in adult males. Haemophilia B is a hereditary bleeding disorder that results in the blood taking longer to clot than normal. The disorder is caused by having a faulty version of the F9 gene. The F9 gene provides instructions for making a protein called coagulation factor IX which is released following injury to a blood vessel to form a clot and prevent further blood loss. A faulty F9 gene results in insufficient production of functional clotting factor protein IX. In severe cases, this can result in spontaneous bleeding into the joints, muscles or brain causing serious complications.

Fidanacogene elaparvovec is a medicinal product administered intravenously. Fidanacogene elaparvovec is a gene therapy that delivers a copy of the gene that encodes for factor IX in a patient's liver cells. Through this, this medicinal product helps to maintain a sustained level factor IX in the blood of adult male with haemophilia B. If licensed, Fidanacogene elaparvovec will offer an additional treatment option for adult males with moderately severe or severe haemophilia B.

PROPOSED INDICATION

For the treatment adult men with the moderately severe to severe haemophilia B.[1-3]

TECHNOLOGY

DESCRIPTION

Fidanacogene elaparvovec (SPK-9001, PF-06838435[4]) is a novel, investigational bio-engineered single-stranded adeno-associated virus (AAV) capsid expressing a high-activity codon-optimized human factor IX variant. It enables endogenous production of factor IX in men with haemophilia B who have low or no factor IX coagulant activity.[5,6]

Fidanacogene elaparvovec is currently in phase II and phase III clinical development for the treatment of adult males with moderately severe or severe haemophilia B. In phase II and phase III clinical trials respectively (NCT03861273 (BENEGENE-2), NCT02484092, NCT03307980) participants will receive a single intravenous infusion.[2,3]

INNOVATION AND/OR ADVANTAGES

Fidanacogene elaparvovec is a novel gene therapy a single-stranded adeno-associated viral (AAV) vector consisting of a bioengineered capsid, liver-specific promoter and factor IX Padua (factor IX–R338L) transgene.[5] Fidanacogene elaparvovec is a gene therapy candidate designed to deliver a healthy copy of the gene encoding for factor IX to the patient's liver cells where the clotting factors are made. Fidanacogene elaparvovec uses a genetically modified adeno-associated virus (AAV) to deliver the transgene to the body. Once delivered to the liver cells, Fidanacogene elaparvovec helps maintain a constant and sustained level of factor IX in the blood of haemophilia B patients.[7] The standard of care for patients with severe and moderately severe haemophilia B is routine prophylaxis. Despite the use of prophylaxis, patients with haemophilia often incur breakthrough bleeding, annualized bleed rates of 2.6 to 4.6, resulting in gradual progression of joint disease over a lifespan has been reported.[8,9] The need for frequent infusions with current therapies may be a barrier for compliance and adherence. And poorer adherence has been significantly associated with an increased risk of breakthrough bleeding episodes and increased target joint bleeds.[10]

Preliminary clinical trials have shown promising results as participants who have been administered fidanacogene elaparvovec have shown significant reduction in bleeding with 99% of them ceasing factor IX infusions. No non-surgical serious adverse side effects from the treatment have been reported.[5,7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Fidanacogene elaparvovec does not currently have Marketing Authorisation in the EU/UK for any indication.

Fidanacogene elaparvovec has the following regulatory designations/awards:

- An orphan drug in the EU in 2018 for the treatment of haemophilia B[11]
- A PRIME status for the treatment of haemophilia B by the EMA in November 2018[12]

PATIENT GROUP

DISEASE BACKGROUND

Haemophilia is a rare condition that affects the blood's ability to clot. It is usually inherited and most people who have it are male. Normally when people cut themselves, substances in the blood known as clotting factors combine with blood cells called platelets to make the blood sticky and stop the bleeding. People with haemophilia do not have as many clotting factors as there should be in the blood so they bleed for longer than usual.[13] In haemophilia B, affected individuals have insufficient levels of a blood protein called clotting factor IX due to a mutation in the F9 gene on the X chromosome.[14]

The main symptom of haemophilia is prolonged bleeding. The symptoms of haemophilia can be mild to severe depending on the level of clotting factors a patient has. Individuals with mild haemophilia have factor IX levels between 5% and 40% of normal; those with moderate haemophilia have levels between 1% and 5% of normal; and individuals with severe haemophilia have factor levels less than 1% of normal.[13,14] Patients with severe haemophilia disease experience frequent spontaneous bleeding episodes often into their joints and muscles and long-term related complications such as osteoporosis.[15] These spontaneous episodes are usually incited by injury or trauma and if left untreated can lead to serious complications in the patient.[14]

CLINICAL NEED AND BURDEN OF DISEASE

The prevalence of haemophilia B (deficiency of factor IX) is estimated to be between 1:35,000 and 1:50,000 males.[16] In England, In 2020-21, there were 326 finished consultant episodes (FCE) for hereditary factor IX deficiency (ICD-10 code D67) resulting in 321 admissions and 121 FCE bed days.[17]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The recommended treatment plan for haemophilia is dependent on the severity of the condition. There are two main types of treatment: preventative treatment and on-demand treatment. Preventative treatment for people with haemophilia B involves recommended injections of nonacog alfa administered twice weekly and Factor IX replacement whereas, on-demand treatment for haemophilia B usually involves injections of nonacog alfa.[18]

CURRENT TREATMENT OPTIONS

For adult men with haemophilia B NHS recommends:[18]

- Preventative treatment: Injections of nonacog alfa twice weekly
- On-demand treatment: Injections of nonacog alfa

PLACE OF TECHNOLOGY

If licensed fidanacogene elaparvovec will offer an additional treatment option for adult male patients with moderately severe to severe haemophilia B.

CLINICAL TRIAL INFORMATION

Trial	**BENEGENE-2; NCT03861273; 2018-003086-33; Phase 3, Open Label, Single Arm Study To Evaluate Efficacy And Safety Of FIX Gene Transfer With PF-06838435 (RAAV-SPARK100-HFIX-PADUA) In Adult Male Participants With Moderately Severe To Severe Hemophilia B (FIX:C <=2%) (Benegene-2)** **Phase III-Recruiting** **Location(s): EU ,UK, USA, Canada and other countries** **Primary completion date: November 2022**
Trial design	Non-randomised, open-label and sequential assignment
Population	n=55 (planned); 18 years and older male with a confirmed diagnosis of moderately severe to severe haemophilia B (Factor IX activity <=2%), who completed 6 months of routine Factor IX prophylaxis therapy during the lead-in study (C0371004/NCT03587116) prior to providing consent at the screening visit for this study; suspension of prophylaxis therapy for haemophilia B after administration of the study drug; agree to contraception until components of the drug are eliminated from their body; laboratory values (hemoglobin, platelets and creatinine) within study specified limits
Intervention(s)	Participants will receive PF-06838435/fidanacogene elaparvovec
Comparator(s)	-
Outcome(s)	- Annualized bleeding rate (ABR) [Time Frame: First 12 months post PF 06838435 infusion] - Vector derived FIX:C level [Time Frame: Week 12 to 12 months post PF 06838435 infusion] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT02484092; **Gene Therapy, Open-label, Dose-escalation Study of PF-06838435 (SPK-9001) [Adeno-associated Viral Vector With Human Factor IX Gene] in Subjects With Hemophilia B** **Phase II**-Completed **Locations:** USA and Australia **Study completion date:** April 2019
Trial design	Open-label and sequential assignment
Population	n= 15 (actual); 18 years and older male with a confirmed diagnosis of haemophilia B (≤2 IU/dL or ≤2% endogenous factor IX), have received ≥50 exposure days to factor IX products, a minimum average of 4 bleeding events per year requiring episodic treatment of factor IX infusions or prophylactic factor IX infusions, no measurable factor IX inhibitor as assessed by the central laboratory and have no prior history of inhibitors to factor IX protein, and who have

	agreed to use reliable barrier contraception until 3 consecutive samples are negative for vector sequences
Intervention(s)	Participants received fidanacogene elaparvovec, as a single intravenous infusion
Comparator(s)	-
Outcome(s)	- Number of participants with clinically significant change from baseline in physical examination findings [Time Frame: Baseline up to week 52] - Number of participants with clinically significant change from baseline in vital signs [Time Frame: Baseline up to Week 52] - Number of participants with clinical laboratory abnormalities reported as TEAE [Time Frame: Baseline up to Week 52] - Number of participants with drug-related TEAE's and serious adverse events (SAE's) [Time Frame: Baseline up to week 52] - Number of participants with positive immune responses against adeno-associated virus vector (AAV) capsid [Time Frame: Baseline up to week 52] - Number of participants who reached >150% vector-derived FIX:C activity level after SPK-9001 infusion [Time Frame: Baseline up to week 52] - Number of participants with FIX inhibitor [Time Frame: Baseline up to week 52] - Incremental recovery of FIX product [Time Frame: Day 0 and week 52] - See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**NCT03307980; A Factor IX (FIX) Gene Transfer, Multi Center Evaluation Of The Long Term Safety And Efficacy Study Of Pf 06838435 And A Dose Escalation Substudy In Individuals With Hemophilia B** **Phase II-Recruiting** **Location(s): USA and Australia** **Primary completion date: May 2028**
Trial design	Open-label and sequential assignment
Population	n=55 (planned); 18 years and older male with a confirmed diagnosis of hemophilia B (≤2 IU/dL or ≤2% endogenous factor IX); able to provide informed consent and comply with requirements of the study; received ≥50 exposure days to factor IX products; no measurable factor IX inhibitor as assessed by the central laboratory and have no prior history of inhibitors to factor IX protein; agree to refrain from donating sperm and either abstain from intercourse or use reliable barrier contraception until 3 consecutive semen samples are negative for vector sequences.
Intervention(s)	Participants will receive fidanacogene elaparvovec, as a single intravenous infusion

Comparator(s)	-
Outcome(s)	- Number of participants with clinically significant changes from baseline in physical examination [Time Frame: Baseline up to 52 weeks] - Number of participants with clinically significant changes from baseline in vital signs [Time Frame: Baseline up to 52 weeks] - Number of participants with clinically significant changes from baseline in laboratory values [Time Frame: Baseline up to 52 weeks] - Number of participants with PF-06838435-related adverse events [Time Frame: Baseline up to 52 weeks] - Immune response against AAV capsid protein and hFIX transgene [Time Frame: Baseline up to 52 weeks] - Number of participants PF-06838435-related elevated hepatic transaminases that fail to improve or resolve [Time Frame: Baseline up to 52 weeks] - Number of participants with clinical thrombotic events [Time Frame: Baseline up to 52 weeks] - Number of participants with FIX inhibitor development [Time Frame: Baseline up to 52 weeks] - Number of participants with hypersensitivity reaction [Time Frame: Baseline up to 52 weeks] - Number of participants with hepatic malignancy [Time Frame: Baseline up to 52 weeks] - Number of participants with PF-06838435-related malignancy [Time Frame: Baseline up to 52 weeks] - Number of participants with PF-06838435-related adverse advents [Time Frame: Year 2 through Year 6] - See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of fidanacogene elaparvovec is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Clinical guideline. Etranacogene dezaparvovec for treating haemophilia B (ID3812). Expected publication date to be confirmed
- NICE Clinical guideline. Valoctocogene roxaparvovec for treating severe haemophilia A (ID3806). Expected publication date to be confirmed.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Haemophilia (All Ages). B05/S/a.

OTHER GUIDANCE

- The Official Journal of the World Federation of Hemophilia. WFH Guidelines for the Management of Hemophilia, 3rd edition. 2020.[19]
- United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO). Clinical Genetic Services for Haemophilia. 2018.[20]
- United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO). Guidelines for the management of acute joint bleeds and chronic synovitis in haemophilia. 2017.[21]
- British Medical Journal (BMJ). Diagnosis and Management of Haemophilia. 2012.[22]

ADDITIONAL INFORMATION

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