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Table S1. Characteristics of Included Studies

Trial name / NCT	Gene therapy	Included studies
Hemophilia A		
Alta / NCT03061201	Giroctocogene fitelparvovec (PF-07055480/SB-525)	- Leavitt (2024): Giroctocogene fitelparvovec gene therapy for severe hemophilia A: 104-week analysis of the phase 1/2 Alta study - ASH 2023: Four-Year Follow-up of the Alta Study, a Phase 1/2 Study of Giroctocogene Fitelparvovec (PF-07055480/SB-525) Gene Therapy in Adults with Severe Hemophilia A - ASH 2022: Updated Results of the Alta Study, a Phase 1/2 Study of Giroctocogene Fitelparvovec (PF-07055480/SB-525) Gene Therapy in Adults with Severe Hemophilia A - ASH 2021: Updated Results of the Alta Study, a Phase 1/2 Study of Giroctocogene Fitelparvovec (PF-07055480/SB-525) Gene Therapy in Adults with Severe Hemophilia a - ASH 2020: Updated Follow-up of the Alta Study, a Phase 1/2 Study of Giroctocogene Fitelparvovec (SB-525) Gene Therapy in Adults with Severe Hemophilia a - ASH 2019: Updated Follow-up of the Alta Study, a Phase 1/2, Open Label, Adaptive, Dose-Ranging Study to Assess the Safety and Tolerability of SB-525 Gene Therapy in Adult Patients with Severe Hemophilia A - ISTH 2019: Initial Results of the Alta Study, a Phase 1/2, Open Label, Adaptive, Dose-ranging Study to Assess the Safety and Tolerability of SB-525 Gene Therapy in Adult Subjects with Severe Hemophilia A
GENEr8-1 / NCT02576795	Valoctocogene roxaparvovec (BMN-270)	- Symington (2024): Long-term safety and efficacy outcomes of valoctocogene roxaparvovec gene transfer up to 6 years post-treatment - Symington (2024): Long-term safety and efficacy outcomes of valoctocogene roxaparvovec gene transfer up to 6 years post-treatment - Laffan (2022): Hemostatic results for up to 6 years following treatment with valoctocogene roxaparvovec, an AAV5-hFVIII-SQ gene therapy for severe hemophilia A - ISTH 2022: Hemostatic results for up to 6 years following treatment with valoctocogene roxaparvovec, an AAV5-hFVIII-SQ gene therapy for severe hemophilia A - ISTH 2021: Hemostatic Response is Maintained for up to 5 Years Following Treatment with Valoctocogene Roxaparvovec, an AAV5-hFVIII-SQ Gene Therapy for Severe Hemophilia A - Pasi (2020): Multiyear Follow-up of AAV5-hFVIII-SQ Gene Therapy for Hemophilia A - Ozelo (2020): A FIRST-IN-HUMAN FOUR-YEAR FOLLOW-UP STUDY OF DURABLE THERAPEUTIC EFFICACY AND SAFETY OF AAV GENE THERAPY WITH VALOCTOCOGENE ROXAPARVOVEC FOR SEVERE HEMOPHILIA A

		- ISTH 2019: First-in-human Evidence of Durable Therapeutic Efficacy and Safety of AAV Gene Therapy Over Three-years with Valoctocogene Roxaparvovec for Severe Haemophilia A (BMN 270-201 Study) - Rangarajan (2017): AAV5–Factor VIII Gene Transfer in Severe Hemophilia A - ASH 2017: Achievement of Normal Circulating Factor VIII Activity Following Bmn 270 AAV5-FVIII Gene Transfer: Interim, Long-Term Efficacy and Safety Results from a Phase 1/2 Study in Patients with Severe Hemophilia a - ASH 2017: Interim Analysis of Immunogenicity to the Vector Capsid and Transgene-Expressed Human FVIII in a Phase-1/2 Clinical Study of Bmn 270, an AAV5-Mediated Gene Therapy for Hemophilia a - ISTH 2017: Interim Results from a Phase 1/2 AAV5-FVIII Gene Transfer in Patients with Severe Hemophilia A
GENEr8-1 / NCT03370913	Valoctocogene roxaparvovec (BMN-270)	- Madan (2024): Three-year outcomes of valoctocogene roxaparvovec gene therapy for hemophilia A - O'Mahoney (2023): Health-related quality of life following valoctocogene roxaparvovec gene therapy for severe hemophilia A in the phase 3 trial GENEr8-1 - Mahlangu (2023): Efficacy and safety of valoctocogene roxaparvovec gene transfer for severe hemophilia A: results from the GENEr8-1 three-year analysis - ISTH 2023: Bleeding, FVIII activity, and safety 3 years after gene transfer with valoctocogene roxaparvovec: Results from GENEr8-1 - ISTH 2023: Gene Therapy in Hemophilia A: the Impact of Valoctocogene Roxaparvovec on Patient Outcomes – Initial Results from Patient Reported Outcomes, Burdens and Experiences (PROBE) from the GENEr8-1 Trial - ISTH 2023: The impact of gene therapy on the musculoskeletal health of patients with severe hemophilia A - O'Mahoney (2022): IMPACT of VALOCTOCOGENE ROXAPARVOVEC GENE TRANSFER for SEVERE HAEMOPHILIA A on HEALTH-RELATED QUALITY of LIFE - Ozelo (2022): Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A. - Long (2021): Early Phase Clinical Immunogenicity of Valoctocogene Roxaparvovec, an AAV5-Mediated Gene Therapy for Hemophilia A - Pasi (2021): Persistence of haemostatic response following gene therapy with valoctocogene roxaparvovec in severe haemophilia A. - ASH 2021: Health-Related Quality of Life Following Valoctocogene Roxaparvovec Gene Therapy for Severe Hemophilia A in the Phase 3 Trial GENEr8-1

		- ASH 2021: Relationship between Endogenous, Transgene FVIII Expression and Bleeding Events Following Valoctocogene Roxaparvovec Gene Transfer for Severe Hemophilia A: A Post-Hoc Analysis of the GENEr8-1 Phase 3 Trial - ISTH 2021: Efficacy and Safety of Valoctocogene Roxaparvovec Adeno-associated Virus Gene Transfer for Severe Hemophilia A: Results from the Phase 3 GENEr8-1 Trial
NCT03003533 / NCT03432520	Dirloctogene samoparvovec (SPK-8011)	- Miesbach (2024): Long-Term FVIII Expression with Reduced Bleeding Following Gene Transfer for Hemophilia A: Follow-up on the Dirloctocogene Samoparvovec Phase I/II Trial - ISTH 2023: Improved Joint Health After Gene Therapy with Dirloctocogene Samoparvovec (SPK-8011) in People with Hemophilia A - ISTH 2023: Improved Quality of Life in People with Hemophilia A Following Gene Therapy with Dirloctocogene Samoparvovec (SPK-8011) - ASH 2022: Long-Term Durable FVIII Expression with Improvements in Bleeding Rates Following AAV-Mediated FVIII Gene Transfer for Hemophilia A: Multiyear Follow-up on the Phase I/II Trial of SPK-8011 - ISTH 2021: Phase I/II Trial of SPK-8011: Stable and Durable FVIII Expression After AAV Gene Transfer for Hemophilia A - George (2021): Multiyear Factor VIII Expression after AAV Gene Transfer for Hemophilia A. - ISTH 2020: Phase I/II Trial of SPK-8011: Stable and Durable FVIII Expression for >2 Years with Significant ABR Improvements in Initial Dose Cohorts Following AAV-Mediated FVIII Gene Transfer for Hemophilia A - George (2018): SPK-8011: Preliminary results from a phase 1/2 trial of investigational gene therapy for hemophilia A - Sullivan (2018): SPK-8011: Preliminary results from a phase 1/2 trial of investigational gene therapy for hemophilia confirm transgene derived increases in FVIII activity that are persistent and stable beyond eight months - ASH 2018: A Phase 1/2 Trial of Investigational Spk-8011 in Hemophilia a Demonstrates Durable Expression and Prevention of Bleeds - ASH 2017: Spk-8011: Preliminary Results from a Phase 1/2 Dose Escalation Trial of an Investigational AAV-Mediated Gene Therapy for Hemophilia a
NCT03734588	SPK-8016	- Sullivan (2021): SPK-8016: Preliminary results from a phase 1/2 clinical trial of gene therapy for hemophilia A
NCT03370172	TAK-754	- Chapin (2021): Results from a phase 1/2 safety and dose escalation study of TAK-754, an aav8 vector with a codon-optimized b-domain-deleted factor VIII transgene in severe hemophilia A

NCT03588299	BAY 2599023 (AAVhu37.hFVIIIco)	- Ferrante (2021): Broad patient eligibility and long-term tolerability in the first-in-human gene therapy study of bay 2599023 in severe haemophilia a - Pipe (2021): Evolution of AAV vector gene therapy is ongoing in hemophilia. Will the unique features of Bay 2599023 address the outstanding needs? - ASH 2021: First-in-Human Dose-Finding Study of AAVhu37 Vector-Based Gene Therapy: BAY 2599023 Has Stable and Sustained Expression of FVIII over 2 Years - ASH 2020: First-in-Human Gene Therapy Study of AAVhu37 Capsid Vector Technology in Severe Hemophilia A - BAY 2599023 has Broad Patient Eligibility and Stable and Sustained Long-Term Expression of FVIII - ISTH 2020: First-in-Human Gene Therapy Study of AAVhu37 Capsid Vector Technology in Severe Hemophilia A: Safety and FVIII Activity Results - ASH 2019: First-in-human Gene Therapy Study of AAVhu37 Capsid Vector Technology in Severe Hemophilia A
NCT03001830GO-8	GO-8 (AAV8-HLP-hFVIII-V3)	- ASH 2023: GO-8: Stable Expression of Factor VIII over 5 Years Following Adeno-Associated Gene Transfer in Subjects with Hemophilia a Using a Novel Human Factor VIII Variant - ASH 2018: GO-8: Preliminary Results of a Phase I/II Dose Escalation Trial of Gene Therapy for Haemophilia a Using a Novel Human Factor VIII Variant
Hemophilia B		
BENEGENE-2 / NCT02484092	Fidanacogene elaparvovec (SPK-9001)	- Rasko (2023): PATTERNS OF JOINT BLEEDS IN PATIENTS WITH HEMOPHILIA B FOLLOWING FIDANACOGENE ELAPARVOVEC ADENO-ASSOCIATED VIRUS GENE THERAPY - ASH 2023: Health-Related Quality of Life in Adults with Hemophilia B after Receiving Gene Therapy with Fidanacogene Elaparvovec - George (2021): Evaluation of liver health after fidanacogene elaparvovec gene therapy: Data from study participants with up to 5 years of follow-up - ASH 2021: Follow-up of More Than 5 Years in a Cohort of Patients with Hemophilia B Treated with Fidanacogene Elaparvovec Adeno-Associated Virus Gene Therapy - ASH 2019: Efficacy and Safety in 15 Hemophilia B Patients Treated with the AAV Gene Therapy Vector Fidanacogene Elaparvovec and Followed for at Least 1 Year - ISTH 2019: Health-related Quality of Life Improvements in Adult Haemophilia B Patients at One Year Follow-up after Receiving SPK-9001 Gene Transfer - George (2017): Hemophilia B Gene Therapy with a High-Specific-Activity Factor IX Variant. - ASH 2017: Spk-9001: Adeno-Associated Virus Mediated Gene Transfer for Hemophilia B Achieves Sustained Factor IX with Minimal Immune Response

		- ASH 2017: Spk-9001: Adeno-Associated Virus Mediated Gene Transfer for Hemophilia B - 1 Year Follow up and Impact of Baseline Characteristics on Transgene-Derived Factor IX Activity and Persistence - ISTH 2017: SPK-9001: Adeno-associated Virus Mediated Gene Transfer for Haemophilia B Achieved Durable Endogenous Prophylaxis at Levels of Activity Sufficient to Achieve Significant Mean Reduction in Annual Bleeding and Infusions Rates in Preliminary Data from an On-going Phase 1/2a Trial - ISTH 2017: Preliminary Results of SPK-9001 Gene Transfer Demonstrate Statistical Improvements on the Health-related Quality-of-Life in Adults with Haemophilia B - George (2016): Preliminary results of a phase 1/2 trial of SPK-9001, a hyperactive FIX variant delivered by a novel capsid, demonstrate consistent factor IX activity levels at the lowest dose cohort - High (2016): Aav-mediated gene therapy for hemophilia B-expression at therapeutic levels with low vector doses - ASH 2016: Spk-9001: Adeno-Associated Virus Mediated Gene Transfer for Hemophilia B Achieves Sustained Mean Factor IX Activity Levels of >30% without Immunosuppression - EHA 2016: AAV-MEDIATED GENE THERAPY FOR HEMOPHILIA B-EXPRESSION AT THERAPEUTIC LEVELS WITH LOW VECTOR DOSES
BENEGENE-2 / NCT03861273	Fidanacogene elaparvovec (SPK-9001)	- ISTH 2023: Efficacy and Safety of Fidanacogene Elaparvovec in Adults with Moderately Severe or Severe Hemophilia B: Results from the Phase 3 BENEGENE-2 Gene Therapy Trial
B-LIEVE / NCT05164471	Verbrinacogene setparvovec (FLT180a)	- Young (2022): Results from B-LIEVE, a phase 1/2 dose-confirmation study of FLT180a AAV gene therapy in patients with hemophilia B - ISTH 2022: Results from B-LIEVE, a Phase 1/2 Dose-Confirmation Study of FLT180a AAV Gene Therapy in Patients with Hemophilia B
B-AMAZE / NCT03369444	Verbrinacogene setparvovec (FLT180a)	- Chowdary (2022): Phase 1–2 Trial of AAVS3 Gene Therapy in Patients with Hemophilia B - Chowdary (2021): Follow-up on a novel adeno associated virus (AAV) gene therapy (FLT180A) achieving normal FIX activity levels in severe hemophilia B (HB) patients (B-AMAZE study) - ASH 2021: Factor IX Expression within the Normal Range Prevents Spontaneous Bleeds Requiring Treatment Following FLT180a Gene Therapy in Patients with Severe Hemophilia B: Long-Term Follow-up Study of the B-Amaze Program - ISTH 2020: A Novel Adeno Associated Virus (AAV) Gene Therapy (FLT180a) Achieves Normal FIX Activity Levels in Severe Hemophilia B (HB) Patients (B-AMAZE Study) - Chowdary (2019): B-amaze, a phase 1/2 trial of a novel investigational adeno ass ociated virus (AAV) gene therapy (FLT180a) in subjects with severe or moderately severe hemophilia B (HB)

		- ISTH 2019: FLT180a: Next Generation AAV Vector for Haemophilia B - Long Term, Follow-up and In-depth Analysis of Transgenic FIX Using One-stage, Chromogenic and Global Assays - ASH 2018: A Single Intravenous Infusion of FLT180a Results in Factor IX Activity Levels of More Than 40% and Has the Potential to Provide a Functional Cure for Patients with Haemophilia B
NCT02396342	AMT-060	- Miesbach (2023): Durability of Factor IX activity and bleeding rate in people with severe or moderately severe haemophilia B after long-term follow-up in the phase 1/2 Study of AMT-060, and phase 2b and phase 3 studies of etranacogene dezaparvovec (AMT-061) - Miesbach (2023): DURABILITY OF RESPONSE AFTER LONG-TERM FOLLOW-UP IN THE PHASE 1/2 STUDY OF AMT-060, AND PHASE 2B AND 3 STUDIES OF ETRANACOGENE DEZAPARVOVEC IN HAEMOPHILIA B - ASH 2022: Durability of Factor IX Activity and Bleeding Rate in People with Severe or Moderately Severe Hemophilia B after 5 Years of Follow-up in the Phase 1/2 Study of AMT-060, and after 3 Years of Follow-up in the Phase 2b and 2 Years of Follow-up in the Phase 3 Studies of Etranacogene Dezaparvovec (AMT-061) - ISTH 2021: Five Year Data Confirms Stable FIX Expression and Sustained Reductions in Bleeding and Factor IX Use Following AMT-060 Gene Therapy in Adults with Severe or Moderate-severe Hemophilia B - Leebek (2020): Stable FIX expression and durable reductions in bleeding and factor IX consumption for up to 4 years following AMT-060 gene therapy in adults with severe or moderate-severe hemophilia B - ASH 2020: AMT-060 Gene Therapy in Adults with Severe or Moderate-Severe Hemophilia B Confirm Stable FIX Expression and Durable Reductions in Bleeding and Factor IX Consumption for up to 5 Years - ASH 2019: Stable FIX Expression and Durable Reductions in Bleeding and Factor IX Consumption for up to 4 Years Following AMT-060 Gene Therapy in Adults with Severe or Moderate-Severe Hemophilia B - ISTH 2019: Stable Expression of FIX and Maintained Reductions in Bleeding and Factor IX Consumption Following AMT-060 Gene Therapy with up to 3.5 Years of Follow Up in Adults with Severe or Moderate-Severe Hemophilia B - Miesbach (2018): Gene therapy with adeno-associated virus vector 5–human factor IX in adults with hemophilia B - ASH 2018: Reduction in Annualized Bleeding and Factor IX Consumption up to 2.5 Years in Adults with Severe or Moderate-Severe Hemophilia B Treated with AMT-060 (AAV5-hFIX) Gene Therapy - ISTH 2017: Updated results from a doseescalation study in adults with severe or moderate-severe hemophilia b treated with AMT-060 (AAV5-HFIX) gene therapy: Up to 1.5 years follow-up

		- ASH 2017: Stable Elevations in FIX Activity and Reductions in Annualized Bleeding Rate over up to 2 Years of Follow-up of Adults with Severe or Moderate-Severe Hemophilia B Treated with AMT-060 (AAV5-hFIX) Gene Therapy - ASH 2016: Interim Results from a Dose Escalating Study of AMT-060 (AAV5-hFIX) Gene Transfer in Adult Patients with Severe Hemophilia B - EHA 2016: FIRST RESULTS FROM A DOSE-ESCALATING STUDY WITH AAV5 VECTOR CONTAINING WILD TYPE HUMAN FACTOR IX GENE THERAPY IN PATIENTS WITH SEVERE OR MODERATELY-SEVERE HAEMOPHILIA B
HOPE-B / NCT03569891	Etranacogene dezaparvovec (AMT-061)	- Gomez (2023): MULTIPLE-YEAR DURABILITY DATA FROM A PHASE 2B TRIAL OF GENE THERAPY WITH ETRANACOGENE DEZAPARVOVEC IN PATIENTS WITH HEMOPHILIA B - Miesbach (2023): Durability of Factor IX activity and bleeding rate in people with severe or moderately severe haemophilia B after long-term follow-up in the phase 1/2 Study of AMT-060, and phase 2b and phase 3 studies of etranacogene dezaparvovec (AMT-061) - Miesbach (2023): DURABILITY OF RESPONSE AFTER LONG-TERM FOLLOW-UP IN THE PHASE 1/2 STUDY OF AMT-060, AND PHASE 2B AND 3 STUDIES OF ETRANACOGENE DEZAPARVOVEC IN HAEMOPHILIA B - ASH 2022: Durability of Factor IX Activity and Bleeding Rate in People with Severe or Moderately Severe Hemophilia B after 5 Years of Follow-up in the Phase 1/2 Study of AMT-060, and after 3 Years of Follow-up in the Phase 2b and 2 Years of Follow-up in the Phase 3 Studies of Etranacogene Dezaparvovec (AMT-061) - Miesbach (2021): Gene Transfer with Etranacogene dezaparvovec (AAV5-Padua hFIX variant) in Adults with Severe or Moderate-Severe Hemophilia B: Two Year Data from a Phase 2b Trial - VonDrygalski (2021): Etranacogene dezaparvovec (AAV5-PADUA HFIX variant) in adults with severe or moderate-severe hemophilia b: Two year data from a phase 2B trial - ISTH 2021: Etranacogene Dezaparvovec (AAV5-Padua hFIX Variant, AMT-061), an Enhanced Vector for Gene Transfer in Adults with Severe or Moderate-severe Hemophilia B: 2.5 Year Data from a Phase 2b Trial - Sawyer (2020): Clearance of Vector DNA from Bodily Fluids in Patients with Severe or Moderate-Severe Hemophilia B Following Systemic Administration of AAV5-hFIX and AAV5-hFIX Padua - ASH 2020: Etranacogene Dezaparvovec (AAV5-Padua hFIX variant), an Enhanced Vector for Gene Transfer in Adults with Severe or Moderate-Severe Hemophilia B: Two Year Data from a Phase 2b Trial - EHA 2020: RECENT PROGRESS IN THE DEVELOPMENT OF AMT-061 (ETRANACOGENE DEZAPARVOVEC) FOR PERSONS WITH SEVERE OR MODERATELY SEVERE HEMOPHILIA B

		- ISTH 2019: AMT-061 (AAV5-padua HFIX variant) an enhanced vector for gene transfer in adults with severe or moderate-severe hemophilia B: Follow-up up to 9 months in a phase 2b trial - Pipe (2019): A single infusion of AMT-061 (AAV5-Padua hFIX) is safe and effective in adults with hemophilia B: Interim results from dose-confirmation phase 2b trial - ASH 2019: One Year Data from a Phase 2b Trial of AMT-061 (AAV5-Padua hFIX variant), an Enhanced Vector for Gene Transfer in Adults with Severe or Moderate-Severe Hemophilia B
HOPE-B / NCT03569891	Etranacogene dezaparvovec (AMT-061)	- Coppens (2024): Etranacogene dezaparvovec gene therapy for haemophilia B (HOPE-B): 24-month post-hoc efficacy and safety data from a single-arm, multicentre, phase 3 trial - Pipe (2024): Etranacogene Dezaparvovec Shows Sustained Efficacy and Safety in Adult Patients With Severe or Moderately Severe Haemophilia B 3 Years After Administration in the HOPE-B Trial - Itzler (2024): Effect of etranacogene dezaparvovec on quality of life for severe and moderately severe haemophilia B participants: Results from the phase III HOPE-B trial 2 years after gene therapy - Pipe (2023): Gene Therapy with Etranacogene Dezaparvovec for Hemophilia B. - Astermark (2023): MONITORING OF FIX ACTIVITY FOLLOWING AAV5-MEDIATED GENE THERAPY WITH ETRANACOGENE DEZAPARVOVEC - Astermark (2023): ANALYSIS OF ELEVATED ALANINE TRANSAMINASE IN HOPE-B, A PHASE 3 RECOMBINANT ADENO-ASSOCIATED VIRAL 5 GENE THERAPY TRIAL IN PEOPLE WITH HAEMOPHILIA B - Itzler (2023): Improvements in health-related quality of life in adults with severe or moderately severe haemophilia B after receiving etranacogene dezaparvovec gene therapy - Miesbach (2023): Durability of Factor IX activity and bleeding rate in people with severe or moderately severe haemophilia B after long-term follow-up in the phase 1/2 Study of AMT-060, and phase 2b and phase 3 studies of etranacogene dezaparvovec (AMT-061) - Miesbach (2023): DURABILITY OF RESPONSE AFTER LONG-TERM FOLLOW-UP IN THE PHASE 1/2 STUDY OF AMT-060, AND PHASE 2B AND 3 STUDIES OF ETRANACOGENE DEZAPARVOVEC IN HAEMOPHILIA B - Klamroth (2023): Indirect treatment comparisons of the gene therapy etranacogene dezaparvovec (CSL222) vs. extended half-life Factor IX therapies for severe or moderately severe hemophilia B - Pipe (2023): Adults with severe or moderately severe haemophilia B receiving etranacogene dezaparvovec in the HOPE-B phase 3 trial experience a stable increase in mean Factor IX activity levels and durable haemostatic protection after 24 months' follow-up - Pipe (2023): Durability of bleeding protection and Factor IX activity in individuals with and without adeno-associated virus serotype 5 neutralising antibodies (Titres <1:700) in the phase 3 HOPE-B trial of etranacogene dezaparvovec gene therapy for haemophilia B

		- Recht (2023): HEALTH-RELATED QUALITY OF LIFE IN THE TWO YEARS FOLLOWING ETRANACOGENE DEZAPARVOVEC GENE THERAPY FOR HAEMOPHILIA B IN THE PHASE 3 HOPE-B TRIAL - ASH 2023: Long-Term Bleeding Protection, Sustained FIX Activity, Reduction of FIX Consumption and Safety of Hemophilia B Gene Therapy: Results from the HOPE-B Trial 3 Years after Administration of a Single Dose of Etranacogene Dezaparvovec in Adult Patients with Severe or Moderately Severe Hemophilia B - ISTH 2023: Phase 3 HOPE-B trial of etranacogene dezaparvovec in severe/moderately severe hemophilia B: A post hoc responder analysis of participants who received full dose and responded to treatment - Miesbach (2022): FINAL ANALYSIS from the PIVOTAL PHASE 3 HOPE-B GENE THERAPY TRIAL: STABLE STEADY-STATE EFFICACY and SAFETY of ETRANACOGENE DEZAPARVOVEC in ADULTS with SEVERE or MODERATELY SEVERE HEMOPHILIA B - von Drygalski (2022): Stable and durable factor IX levels in hemophilia B patients over 3 years post etranacogene dezaparvovec gene therapy. - ASH 2022: Durability of Bleeding Protection and Factor IX Activity Levels Are Demonstrated in Individuals with and without Adeno-Associated Virus Serotype 5 Neutralizing Antibodies (Titers <1:700) with Comparable Safety in the Phase 3 HOPE-B Clinical Trial of Etranacogene Dezaparvovec Gene Therapy for Hemophilia B - ASH 2022: Durability of Factor IX Activity and Bleeding Rate in People with Severe or Moderately Severe Hemophilia B after 5 Years of Follow-up in the Phase 1/2 Study of AMT-060, and after 3 Years of Follow-up in the Phase 2b and 2 Years of Follow-up in the Phase 3 Studies of Etranacogene Dezaparvovec (AMT-061) - ASH 2022: Adults with Severe or Moderately Severe Hemophilia B Receiving Etranacogene Dezaparvovec in the HOPE-B Phase 3 Clinical Trial Continue to Experience a Stable Increase in Mean Factor IX Activity Levels and Durable Hemostatic Protection after 24 Months' Follow-up - ISTH 2022: Improvements in Health-Related Quality of Life in Adults with Severe or Moderately Severe Hemophilia B After Receiving Etranacogene Dezaparvovec Gene Therapy - Pipe (2021): Efficacy and safety of etranacogene dezaparvovec in adults with severe or moderate-severe hemophilia B: First data from the phase 3 HOPE-B gene therapy trial - ASH 2021: First Data from the Phase 3 HOPE-B Gene Therapy Trial: Efficacy and Safety of Etranacogene Dezaparvovec (AAV5-Padua hFIX variant; AMT-061) in Adults with Severe or Moderate-Severe Hemophilia B Treated Irrespective of Pre-Existing Anti-Capsid Neutralizing Antibodies

		- EHA 2021: CLINICAL OUTCOMES IN ADULTS WITH HEMOPHILIA B WITH AND WITHOUT PRE-EXISTING NEUTRALIZING ANTIBODIES TO AAV5: 6 MONTH DATA FROM THE PHASE 3 ETRANACOGENE DEZAPARVOVEC HOPE-B GENE THERAPY TRIAL - EHA 2021: 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 - ISTH 2021: 52 Week Efficacy and Safety of Etranacogene Dezaparvovec in Adults with Severe or Moderate-severe Hemophilia B: Data from the Phase 3 HOPE-B Gene Therapy Trial - ISTH 2021: Clinical Outcomes in Adults with Hemophilia B with and without Pre-existing Neutralizing Antibodies to AAV5: 6 Month Data from the Phase 3 Etranacogene Dezaparvovec HOPE-B Gene Therapy Trial - Castaman (2020): Development of amt-061 (etranacogene dezaparvovec) for persons with severe or moderately severe hemophilia b
NCT01687608	BAX335	- ASH 2022: BAX 335 Hemophilia B Gene Therapy Phase 1/2 Clinical Trial: Long-Term Safety and Efficacy Follow-up - Konkle (2021): BAX 335 hemophilia B gene therapy clinical trial results: potential impact of CpG sequences on gene expression - ISTH 2017: An Analysis of Bleeding Rates and Factor IX Consumption in the Phase I/II BAX 335 Gene Therapy Trial in Subjects with Hemophilia B - ISTH 2015: Update on a phase 1/2 open-label trial of BAX335, anadeno-associated virus 8 (AAV8) vector-based genetherapy program for hemophilia B"
NCT00979238	scAAV2/8-LP1-hFIXco	- ASH 2023: Stable Therapeutic Transgenic FIX Levels for More Than 10 Years in Subjects with Severe Hemophilia B Who Received scAAV2/8-LP1-Hfixco Adeno-Associated Virus Gene Therapy - ASH 2018: Adeno-Associated Mediated Gene Transfer for Hemophilia B:8 Year Follow up and Impact of Removing ""Empty Viral Particles"" on Safety and Efficacy of Gene Transfer - Nathwani (2014): Long-term safety and efficacy of factor IX gene therapy in hemophilia B. - Tuddenham (2012): Gene therapy for severe hemophilia B - Davidoff (2012): Stable factor IX activity following AAV-mediated gene transfer in patients with severe hemophilia B - Nathwani (2011): Adenovirus-Associated Virus Vector–Mediated Gene Transfer in Hemophilia B
101HEMB01 / NCT02618915	DTX101	- ASH 2017: 101HEMB01 Is a Phase 1/2 Open-Label, Single Ascending Dose-Finding Trial of DTX101 (AAVrh10FIX) in Patients with Moderate/Severe Hemophilia B That Demonstrated Meaningful but Transient Expression of Human Factor IX (hFIX)

NCT04135300	BBM-H901	- Xue (2022): Safety and activity of an engineered, liver-tropic adeno-associated virus vector expressing a hyperactive Padua factor IX administered with prophylactic glucocorticoids in patients with haemophilia B: a single-centre, single-arm, phase 1, pilot trial
NCT00515710	AAV2-hFIX16	- George (2020): Long-Term Follow-Up of the First in Human Intravascular Delivery of AAV for Gene Transfer: AAV2-hFIX16 for Severe Hemophilia B

Table S2. Sensitivity analysis for Hemophilia A outcomes

Outcome	Outlier 1	Removing Outlier 1		Outlier 2	Removing Outliers 1& 2	
		Random effect (95% CI)	I^2 value		Random effect (95% CI)	I^2 value
(c) ALT elevation*	SPK-8016, phase 1/2	0.77 (0.62, 0.87)	72%	BAY 2599023, phase 1/2	0.81 (0.67, 0.90)	67%

*Note: there was no outliers detected by using the method we described above. Instead, we used the Z-score method to detect the outlier. The study with the largest absolute value Z-score was identified as the outlier and removed in the sensitivity analysis.

Table S3. Sensitivity analysis for Hemophilia B outcomes

Outcome	Outlier 1	Removing Outlier 1		Outlier 2	Removing Outliers 1& 2	
		Random effect (95% CI)	I^2 value		Random effect (95% CI)	I^2 value
(a) ABR	BBM-H901	-3.01 (-3.84, -2.17)	61%	scAAV2/8-LP1-hFIXco, phase 1	-2.82 (-3.66, -1.98)	3%
(b) AIR*	Etranaco. dex., phase 3	-54.00 (-61.33, -47.39)	0%	--		
(d) factor IX level at 12 months*	Etranaco. dex., phase 3	25.55 (15.76, 35.35)	66%	Etranaco. dex., phase 2b	23.37 (19.48, 27.25)	0%

*Note: for outcomes “AIR” and “factor IX level at 12 months”, there was no outliers detected by using the method we described above. Instead, we used the Z-score method to detect the outlier. The study with the largest absolute value Z-score was identified as the outlier and removed in the sensitivity analysis.

Search strategy

Terms

- “Hemophilia A” OR “Haemophilia A”
- “Factor 8” OR “Factor VIII” OR “F8 protein, human” OR "VIII activity"
- “Hemophilia B” OR “Haemophilia B”
- “F9 protein” OR OR “Factor 9” OR “Factor IX” OR “F9 protein” OR "IX activity"
- “Gene therapy” OR “Gene therapies” OR “Genetic therapy” OR “Genetic vectors”

Search queries

- Cochrane: 1
    - “hemophilia gene”
- Embase: 2917
    - ('hemophilia a'/exp OR 'haemophilia a':ti,ab OR 'factor 8':ti,ab OR 'blood clotting factor 8'/exp OR 'factor viii':ti,ab OR 'f8 protein, human':ti,ab OR 'viii activity':ti,ab OR 'hemophilia b'/exp OR 'haemophilia b':ti,ab OR 'factor 9':ti,ab OR 'blood clotting factor 9'/exp OR 'factor ix':ti,ab OR 'f9 protein':ti,ab OR 'ix activity':ti,ab) AND ('gene therapy':ti,ab OR 'gene therapies':ti,ab OR 'genetic therapy':ti,ab OR 'gene vector':ti,ab)
- Pubmed: 1878
    - ("Hemophilia A"[mesh] OR "Haemophilia A"[tiab] OR "Factor 8"[tiab] OR "Factor VIII"[tiab] OR "F8 protein, human"[Supplementary Concept] OR "VIII activity"[tiab] OR "F9 protein"[tiab] OR "Hemophilia B"[mesh] OR "Haemophilia B"[tiab] OR "Factor 9"[tiab] OR "Factor IX"[tiab] OR "F9 protein"[tiab] OR "IX activity"[tiab]) AND ("gene therap*"[tiab] OR "Genetic therapy"[mesh] OR "Genetic vectors"[mesh])
- Scopus: 2998
    - (TITLE-ABS-KEY (("Hemophilia A" OR "Haemophilia A" OR "Factor 8" OR "Factor VIII" OR "F8 protein, human" OR "VIII activity" OR "F9 protein" OR "Hemophilia B" OR "Haemophilia B" OR "Factor 9" OR "Factor IX" OR "F9 protein" OR "IX activity")) AND TITLE-ABS-KEY (("Gene therapy" OR "Gene therapies" OR "Genetic therapy" OR "Genetic vectors")))