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HEALTH TECHNOLOGY BRIEFING
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Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B

NIHRIO ID	7279	**NICE ID**	9768
Developer/Company	UniQure NV	**UKPS ID**	Not available

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

SUMMARY

Etranacogene dezaparvovec is 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.

Etranacogene dezaparvovec is given to patients by intravenous injection. It works by using a harmless viral vector to insert a highly functional copy of the F9 gene. This means that the body can make more functional factor IX clotting protein so the blood does not take as long to clot following an injury and there is no spontaneous bleeding into the joints, muscles or brain. If licensed, etranacogene dezaparvovec will offer an additional treatment option for adult males with moderately severe or severe haemophilia B.

PROPOSED INDICATION

Treatment of moderately severe or severe haemophilia B in adult males.[1-3]

TECHNOLOGY

DESCRIPTION

Etranacogene dezaparvovec (AMT-061) is administered intravenously and is designed to provide a highly functional copy of the F9 gene called FIX Padua to help the body make more of the factor IX protein. FIX Padua is different from the normal healthy copy of the F9 gene; it is a variant with a change that renders the produced factor IX protein eight times more active than normal. Etranacogene dezaparvovec uses a viral vector created from parts of harmless virus called adeno-associated virus 5 (AAV5) to deliver the gene to the body.[4,]

Etranacogene dezaparvovec is currently in development for the treatment of adult males with moderately severe or severe haemophilia B. In the phase III clinical trial HOPE-B (NCT03569891) participants received a single intravenous infusion of etranacogene dezaparvovec.[3]

INNOVATION AND/OR ADVANTAGES

In the UK, current treatment options for people with haemophilia B include prophylactic administration of an engineered version of factor IX.[5] However, due to the short half-life of the clotting factors, replacement is required every two to three days. The frequency of these clotting factor intravenous infusions can lead to complications such as infections and thrombosis.[6] Furthermore, some people who take blood clotting factor medicine develop antibodies in their immune system called inhibitors that make the medicine less effective.[5]

Etranacogene dezaparvovec is a gene therapy that replaces the function of mutant genes that lead to insufficient factor IX production, thereby increasing the natural production of factor IX.[4,6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Etranacogene dezaparvovec does not currently have Marketing Authorisation in the EU/UK for any indication.

Etranacogene dezaparvovec has the following regulatory designations/awards for the treatment of haemophilia B:

- Awarded an orphan drug designation in March 2018 by the EMA.[7]
- Awarded PRIME designation in April 2017 by the EMA.[8]
- Granted a breakthrough therapy designation by the US Food and Drug Administration (FDA) in January 2017.[8]

Etranacogene dezaparvovec is not currently in phase II or III development for any other indication.[9]

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.[10] 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.[11]

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.[10] 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.[11] Patients with moderate disease do not often have spontaneous bleeding; however, they do have prolonged or delayed bleeding after relatively minor trauma. They are usually diagnosed before age five to six years and the frequency of bleeding episodes varies from once a month to once a year.[12] Patients with severe disease experience lifelong symptoms from infancy onwards with frequent spontaneous bleeding episodes often into their joints and muscles.[13,14] Serious complications can result from bleeding into the joints, muscles, brain or other internal organs.[15]

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 2018-19, there were 469 finished consultant episodes (FCE) for hereditary factor IX deficiency (ICD-10 code D67) resulting in 455 admissions and 198 FCE bed days.[17]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The recommended treatment plan for haemophilia depends on how severe the condition is. There are two main types of treatment: preventative treatment and on-demand treatment.[5] Preventative treatment is given regularly as an intravenous injection and aims to replace the missing or reduced factor IX with a man-made substitute.[18] Preventative treatment for people with haemophilia B involves twice weekly injections of nonacog alfa.[5]

On-demand treatment is given following an injury or as part of planning surgery to boost factor IX. It is given as an injection on a temporary basis to reduce the side effects of bleeding following an injury or during surgery.[18] On-demand treatment for haemophilia B usually involves injections of nonacog alfa.[5]

People with haemophilia B should not use non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen as this greatly increases the risk of bleeding.[18]

CURRENT TREATMENT OPTIONS

Preventative treatment:[5]
Twice weekly injections of nonacog alfa

On-demand treatment:[5]
Injections of nonacog alfa

PLACE OF TECHNOLOGY

If licensed, etranacogene dezaparvovec will offer the first gene therapy treatment option for adult males with moderately severe or severe haemophilia B.

CLINICAL TRIAL INFORMATION

Trial	**HOPE-B**, NCT03569891; Phase III, Open-label, Single-dose, Multi-center, Multinational Trial Investigating a Serotype 5 Adeno-associated Viral Vector Containing the Padua Variant of a Codon-optimized Human Factor IX Gene (AAV5- hFIXco-Padua, AMT-061) Administered to Adult Subjects With Severe or Moderately Severe Haemophilia B **Phase III - ongoing** **Locations:** 8 EU countries (incl UK) and the USA
Trial design	Open-label, Single-dose, Single Group Assignment
Population	N=54 males; adults aged 18 years and older; congenital haemophilia B classified as severe or moderately severe; more than 150 previous exposure days of treatment with factor IX protein
Intervention(s)	Single intravenous infusion of etranacogene dezaparvovec
Comparator(s)	No comparator
Outcome(s)	Primary outcome: Factor IX activity levels [Time frame: 26 weeks] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT03489291; Phase IIb, Open-label, Single-dose, Single-arm, Multi-center Trial to Confirm the Factor IX Activity Level of the Serotype 5 Adeno-associated Viral Vector Containing the Padua Variant of a Codon-optimized Human Factor IX Gene (AAV5-hFIXco-Padua, AMT-061) Administered to Adult Subjects With Severe or Moderately Severe Haemophilia B **Phase IIb - ongoing** **Location:** United States
Trial design	Open-label, Single-dose, Single-arm, Multi-centre trial

Population	N=3; males; adults aged 18 years and older; congenital haemophilia B classified as severe or moderately severe; more than 20 previous exposure days of treatment with factor IX protein
Intervention(s)	Single intravenous infusion of etranacogene dezaparvovec
Comparator(s)	No comparator
Outcome(s)	Primary outcome: Factor IX activity levels [Time frame: 6 weeks] See trial record for full list of other outcomes
Results (efficacy)	Mean factor IX activity for the three patients at 52 weeks after administration was 41% of normal. At one year after dosing, no patient in the study has reported any bleeding events and all patients have remained free of prophylaxis after receiving AMT-061.[19]
Results (safety)	Two adverse events (AE) judged to be possibly related to entracogene dezaparvovec were reported, both in Participant 1. The first was transient, self-limiting headache on day of dosing and the second was a mile elevation in C-reactive protein level on day 14 post treatment (7.4mg/L; reference range, 0-3mg/L) that resolved without intervention. There were no serious AEs or deaths during the study.[20] There was no indication of clinically relevant liver toxicity.[20]

Trial	NCT02396342; Phase I/II, Open-label, Uncontrolled, Single-dose, Dose-ascending, Multi-centre Trial Investigating an Adeno-associated Viral Vector Containing a Codon-optimized Human Factor IX Gene (AAV5-hFIX) Administered to Adult Patients With Severe or Moderately Severe Haemophilia B **Phase I/II - ongoing** **Locations:** Denmark, Germany and Netherlands
Trial design	Open-label, Single-dose, Single-arm, Multi-centre trial
Population	N=10; males; adults aged 18 years and older; congenital haemophilia B classified as severe or moderately severe; more than 150 previous exposure days of treatment with factor IX protein
Intervention(s)	Single intravenous infusion of AMT-060
Comparator(s)	No comparator
Outcome(s)	Primary outcome: Adverse Events [Time frame: Five years] See trial record for full list of other outcomes

Results (efficacy)	A single infusion of AMT-060 was well tolerated and resulted in a stable and clinically relevant increase in FIX activity. The therapy also led to a 53% decrease in patients' mean annualized spontaneous bleeding rate (ASBR) and the need for additional FIX use was reduced by 81%. In the higher-dose cohort, annualized FIX use decreased by 73% and mean ASBR was reduced by 70% from 3.0 – 0.9.[21]
Results (safety)	Six participants experienced a total of 14 treatment related adverse events (TRAE) including: liver enzymes increased, pyrexia, anxiety, palpitations, headache, prostatitis and rash. Most events were classified as mild, some as moderate. Three protocol-defined serious adverse events were classified as possibly or probably related to treatment: mild, asymptomatic elevations in liver enzymes; short, self-limiting fever in the first 24 hours after AMT-060; and elevation in ALT levels.[22]

ESTIMATED COST

The estimated cost of AMT-061 is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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

OTHER GUIDANCE

- United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO). Clinical Genetic Services for Haemophilia. 2018.[23]
- United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO). Guidelines for the management of acute joint bleeds and chronic synovitis in haemophilia. 2017.[24]
- British Medical Journal (BMJ). Diagnosis and Management of Haemophilia. 2012.[25]

ADDITIONAL INFORMATION

UniQure did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so

that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

REFERENCES

1 Clinicaltrials.gov. *Dose Confirmation Trial of AAV5-hFIXco-Padua. Trial ID*. 2018. Status: Available from: https://clinicaltrials.gov/ct2/show/NCT03489291 [Accessed 21 April 2020].

2 Clinicaltrials.gov. *Trial of AAV5-hFIX in Severe or Moderately Severe Hemophilia B. Trial ID*. 2015. Status: Available from: https://clinicaltrials.gov/ct2/show/NCT02396342 [Accessed 21 April 2020].

3 Clinicaltrials.gov. *HOPE-B: Trial of AMT-061 in Severe or Moderately Severe Hemophilia B Patients. Trial ID*. 2018. Status: Available from: https://clinicaltrials.gov/ct2/show/NCT03569891 [Accessed 20 April 2020].

4 Hemophilia News Today. *AMT-061*. 2020. Available from: https://hemophilianewstoday.com/amt-061/ [Accessed 20 April 2020].

5 National Health Service (NHS). *Haemophilia: Treatment*. 2017. Available from: https://www.nhs.uk/conditions/haemophilia/treatment/ [Accessed 20 April 2020].

6 Sharma, A., Easow Mathew M., Sriganesh V., Reiss U. M. *Gene therapy for haemophilia*. The Cochrane database of systematic reviews. 2016;12(12):CD010822-CD. Available from: 10.1002/14651858.CD010822.pub3 https://doi.org/10.1002/14651858.CD010822.pub3

7 European Medicines Agency (EMA). *Public summary of opinion on orphan designation: Recombinant adeno-associated viral vector containing a codon-optimized Padua derivative of human coagulation factor IX cDNA for the treatment of haemophilia B*. 2018. Available from: https://www.ema.europa.eu/en/documents/orphan-designation/eu/3/18/1999-public-summary-opinion-orphan-designation-recombinant-adeno-associated-viral-vector-containing_en.pdf [Accessed 20 April 2020].

8 UniQure. *Advancing AMT-061 in Hemophilia B*. 2017. Available from: http://uniqure.com/investors-newsroom/uniQure_AMT-061_Final_Presentation_PDF.pdf [Accessed 20 April 2020].

9 Clinicaltrials.gov. *Search for AMT-061 studies: Phase II and III*. 2020. Available from: https://clinicaltrials.gov/ct2/results?cond=AMT-061&term=&type=&rslt=&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 20 April 2020].

10 National Health Service (NHS). *Overview: Haemophilia*. 2017. Available from: https://www.nhs.uk/conditions/haemophilia/ [Accessed 19 April 2020].

11 National Organization for Rare Disorders (NORD). *Rare Disease Database: Hemophilia B*. 2020. Available from: https://rarediseases.org/rare-diseases/hemophilia-b/ [Accessed 19 April 2020].

12 Konkle, B. A., Huston H., Nakaya Fletcher S. *Hemophilia A*. 1993. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1404/ [Accessed 23 April 2020].

13 National Hemophilia Foundation. *Hemophilia B*. 2020. Available from: https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-B [Accessed 19 April 2020].

14 Knott, L., Gronow H. *Haemophlia B*. 2014. Available from: https://patient.info/doctor/haemophilia-b-factor-ix-deficiency [Accessed 19 April 2020].

15 UniQure. *UniQure has built a potential first and best in-class hemophilia gene therapy program*. 2020. Available from: http://uniqure.com/gene-therapy/hemophilia.php [Accessed 20 April 2020].

16 NHS England. *B05/S/a: 2013/14 NHS Standard Contract For Haemophilia (All Ages)*. 2013. Available from: https://www.england.nhs.uk/wp-content/uploads/2013/06/b05-haemophilia.pdf [Accessed 20 April 2020].

17 NHS Digital. *Hospital Admitted Patient Care Activity 2018-19: Diagnosis*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19 [Downloaded 19 September 2019].

18 Great Ormand Street Hospital. *Haemophilia B*. 2020. Available from: https://www.gosh.nhs.uk/conditions-and-treatments/conditions-we-treat/haemophilia-b [Accessed 20 April 2020].

19 UniQure. *UniQure Announces One-Year Follow-Up Data from the Phase IIb Study of Etranacogene Dezaparvovec and Long-Term Follow-Up Data for AMT-060 in Patients with Hemophilia B.* 2019. Available from: https://tools.eurolandir.com/tools/Pressreleases/GetPressRelease/?ID=3677182&lang=en-GB&companycode=nl-qure&v= [Accessed 21 April 2020].

20 Von Drygalski, A., Giermasz A., Castaman G., Key N. S., Lattimore S., Leebeek F. W. G., et al. *Etranacogene dezaparvovec (AMT-061 phase 2b): normal/near normal FIX activity and bleed cessation in hemophilia B*. Blood advances. 2019;3(21):3241-7. Available from: 10.1182/bloodadvances.2019000811 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6855101/

21 Hemophilia News Today. *uniQure Gene Therapy AMT-060 Shows Long-term Efficacy in Hemophilia B patients*. 2018. Available from: https://hemophilianewstoday.com/2018/01/15/uniqure-hemophilia-b-gene-therapy-amt-060-shows-long-term-efficacy/ [Accessed 15 May 2020].

22 Miesbach, W., Meijer K., Coppens M., Kampmann P., Klamroth R., Schutgens R., et al. *Gene therapy with adeno-associated virus vector 5-human factor IX in adults with hemophilia B*. Blood. 2018;131(9):1022-31. Available from: 10.1182/blood-2017-09-804419 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5833265/

23 Collins, P. W., Liesner R., Makris M., Talks K., Chowdary P., Chalmers E., et al. *Treatment of bleeding episodes in haemophilia A complicated by a factor VIII inhibitor in patients receiving Emicizumab. Interim guidance from UKHCDO Inhibitor Working Party and Executive Committee*. Haemophilia. 2018 May;24(3):344-7. Available from: 10.1111/hae.13495 https://doi.org/10.1111/hae.13495

24 Hanley, J., McKernan A., Creagh M. D., Classey S., McLaughlin P., Goddard N., et al. *Guidelines for the management of acute joint bleeds and chronic synovitis in haemophilia: A United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) guideline*. Haemophilia. 2017 Jul;23(4):511-20. Available from: 10.1111/hae.13201 https://doi.org/10.1111/hae.13201

25 Fijnvandraat, K., Cnossen M. H., Leebeek F. W. G., Peters M. *Diagnosis and management of haemophilia*. BMJ : British Medical Journal. 2012;344:e2707. Available from: 10.1136/bmj.e2707 http://www.bmj.com/content/344/bmj.e2707.abstract

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