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HEALTH TECHNOLOGY BRIEFING
APRIL 2020

Valoctocogene Roxaparvovec for Severe Haemophilia A

NIHRIO ID	20417	**NICE ID**	9791
Developer/Company	BioMarin Pharmaceutical Inc.	**UKPS ID**	N/A

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Valoctocogene roxaparvovec is in development for the treatment of adult with severe haemophilia A. Haemophilia A is a rare bleeding disorder, whereby the blood does not clot properly due to the lack of or dysfunction of factor VIII clotting protein. In severe haemophilia A, this causes frequent spontaneous bleeding, including in muscles and joints. The inability of their blood to clot means that patients are at high risk of internal bleeding, including from the brain, increasing their mortality risk.

Valoctocogene roxaparvovec is a gene therapy; it can modify the genes (functional units of heredity) of individuals with haemophilia A so that they can produce the clotting protein needed to allow the blood to clot. If licensed, valoctocogene roxaparvovec would be the first gene therapy for severe haemophilia A. Valoctocogene roxaparvovec administered as a single treatment would be sufficient to maintain normal levels of factor VIII in adult males with severe haemophilia A, and might reduce the need for regular factor VIII prophylaxis (preventative treatment).

PROPOSED INDICATION

Treatment of adults with severe haemophilia A (congenital factor VIII deficiency) without detectable antibodies to adeno associated virus serotype 5 (AAV5)[a]

TECHNOLOGY

DESCRIPTION

Valoctocogene roxapavovec (BMN-270) is a recombinant codon-optimised AAV5 vector that encodes a B-domain-deleted human factor VIII (AAV5-hFVIII-SQ), which is a clotting factor that is an essential part of the coagulation cascade and therefore blood clotting – with a hybrid liver-specific transcription promoter.[1] Thus, it restores factor VIII plasma concentrations to levels which are adequate for normal clotting in haemophilia A.[2]

In the phase III clinical trial (NCT03370913; BMN 270-301) patients were administered a single dose of valoctocogene roxaparvovec at a dose of 6E13vg/kg intravenously.[3]

INNOVATION AND/OR ADVANTAGES

Valoctocogene roxaparvovec is a gene therapy; currently there are no gene therapies available for patients with severe haemophilia A. A single infusion is sufficient to maintain plasma factor VIII at therapeutic levels (≥1 IU/dL) for at least three years without the need for, or only minimal use of additional on demand factor VIII in the majority of patients.[4]

In the phase I/II trial (NCT02576795), administration of valoctocogene roxaparvovec in participants with haemophilia A resulted in sustained, clinically relevant benefit, as measured by a substantial reduction in annualised rates of bleeding events and completed cessation of prophylactic factor VIII use in all participants who had received 4x1013vg per kilogram or 6x1013vg per kilogram of the gene therapy.[4]

In the UK, current treatment options for people with severe haemophilia A include prophylactic administration of factor VIII replacement, which presents a great burden for the patients and difficulties for adherences, and still does not fully prevent breakthrough bleeding events. Patients with severe Haemophilia A still experience up to six bleeding events per year in clinical practice.[5] Therefore, factor VIII replacement is still required in the event of these breakthrough bleeds.[5-7]

Valoctocogene roxaparvovec is an advanced therapy medicinal product (ATMP) based on the classification by the European Medicines Agency (EMA)[8] and will be assessed by the Committee for Advanced Therapies (CAT), which will inform the Committee for Medicinal Products for Human Use (CHMP).[a]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Valoctocogene roxaparvovec does not currently have marketing authorisation in the EU/UK for any indication.

Valoctocogene roxaparvovec was granted US Orphan Drug Designation (February 2016) and US Breakthrough Therapy (October 2017) status by the US Food and Drug Administration

[a] Information provided by BioMarin Pharmaceutical Inc

(FDA)[9] and was granted EU Orphan Drug Designation (March 2016)[10] and EU Prime Designation (February 2017) by the EMA.[9]

PATIENT GROUP

DISEASE BACKGROUND

Haemophilia A is a rare, X-lined hereditary bleeding disorder caused by blood clotting proteins either being partly or completely missing; with haemophilia A there is a deficiency of clotting factor VIII.[7,11]

Haemophilia is caused by a genetic mutation found on the X chromosome and therefore mainly affects boys and men.[12] Males only have only one X chromosome, therefore one altered copy of the gene in each cell is sufficient to cause the condition. As females have two X chromosomes, a mutation would have to occur in both copies of the gene to cause the disorder. As it is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders much more frequently than females.[13] However, women can be carriers of the affected gene and may experience symptoms.[11]

The symptoms of haemophilia A include a tendency to bruise easily; excessive bleeding from cuts; a tendency to bleed into joints and muscles (causing pain, swelling, and limitation of joint movement).[11]

Haemophilia A is classed as mild, moderate or severe, depending on the level of factor VIII in the blood.[11] With severe haemophilia, joint bleeding is more frequent and severe; in children this can cause spontaneous bleeding from the nose, gums, muscles and joints.[14] In older adults, repeated exposure to joint bleeds can result in joint arthropathy that can worsen over time and lead to chronic pain and limited function, which significantly impacts health related quality of life, and may require the patients to have hip or knee replacements.[15]

Patients with severe haemophilia A also experience a larger impact on activities of daily living compared to patients with mild and moderate haemophilia A .[16] In addition, over 70% of patients with severe haemophilia A report experiencing chronic pain, which has a significant impact on quality of life.[16] Individuals with severe haemophilia A experience poorer quality of life compared to those with mild or moderate haemophilia A.[17]

CLINICAL NEED AND BURDEN OF DISEASE

Bleeding disorders are rare and complex, with haemophilia being the most widely recognised. Of the two main types of haemophilia, haemophilia A is the most common, with a prevalence of between 1:5000 and 1:10000 in males in England.[18] Severe haemophilia A (factor VIII levels < 1% of normal levels) represents approximately 60% of cases.[19]

The prognosis for haemophilia A is favourable if therapy is administered early, and the treatment is administered as prescribed.[20] However, compared to patients with milder forms of haemophilia A, those with severe disease are prone to spontaneous bleeding, including sub-clinical bleeds. Untreated severe haemophilia A can result in 18-47 bleeds per year,[21] which can lead to significant bleeding complications, such as frequent joint bleeds or haemarthosis.[22]

Treatment guidelines recommend the use of prophylactic factor VIII treatment for individuals with severe Haemophilia A to minimise the time spent below the 1% factor VIII activity threshold, where the likelihood of experiencing spontaneous bleeding events is substantially higher.[23]

In addition, management of haemophilia A incurs a substantial economic burden in terms of both direct and indirect costs. Drug expenditure for prophylaxis make up the vast majority of direct costs.[24] In 2018-19 in England, there were 2,893 finished consultant episodes (FCE) for hereditary factor VIII deficiency (ICD-10 code D66.X) which resulted in 2,096 day cases and 2,780 FCE bed days.[25]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The treatment of haemophilia A depends on how severe the condition is. The treatment is either preventative – used to prevent bleeding – or on-demand – during an episode of prolonged bleeding. Patients with severe haemophilia A are given preventative treatment plus additional factor VIII replacement in the event of breakthrough bleeds.[15]

Multiple factor VIII replacement therapies are available in the UK as a preventative treatment for patients with haemophilia A. Octocog alfa is a preventative treatment recommended by NHS guidelines, and is an engineered version of factor VIII that is injected every 48hours.[15] Patients can develop inhibitors (antibodies) against these factor VIII injections so that they no longer have sufficient factor VIII for blood clotting.[26] If patients develop inhibitors against factor VIII replacement, they are offered emicizumab, a monoclonal antibody that bridges factor IX and X to restore factor VIII function.[6]

In addition to preventative injections, individuals with haemophilia A avoid medications that can cause blood thinning, such as non-steroidal anti-inflammatories, as well as sports that may cause a head injury.[26] Older adults with haemophilia A may have joint damage and may therefore require hip or knee replacements.[15]

CURRENT TREATMENT OPTIONS

In the UK, multiple factor VIII replacement therapies are available as preventative treatment for patients with haemophilia A. Some of these include:[27]

- Recombinants third generation: antihemophilic factor recombinants (Advate®, Kovaltry®), turoctocog alfa (Novoeight®), moroctocog alfa (ReFacto AF®)
- Recombinant fourth generation: simoctocog alfa (Nuwiq®)
- Recombinant EHL: efmoroctocog alfa (Elocta®)
- Emicizumab (Hemlibra®)

PLACE OF TECHNOLOGY

If licensed, valoctocogene roxaparvovec would offer a disease-modifying treatment option for adults with severe haemophilia A, and would replace the use of prophylactic factor VIII treatment, or minimise the use of factor VIII.

CLINICAL TRIAL SUMMARY INFORMATION

Trial	**BMN270-301 (NCT03370913); EudraCT 2017-003215-19;** A Phase 3 Open-Label, Single-Arm Study To Evaluate The Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Hemophilia A Patients With Residual FVIII Levels ≤ 1 IU/dL Receiving Prophylactic FVIII Infusions

	Phase III **Locations:** Europe (including UK), USA and other countries
Trial design	Single group assignment, open label
Population	N=134, adult males (18 and over), severe haemophilia A
Intervention(s)	Single administration of valoctocogene roxaparvovec at a dose of 6E13 vg/kg
Comparator(s)	No comparator.
Outcome(s)	Change of the median FVIII activity [Time Frame: 52 weeks] For full list of outcomes, see trial registry
Results (efficacy)	-
Results (safety)	-

Trial	NCT02576795; EudraCT 2014-003880-38; A Phase 1/2, Dose-Escalation, Safety, Tolerability and Efficacy Study of Valoctocogene Roxaparvovec, an Adenovirus-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Patients With Severe Haemophilia A **Phase I/II** **Locations:** UK
Trial design	Single group assignment, open label
Population	N=15, adult males (18 and over), severe haemophilia A
Intervention(s)	BMN 270 is administered as a single IV Infusion
Comparator(s)	No comparator
Outcome(s)	- Number of participants with treatment-related adverse events, as assessed by Common Terminology Criteria for Adverse Events (CTCAE) v4.03 for 5 years following valoctocogene roxaparvovec infusion. [Time Frame: 61 Months] - To determine the dose of AAV5-hFVIII-SQ required to achieve expression of FVIII at or above 5% of normal activity (>5 IU/dL) at 16 weeks after infusion. [Time Frame: 61 Months] - The kinetics, duration and magnitude of AAV-mediated FVIII activity in individuals with haemophilia A will be determined and correlated to an appropriate BMN 270 dose. For full list of outcomes, see trial registry
Results (efficacy)	Gene therapy with AAV5-hFVIII-SQ vector in participants with haemophilia A resulted in sustained, clinically relevant benefit, as measured by a substantial reduction in annualised rates of bleeding events and completed cessation of prophylactic factor VIII use in all participants who had received 4x1013vg per kilogram or 6x1013vg per kilogram of the gene therapy[28]
Results (safety)	No inhibitor development, thromboses, deaths, or persistent changes in liver-function tests were observed [28]

ESTIMATED COST

The cost of valoctocogene roxaparvovec is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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

OTHER GUIDANCE

- United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO). Clinical Genetic Services for Haemophilia. 2018.[29]
- United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO). Guidelines for the management of acute joint bleeds and chronic synovitis in haemophilia. 2017.[30]
- United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO). Guideline for the diagnosis and management of the rare coagulation disorders. 2014.[31]
- The Official Journal of the World Federation of Hemophilia. Guidance for the management of hemophilia. 2012.[32]
- British Society for Haematology. Use of prophylactic factor VIII concentrate in children and adults with severe haemophilia A. 2010.[33]
- United Kingdom Haemophilia Centre Doctors' Organisation (UKHC DO). Emergency and out of hours care for patients with bleeding disorders – standards of care for assessment and treatment. 2009.[34]
- United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO). A review of inherited platelet disorders with guidelines for their management on behalf of the UKHCDO. 2006.[35]

ADDITIONAL INFORMATION

REFERENCES

1 Rangarajan, S., Walsh L., Lester W., Perry D., Madan B., Laffan M., et al. *AAV5-Factor VIII Gene Transfer in Severe Hemophilia A.* New England Journal of Medicine. 2017;277(26):2519-30. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29224506

2 Global Data. *Drug: valoctocogene roxaparvovec.* Available from: https://pharma.globaldata.com/DrugsView/ProductView?ProductId=257995&ProductType=0,1 [Accessed 26 Mar 2020].

3 Clinicaltrials.gov. *Single-Arm Study To Evaluate The Efficacy and Safety of Valoctocogene Roxaparvovec in Hemophilia A Patients (BMN 270-301).* Available from: https://clinicaltrials.gov/ct2/show/NCT03370913 [Accessed 23 Apr 2020].

4 Pasi, K., Rangarajan S., Mitchell N., Lester W. *Multiyear Follow-up of AAV5-hFVIII-SQ Gene Therapy for Hemophilia A*. The New England Journal of Medicine. 2020;382:29-40. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa1908490

5 Berntorp, E., Dolan G., Linari S., Santagostino E., Tosetto A., Castaman G., et al. *European retrospective study of real-life haemophilia treatment.* Haemophilia. 2017;23(1):105-14. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27761962

6 The Haemophilia Society. *What types of haemophilia treatment are available in the UK?* Available from: https://haemophilia.org.uk/resources/faqs/what-types-of-haemophilia-treatment-are-available-in-the-uk/ [Accessed 26 Mar 2020].

7 Cook, K., Forbes S., Adamski K., Ma J., Chawla A., Garrison Jr L. *Assessing the potential cost-effectiveness of a gene therapy for the treatment of hemophilia A*. Journal of Medical Economics. 2019. Available from: https://doi.org/10.1080/13696998.2020.1721508

8 Specialist Pharmacy Service. *Valoctocogene roxaparvovec.* Available from: https://www.sps.nhs.uk/medicines/valoctocogene-roxaparvovec/ [Accessed 23 Apr 2020].

9 Biomarin. *BioMarin Provides 3 Years of Clinical Data from Ongoing Phase 1/2 Study of Valoctocogene Roxaparvovec Gene Therapy for Severe Hemophilia A.* Available from: https://investors.biomarin.com/2019-05-28-BioMarin-Provides-3-Years-of-Clinical-Data-from-Ongoing-Phase-1-2-Study-of-Valoctocogene-Roxaparvovec-Gene-Therapy-for-Severe-Hemophilia-A [Accessed 07 Apr 2020].

10 European Medicines Agency. *EU/3/16/1622.* Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3161622 [Accessed 07 Apr 2020].

11 The Haemophilia Society. *Bleeding disorders - Haemophilia A.* Available from: https://haemophilia.org.uk/bleeding-disorders/haemophilia-a/ [Accessed 26 Mar 2020].

12 National Health Service. *Causes - haemophilia.* Available from: https://www.nhs.uk/conditions/haemophilia/causes/ [Accessed 26 Mar 2020].

13 Genetics Home Reference. *What are the different ways in which a genetic condition can be inherited?* Available from: https://ghr.nlm.nih.gov/primer/inheritance/inheritancepatterns [Accessed 23 Apr 2020].

14 National Health Service. *Haemophilia - symptoms.* Available from: https://www.nhs.uk/conditions/haemophilia/symptoms/ [Accessed 26 Mar 2020].

15 National Health Service. *Haemophilia - treatment.* Available from: https://www.nhs.uk/conditions/haemophilia/treatment/ [Accessed 26 Mar 2020].

16 Noone, D., Chai-Adisaksopha C., Curtis R., Frick N., Nichol M., Noone D., et al. The effect of haemophilia on activites of daily living (ADL): Probe cohort. *European Conference of Rare Diseases & Orphan Products (ECRD)* 2018.

17 Carroll, L., Benson G., Lambert J., Benmedjahed K., Zak M., Le X. *Real-world utilities and health-related quality-of-life data in hemophilia patients in France and the United Kingdom*. Patient preference and adherence. 2019;13:941-57. Available from: https://doi.org/10.2147/PPA.S202773

18 National Health Service England. *2013/14 NHS STANDARD CONTRACT FOR HAEMOPHILIA (ALL AGES)*. B05/S/a. NHS England,; 2013/14. Available from: https://www.england.nhs.uk/wp-content/uploads/2013/06/b05-haemophilia.pdf Accessed: 06 Apr 2020

19 National Hemophilia Foundation. *Hemophilia A.* Available from: https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-A [Accessed 27 Mar 2020].

20 Orpha.net. *Haemophila A - ORPHA:98878.* Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=98878 [Accessed 27 Mar 2020].

21 Manco-Johnson, M., Kempton C., Reding M., Lissitchkov T., Goranov S., Gercheva L., et al. *Randomized, controlled, parallel-group trial of routine prophylaxis vs. on-demand treatment with sucrose-formulated recombinant factor VIII in adults with severe hemophilia A (SPINART).* Journal of Thrombosis and Haemostasis. 2013;12(1):119-22. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/jth.12202

22 Staber, J., Pollpeter M. *Shortened Lifespan and Lethal Hemorrhage in a Hemophilia A Mouse Model. PLoS One*. PloS one. 2016;11(5):e0154857. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0154857

23 Collins, P., Blanchette V., Fischer K., Bjorkman S., Oh M., Fritsch S., et al. *Break-through bleeding in relation to predicted factor VIII levels in patients receiving prophylactic treatment for severe hemophilia A*. Journal of Thrombosis and Haemostasis. 2009;7(3). Available from: https://doi.org/10.1111/j.1538-7836.2008.03270.x

24 O'Haraa, J., Hughes D., Camp C., Burke T., Carroll L., Garcia Diego D.-A. *The cost of severe haemophilia in Europe: the CHESS study*. Orphanet Journal of Rare Diseases. 2017;106:12-106. Available from: https://ojrd.biomedcentral.com/articles/10.1186/s13023-017-0660-y

25 Office for National Statistics. *Hospital Admitted Patient Care Activity, 2018-19: Diagnosis.* 2018-2019. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19 [Accessed 19 Sep 2019].

26 Great Ormond Street Hospital. *Haemophilia.* Available from: https://www.gosh.nhs.uk/conditions-and-treatments/conditions-we-treat/haemophilia-0 [Accessed 26 Mar 2020].

27 United Kingdom Haemophilia Centres Doctors' Organisation (UKHCDO) National Haemophilia Database. *UKHCDO Annual Report 2019 including Bleeding Disorder Statistics for 2018/2019*. United Kingdom Haemophilia Centres Doctors' Organisation (UKHCDO); 2019. Available from: http://www.ukhcdo.org/home-2/annual-reports/ Accessed: 23 Apr 2020

28 Pasi, K., Rangarajan S., Mitchell N., Lester W., Symington E., Madan B., et al. *Multiyear Follow-up of AAV5-hFVIII-SQ Gene Therapy for Hemophilia A*. New England Journal of Medicine. 2020;382(1):29-40. Available from: https://www.ncbi.nlm.nih.gov/pubmed/31893514

29 United Kingdom Haemophilia Centre Doctors' Organisation. *Clinical Genetic Services for Haemophilia.* 2018. Available from: http://www.ukhcdo.org/wp-content/uploads/2015/12/Guidelines_on_genetics_services_for_haemophilia_v5-3_1_final.pdf [Accessed 27 Mar 2020].

30 Hanely, J., MCkernan A., Creagh M., Classey S., Mclaughlin P., Goddard N., et al. *Guidelines for the management of acute joint bleeds and chronic synovitis in haemophilia*. Haemophilia. 2017:1-10. Available from: https://onlinelibrary.wiley.com/doi/10.1111/hae.13201

31 Mumford, A., Ackroyd S., Alikhan R., Bowles L., Chowdary P., Grainger J., et al. *Guideline for the diagnosis and management of the rare coagulation disorders*. British Journal of haematology. 2014;167:304-26. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.13058

32 Srivastava, A., Brewer A., Mauser-Bunschoten E., Key N., Kitchen S., Llinas A., et al. *Guidelines for the management of hemophilia*. Hemophilia. 2012;19(1):1-47. Available from: https://doi.org/10.1111/j.1365-2516.2012.02909.x

33 Richards, M., Williams M., Chalmers E., Liesner R., Collins P., Vidler V., et al. *A United Kingdom Haemophilia Centre Doctors' Organization guideline approved by the British Committee for Standards in Haematology: guideline on the use of prophylactic factor VIII concentrate in children and adults with severe haemophilia A*. British Journal of haematology. 2010;149(4):498-507. Available from: https://doi.org/10.1111/j.1365-2141.2010.08139.x

34 Hanely, J., Mathias M., Franklin E., Harrington C., Chapman O., Talks K., et al. *Emergency and out of hours care for patients with bleeding disorders – Standards of care for assessment and treatment.* Last Update Date: Available from: http://www.ukhcdo.org/wp-content/uploads/2015/12/EmergencyCareStandardsFinalVersionJune2009-For-Website.pdf [Accessed

35 Bolton-Maggs, P., Chalmers E., Collins P., Harrison P., Kitchen S., Liesner R., et al. *A review of inherited platelet disorders with guidelines for their management on behalf of the UKHCDO*. British Journal of haematology. 2006;135:603-33. Available from: https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1365-2141.2006.06343.x