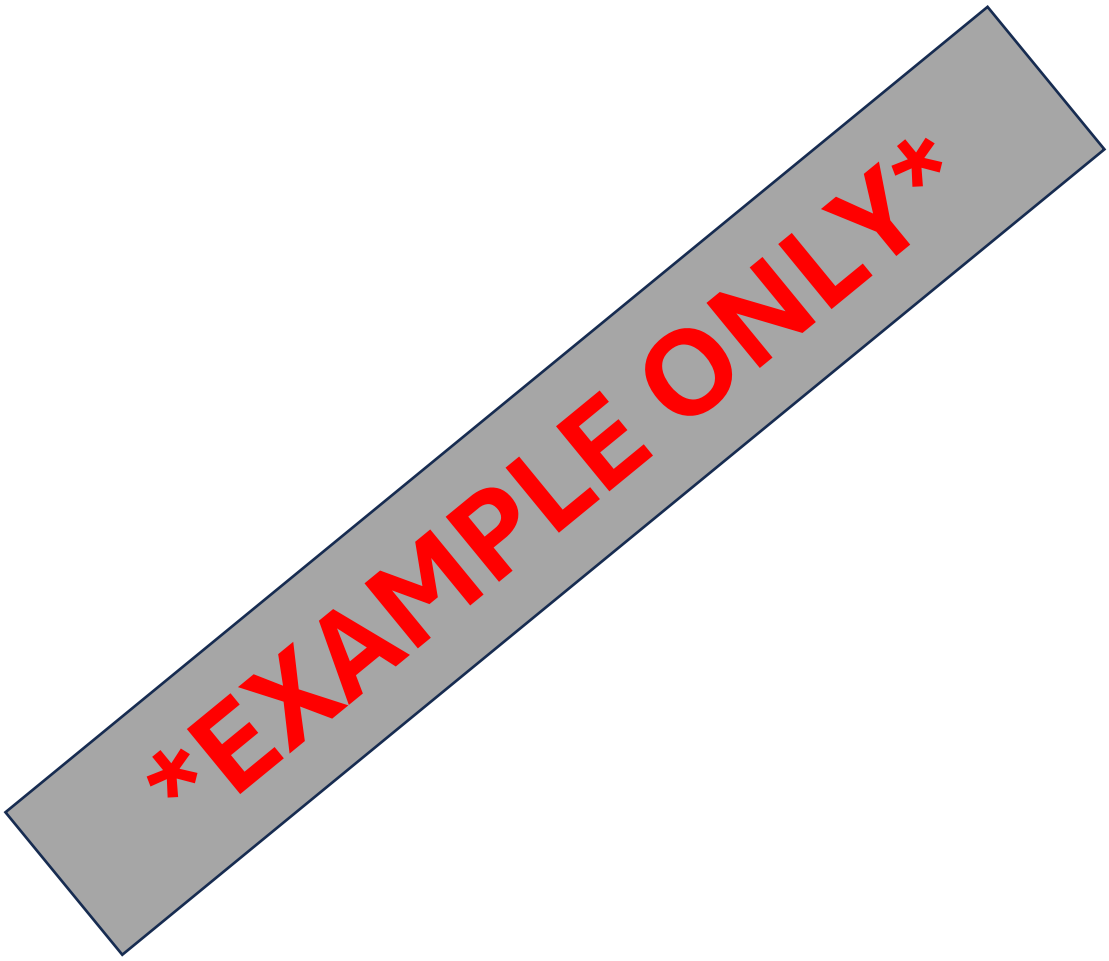
Project Number:	XXXXXX
Assignment:	Conference Coverage Recap of one of the posters presented at the American Society of Hematology (ASH) annual meeting Capture key points from the poster
Word Count:	~900 words
End Deliverable:	ASH Conference Recap in AJMC supplement (several articles recapping sessions / posters from the 2020 American Society of Hematology annual meeting)
Writer:	Amber L Schilling
Today's Date:	December 9, 2020
Due Date for 1st Draft:	December 14, 2020
Audience:	Payers, healthcare policy experts, clinical decision makers, policy makers, and providers all associated with cancer care; evidence-based oncology (EBO)



After 54 adult male patients with severe or moderately severe hemophilia B were given a single IV dose of entranacogene dezaparvovec, a novel gene therapy under investigation for use in hemophilia B, activity of clotting factor IX (FIX) increased significantly from baseline into the mild-to-normal range at 26 weeks. [Pipe,2020;para1,ln1;para2,ln1-2;para3,ln1-2;para3,ln4;para4,ln1-2;para4,ln4-6;para5,ln2-4] This is a preliminary, interim finding of the **H**ealth **O**utcomes with **P**adua gene **E**valuation in Hemophilia **B** trial (HOPE-B; NCT0356981), a phase 3 trial assessing efficacy and safety of entranacogene dezaparvovec, which will continue for a total of 5 years. [Pipe,2020,para2,ln1-2;para3,ln5]

Hemophilia is a congenital bleeding disease caused by a deficiency in clotting factor VIII (FVIII; hemophilia A) or IX (FIX; hemophilia B).[WFH_Guidelines,2020;p19,col1,sect2.1,bullet1] The disorder is rare, affecting predominately males who inherit an affected maternal X chromosome coding for a pathogenic variant of the *F8* or *F9* clotting factor gene, with an estimated prevalence at birth of 24.6 and 5.0 cases per 100,000 males for hemophilia A and B, respectively.[WFH_Guidelines,2020;p19,col1,bullet3;p19,col1,bullet4;p19,col2,bullet2] Most (80-85%) cases are diagnosed as hemophilia A and the remainder (15-20%) as hemophilia B.[WFH_guidelines,2020;p19,col1,bullet3] As current treatments are not curative, hemophilia is a lifelong disease characterized by spontaneous and / or prolonged hemorrhaging, musculoskeletal complications from hemarthrosis (joint bleeds), and a variety of other sequelae.[WFH_Guidelines,2020;p19,col2,bullet2;col2,bullet1,sub-bullet1-3;p21,table2-2;p125,col1,bullet1,3,4] Hemophilia severity is defined according to the level of deficient clotting factor relative to normal: mild (< 40% but > 5% of normal); moderate (≤ 5% but ≥ 1% of normal); and severe (< 1% of normal).[WFH_Guidelines,2020;p20,table2-1][Blanchette,2014;p1935,col2,para2,ln1-4]

For the past 50 years, the primary focus for hemophilia treatment has been on clotting factor replacement therapy to both treat and prevent bleeds. According to the World Federation of Hemophilia (WFH) 2020 treatment guidelines, the current standard of care remains use of exogenous clotting [illegible] concentrates (CFCs).[WFH_Guidelines,2020;p68,col2,sect5.7,bullet1;p61,col1,sect5.3,bullet1;p59,col1,sect5.1,bullet2;p10,col2,se[illegible]ol1,sect1.8,bullet1;p59,col1,sect5.1,bullet2;p61,col1,sect5.3,bullet1] However, CFCs can be cumbersome for several [illegible]e an inherently short half-life and therefore come with the need for frequent dosing; 2) th[illegible]ffective and cause anaphylaxis if the patient develops autoantibodies ("inhibitors")[illegible]otting factors; and 3) they are not curative and therefore must be administered over th[illegible]me to maintain hemostasis.[WFH_Guidelines,2020;p63,col1,bullet9;p64,col2,sect5.4,bullet1;p68,col2,bu[illegible]2;p102,col2,bullet7p102,col2,bullet11][Blanchette,2014;p1935,col2,para3,ln1-3]

Although half-life extenders and bypassing agents h[illegible]overcome some of these challenges, the approach remains non-curative, costly, and h[illegible]reduced quality of life due to the need for lifelong injections.[WFH_Guidelines,2020;p63,col1,b[illegible]2;p63,col2,bullet6;p64,col1,bullet1;p64,col2,sect5.4,bullet1;p10[illegible]241,para2,ln1-4][Spronck,2019;p221,col2,para2,ln11-16] A gene therapy could ameliorate these challen[illegible]curative if it could successfully induce endogenous expression of the deficient clotting[illegible]para2,ln5-7][Konkle,2020;p4,para1,ln2-4] However, a key barrier to gene therapy has been selecting[illegible]A transfer that does not become neutralized by the patient's own immune syste[illegible]e for gene transfer.[Konkle,2020;p4,para1,ln4-7][Makusic,2014;p3068,col2,para1,ln[illegible],2014;p3195,col1,para1(entire)]

In an animal stud[illegible]no-associated virus 5 (AAV5) vector was utilized to transfer the human genetic varian[illegible]dua) gene into host DNA within hepatocytes. The h*FIX*-Padua variant is a hyperactive F[illegible]been shown to demonstrate a 5- to 10-fold increase in FIX activity relative to the wild-type.[F[illegible]n6-8] AAV5-h*FIX* was injected into non-human primates (NHPs) at several doses, and was found to [illegible]increasing levels of circulating hFIX protein levels, ranging from 1-2% of normal human levels in the l[illegible]w dose group to 60% in the high dose group.[Spronck,2019;p227,col2,para2(entire);p222,col2,para3,ln1-4;p222,col2,para3,ln10-13;p228,col2,para2,ln1-5] Increased expression of FIX was maintained up to 26 weeks post-treatment with single dose.[Spronck,2019;p227,col2,para2,ln3-4] The average increase from baseline of FIX activity detected was 58.9%.[Spronck,2019;p223,col1,para2,ln5-7]

Data from a small, open-label, single-dose, multicenter phase 2b dose confirmation study found that etranacogene dezaparvovec, a gene therapy that utilizes the nonpathogenic adeno-associated virus 5 (AAV5) vector to transfer the human genetic variant *FIX*-Padua (h*FIX*-Padua) gene into host DNA within hepatocytes, increased endogenous FIX activity in 3 patients with moderate to severe hemophilia B (FIX activity at baseline ≤ 1% of normal).[Konkle,2020;p1,para1,ln1-2;p4,para1,ln2-4][Dryganski,2019;p3242,col2,para1,ln1-3;p3242,col2,para2,ln1-2;p3245,col1,para5,ln1;p3242,col1,para2,ln1-2;p3242,col1,para2,ln14-15;p3242,col1,para2,ln20;p3242,col1,para3,ln3-9;p3242,col2,para2,ln1-2;p3243,col1,para1,ln1-4;p3244,table1;p3245,col2,para2,ln6-12][Spronck,2019;p224,col2,para2,ln9] After receipt of 1 dose of the study drug (500 mL infusion of 2 x 10^{13} genome copies/kg (cg/kg), endogenous mean FIX activity increased to 31% of normal at 6 weeks (individual levels of 37.8%, 23.9%, and 30.0% in participants 1 through 3, respectively), to 38.0% at 12 weeks (individual levels 37.9%, 24.9%, and 51.1%, respectively), and to 47% at 26 weeks (individual levels of 51.0%, 33.2%, and 57.0%, respectively).[Dryganski,2019;p3243,col2,heading5;p3243,col1,para4,ln1-2;p3244,col1,para1,ln5-13]

Of note is that all patients in the phase 2b trial had neutralizing antibod to the AAV5 vector at screening, a fact that has been previously predicted to preclude suc fer.
Given that the presence of pre-existing anti-AAV5 NAbs did n ith AAV5-mediated gene transfer in the phase 2b study and that clinical trials investig ve historically excluded patients who have neutralizing antibodies to the vector c s a promising finding.
[Drygalski,2019;p3244,table1;p3245,col1,para2,ln1-2;p3245,col2,para5(entire);p 1,para3,ln5-8]

Results of the dose-finding phase 2b trial were d for the HOPE-B trial, a larger, phase 3 trial of entranacogene dezaparvovec.[Drygalsk The HOPE-B trial is an ongoing, open-label, single-dose, single-arm, multi-national t n severe or moderate-severe hemophilia B that was designed to assess safety and ef e dezaparvovec at 26 weeks and at 52 weeks.[Pipe,2020;para2(entire);para3,ln1-2;l and at 52 weeks was a primary efficacy endpoint; adverse events were a secon a3,ln5-6;ln8]

Consistent with the d phase 2b trial, as well as trials including nonhuman primates, HOPE-B did not e evalent anti-AAV5 NAb titers.[Pipe,2020;para1,ln3-5;para5,ln4] Participants (n = 44 severe and re hemophilia B; 42.6% had NAbs to AAV5 at baseline) were given a single IV d ezaparvovec at 2 x 10^{13} cg/kg.[Pipe,2020;para4,ln1;para3,ln4-5;para4,ln3] At week 26, FIX activity l an of 37.2%, which represented a change from baseline of 36.0% (P < .000 st treatment-related adverse events reported were mild (81.5%), with headache and i cing among the most common.[Pipe,2020;para4,ln11-16] No treatment-related serious adverse eve d, and there were no deaths.[Pipe,2020;para4,ln11-16] Seven patients had an infusion-related reacti infusion was discontinued in 1; 9 patients had treatment-related elevations in liver enzyme 020;para4,ln11-16]

Overall, entranacogene dezaparvovec shows promise as a novel gene therapy in patients with hemophilia B, owing to animal studies in NHPs, the dose-confirmation phase 2b trial, and the preliminary results of the HOPE-B trial.

References:

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