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26 WEEK EFFICACY AND SAFETY OF ETRANACOGENE DEZAPARVOVEC (AAV5-PADUA HFIX VARIANT; AMT-061) IN ADULTS WITH SEVERE OR MODERATE-SEVERE HEMOPHILIA B TREATED IN THE PHASE 3 HOPE-B CLINICAL TRIAL

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Steven Pipe[1], Frank W.G. Leebeek[2], Michael Recht[3], Nigel S Key[4], Susan Lattimore[3], Giancarlo Castaman[5], Paul van der Valk[6], Kathelinje Peerlinck[7], Michiel Coppens[8], Niamh M O'Connell[9], K John Pasi[10], Peter Kampmann[11], Karina Meijer[12], Annette von Drygalski[13], Guy Young[14], Cedric Hermans[15], Jan Astermark[16], Robert Klamroth[17], Richard Lemons[18], Nathan Visweshwar[19], Shelley Crary[20], Syed R S Kazmi[21], Emily Symington[22], Miguel A Escobar[23], Esteban Gomez[24], Rebecca Kruse-Jarres[25], Adam Kotowski[26], Doris Quon[27], Michael Wang[28], Alison P Wheeler[29], Eileen K Sawyer[30, 31], David Cooper[30, 32], Valerie Ferriera[30, 32], Wolfgang Miesbach[33]

[1] University of Michigan, Ann Arbor, United States
[2] Erasmus MC, University Medical Center, Rotterdam, Netherlands
[3] Oregon Health & Science University, Portland, United States
[4] University of North Carolina, Chapel Hill, United States
[5] Center for Bleeding Disorders and Coagulation, Careggi University Hospital, Florence, Italy
[6] Universitair Medisch Centrum, Utrecht, Netherlands
[7] Department of Vascular Medicine and Haemostasis and Haemophilia Centre, University Hospitals Leuven, Leuven, Belgium
[8] Department of Vascular Medicine, Amsterdam University Medical Centers, Amsterdam, Netherlands
[9] The National Coagulation Centre, St James's Hospital, Dublin, Ireland
[10] Royal London Haemophilia Centre, Barts and the London School of Medicine and Destistry, London, United Kingdom
[11] Rigshospitalet, Copenhagen, Denmark
[12] University Medical Center Groningen, Groningen, Netherlands
[13] University of California San Diego, La Jolla, United States
[14] Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, United States
[15] Cliniques Universitaires Saint-Luc, Universite Catholique de Louvain, Brussels, Belgium
[16] Skane University Hospital, Malmo, Sweden
[17] Vivantes Klinikum im Friedrichshain, Berlin, Germany
[18] University of Utah, Salt Lake City, United States
[19] University of South Florida, Tampa, United States
[20] University of Arkansas for Medical Sciences, Little Rock, United States
[21] University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom
[22] Cambridge University - Addenbrooke's Hospital, Cambridge, United Kingdom
[23] University of Texas Health Science Center at Houston, Houston, United States
[24] Phoenix Children's Hospital, Phoenix, United States
[25] Bloodworks Northwest, Seattle, United States
[26] WNY Bloodcare, New York, United States
[27] Los Angeles Orthopedic Hospital, Orthopedic Hemophilia Treatment Center, Los Angeles, United States
[28] University of Colorado Hemophilia and Thrombosis Center, Anschutz Medical Campus, Aurora, United States
[29] Vanderbilt University Medical Center, Nashville, United States
[30] uniQure BV, Amsterdam, Netherlands
[31] Uniqure Inc, Lexington, United States
[32] uniQure Inc, Lexington, United States

[33] University Hospital Frankfurt, Frankfurt, Germany

Background: Etranacogene dezaparvovec is an investigational gene therapy for hemophilia B (HB) comprising an adeno-associated virus serotype 5 (AAV5) vector containing a codon-optimized Padua variant human factor IX (FIX) gene with a liver specific promoter. Early clinical studies and nonhuman primate data suggest that generally prevalent titers of anti-AAV5 NAbs may not preclude successful transduction with etranacogene dezaparvovec.

Aims: A Phase 3, **H**ealth **O**utcomes with **P**adua gene; **E**valuation in Hemophilia **B** (HOPE-B; NCT03569891) trial is ongoing to further assess efficacy and safety of etranacogene dezaparvovec in adults with HB with a wide range of pre-existing NAbs to AAV5. Here we report outcomes at 26 weeks (wks).

Methods: HOPE-B is a Phase 3, open-label, single-dose, single-arm, multi-national trial in adult males with severe or moderate-severe HB (FIX≤2%). All participants (pts) received routine FIX prophylaxis prior to study and were not excluded based on pre-existing NAbs to AAV5. A 6 month prospective lead-in period was followed by a single intravenous dose of etranacogene dezaparvovec ($2x10^{13}$ gc/kg) without prophylactic immunosuppression. Pts will be followed for 5yrs. The co-primary endpoints are change in FIX activity at 26 and 52wks and 52wk annualized bleeding rate compared to lead in. Secondary endpoints include factor replacement use, adverse events (AEs), and reactive use of corticosteroids.

Results: 54 pts were dosed and completed 26wks of follow-up. Mean age (±SD) was 41.5 (15.8) yrs. 38/54 pts (70.4%) had bleeds (n=123) during the lead-in despite prophylaxis, and 23/54 (42.6%) had NAbs to AAV5 at baseline. Following treatment, FIX activity increased rapidly to a mean (SD; min,max) of 37.2% (±19.6; 1.0, 97.1) at wk26, representing a mean (SD; min,max) change from baseline of 36.0% (±19.7; 0, 96.1 p<0.0001, confirmed by per-protocol sensitivity analysis). No correlation of pre-existing NAbs with FIX activity was identified up to a titer of 678.2; n=52, R^2 = 0.078); one individual had a NAb titer of 3212.3 and did not respond. One additional pt received a partial dose and remained on prophylaxis; all other pts (52/54; 96.3%) successfully discontinued routine prophylaxis. 39/54 (72.2%) pts reported 0 bleeds in the first 26wks post-treatment; 15 pts reported a total of 21 bleeds. Mean (SD) annualized FIX consumption (IU/yr/pt) was 292,304 (±171,079) during lead-in, decreasing to 12,622 (±36,466) at wk26 (96.0% reduction, N=54). Overall, 37/54 (68.5%) pts experienced any treatment-related AE post-treatment, the majority of which (81.5%) were mild. No deaths occurred and no treatment-related SAEs were reported. 7 pts had infusion-related reactions; the infusion was discontinued in 1 pt. Treatment-related elevations in liver enzymes were reported in 9 pts who received steroids per protocol. All discontinued steroid use prior to wk26 and FIX activity was preserved in the mild range. Additionally, the most frequent treatment-related AEs were headache (13.0%) and influenza-like illness (13.0%). No inhibitors to FIX were reported and no relationship between safety and NAbs was observed.

Summary/Conclusion: Following a single dose of etranacogene dezaparvovec, FIX activity increased, without the need for prophylactic immunosuppression, into the mild-to-normal range at 26wks in pts with severe/moderately severe HB. Pts were able to discontinue prophylaxis and bleeding was abolished in the majority. Safety was consistent with early phase AAV5 studies and together these data support a favorable safety and efficacy profile.

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