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ABSTRACTS

Main Congress Oral Abstracts

OR01 | Results of the first-in-human investigation of HMB-001 for prophylactic management of glanzmann thrombasthenia

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Introduction: Glanzmann thrombasthenia (GT) is a rare and severe bleeding disorder caused by deficiency of integrin αIIbβ3, a platelet receptor essential for platelet aggregation. People with GT experience debilitating and sometimes life-threatening bleeding episodes. To date, there are no effective prophylactic options. HMB-001 is a bispecific antibody being developed by Hemab Therapeutics to prevent or reduce the frequency of bleeding episodes in patients with GT. HMB-001 works by binding to and accumulating endogenous activated coagulation factor VII (FVIIa) and targeting it to the surface of activated platelets at the site of vascular injury. This increases the activity of FVIIa to levels that are therapeutically effective. Our Phase 1/2 clinical study aims to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of HMB-001 in individuals with GT.

Methods: The ongoing phase 1/2 study is composed of three parts: part A (single ascending dose); part B (multiple ascending dose) and part C (open label extension). The study includes male and female participants aged 18–65 years old, who have a definitive diagnosis of GT.

Results: Participants included in part A of the study received HMB-001 subcutaneously at dose levels of 0.2 mg/kg, 0.5 mg/kg or 1.25 mg/kg, respectively. At the time of the abstract submission, there were no reported treatment-related adverse events. Pharmacodynamic data showed positive proof of mechanism with a dose-dependent increase in factor VII and factor VIIa as well as signs of coagulation activation based on a dose-dependent reduction in prothrombin time. The pharmacokinetic profile indicates a dose-dependent response and is supportive of infrequent, subcutaneous dosing. Further details of safety, tolerability, pharmacodynamics, and pharmacokinetics will be summarized.

Discussion/Conclusion: The initial safety, tolerability, pharmacodynamics and pharmacokinetics results from part A of the phase 1/2 study are encouraging and support the further development of HMB-001 as a potential prophylactic treatment for GT.

Disclosure of Interest: S. Sivapalaratnam: None declared, S. Austin: None declared, A. Gosnell Employee of: Hemab Therapeutics, U. Lorch: None declared, T. York: None declared, A. Want: None declared, C. Rea Employee of: Hemab Therapeutics.

OR02 | Safety and efficacy of valoctocogene roxaparvovec with prophylactic corticosteroids: 1-year GENEr8-3 results

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Introduction: We assessed the safety and efficacy of valoctocogene roxaparvovec, an adeno-associated virus vector serotype 5 (AAV5) gene therapy for persons with severe haemophilia A (SHA), with prophylactic corticosteroids (CS).

Methods: In the phase 3b, single-arm, open-label GENEr8-3 study (NCT04323098), adult males with SHA (factor VIII [FVIII] activity ≤1 IU/dL) received 6×10^{13} vg/kg valoctocogene roxaparvovec and prophylactic CS starting day 1 (40 mg prednisolone equivalent weeks 0–8, taper to 5 mg weeks 9–19). Additional CS were used for alanine aminotransferase (ALT) elevations (>upper limit of normal or ≥1.5× baseline). Inclusion criteria included ≥12 months HA prophylaxis, ≥150 FVIII concentrate exposure days and no FVIII inhibitor history. Exclusion criteria included pre-existing anti-AAV5 antibodies (titers < minimum dilution for ≤25% of participants) and significant liver dysfunction. Analysis populations were intent-to-treat (ITT; received valoctocogene roxaparvovec) for safety analyses and modified ITT (mITT; on adequate prophylaxis at baseline) for efficacy analyses. The primary efficacy endpoint was change from baseline

in chromogenic FVIII activity at week 52 (2-sided *t*-test). Secondary endpoints were annualized FVIII use (AFU) and annualized treated bleeding rate (AtBR) during the post-HA prophylaxis period (5 weeks post infusion or end of HA prophylaxis + washout period). CS use and safety were assessed.

Results: To date, 22 participants (mean age, 28.0 years) received valoctocogene roxaparvovec; all remain on study. Mean week 52 FVIII activity increased from imputed baseline of 1–16.1 IU/dL (standard deviation [SD], 22.4; median, 7.7; mITT, $n = 21$; $P = .0057$). Post-prophylaxis mean AFU was 382.3 IU/kg/year (SD, 757.3; median, 37.1; −91.6% from baseline) and mean AtBR was 1.9 bleeds/year (SD, 3.7; median, .0; −67.1% from baseline). To date, 22 participants had an adverse event (AE), 20 had a treatment-related AE and five had an infusion-related reaction. ALT elevation occurred in 20 participants and steroid-related AEs occurred in 19 participants; 14 participants used reactive CS. No treatment- or immunosuppressant-related serious AEs occurred. No malignancies or FVIII inhibitors were reported. No AEs led to discontinuation.

Discussion/Conclusion: Compared to previous trials using reactive CS, prophylactic CS yielded lower FVIII activity and conferred no benefit for safety or CS burden.

Disclosure of Interest: M. Ozelo Consultant for: Bayer, BioMarin Pharmaceutical Inc., Pfizer, Sanofi, and Takeda, Speaker Bureau of: BioMarin Pharmaceutical Inc., Novo Nordisk, Pfizer, Roche, Sanofi, and Takeda, J. Mason: None declared, A. Dunn Grant/Research support from: BioMarin Pharmaceutical Inc., Novo Nordisk, Sanofi, Pfizer, Spark and Takeda, Consultant for: CSL Behring, Roche, HemaBiologics, Biomarin, uniQure, and The National Haemophilia Bleeding Disorders Foundation and World Federation of Haemophilia USA, P. Ribeiro Villaça Grant/Research support from: BioMarin Pharmaceutical Inc., Novartis, and Takeda, Consultant for: Bayer, CSL Behring, Novo Nordisk, Roche, Sanofi, Takeda, Speaker Bureau of: Bayer, BioMarin, Novo Nordisk, Roche, Sanofi, and Takeda, M.-C. Shen: None declared, S. Agarwal Shareholder of: BioMarin Pharmaceutical Inc., Employee of: BioMarin Pharmaceutical Inc., U. Imtiaz Shareholder of: BioMarin Pharmaceutical Inc., Employee of: BioMarin Pharmaceutical Inc., H. Liu Shareholder of: BioMarin Pharmaceutical Inc., Employee of: BioMarin Pharmaceutical Inc., T. Robinson Shareholder of: BioMarin Pharmaceutical Inc., Employee of: BioMarin Pharmaceutical Inc.

OR03 | First report of a long-term follow-up extension study 6 years after gene therapy with AMT-060 in adults with hemophilia B confirms safety and stable FIX expression and sustained reductions in factor IX use

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Introduction: AMT-060 is an adeno-associated virus serotype 5 (AAV5) vector encoding a codon-optimised wild-type human factor IX (FIX) gene, driven by a liver-specific promoter. As the predecessor of etranacogene dezaparvovec (Padua FIX variant), it has a same vector backbone, except the two-nucleotide change in the human FIX coding sequence which enhances FIX activity. The Phase I/II study included 10 patients with haemophilia B (FIX activity ≤2 IU/dL) who received a single intravenous infusion of AMT-060 (5×10^{12} gc/kg [Cohort 1; $n = 5$] or 2×10^{13} gc/kg [Cohort 2; $n = 5$]). Nine out of ten patients were prophylaxis free after administration of AMT-060. Using the one-stage activated partial thromboplastin time (aPTT) assay, mean FIX activity as reported initially was 4.4 IU/dL at 52 weeks in Cohort 1 and 6.9 IU/dL at 26 weeks in Cohort 2.

Methods: Patients who successfully completed all assessments during 5 years of follow-up in the study were enrolled in the open-label, Phase I/IIb extension study (NCT05360706). Here, we report the first year of follow-up in the extension study; representing 6 years after AMT-060 administration.

Results: Overall, four patients from Cohort 1 (including one patient who remained on FIX prophylaxis) and five patients from Cohort 2 enrolled in the extension study. FIX activity, using the one-stage aPTT assay, remained stable at Year 6; ranging from 3.1—14.8 IU/dL in Cohort 1 and 3.0—7.1 IU/dL in Cohort 2. Mean (SD) and median FIX activity were 7.5 IU/dL (6.4) and 4.6 IU/dL in Cohort 1, and 5.5 IU/dL (1.5) and 5.8 IU/dL in Cohort 2, respectively. Mean (SD) annualised FIX consumption during Year 6 (excluding surgeries and patient who remained on FIX prophylaxis) was 656.3 (1136.8) IU/year (or 7.5 [12.9] IU/kg/year) in Cohort 1 ($n = 3$) and 0 in Cohort 2 ($n = 5$). No new safety events were identified during Year 6, and no patient returned to prophylaxis.

Discussion/Conclusion: Gene therapies for haemophilia A and B, including etranacogene dezaparvovec, were recently authorised in Europe. Durability of factor expression is a key consideration in the decision-making process for patients and physicians. This 6-year follow-up after AMT-060 administration confirms the safety, durability and stability of FIX expression after AAV-based gene therapy reported previously.

Disclosure of Interest: W. Miesbach Grant/Research support from: Bayer, Biogen Idec, Biotest, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi, Takeda, and UniQure, Consultant for: Biogen Idec, Biotest, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi, Takeda, and UniQure, K. Meijer Consultant for: uniQure; and honoraria from Bayer and Octopharma, with fees paid to the institution, Speaker Bureau of: Alexion, Bayer and CSL Behring, M. Coppens Grant/Research support from: Bayer, CSL Behring, Daiichi Sankyo, Novo Nordisk and Roche, Consultant for: Alexion/AstraZeneca, Bayer, CSL Behring, Sobi and Viatris,

P. Kampmann Speaker Bureau of: speaker fees from uniQure and BioMarin and sat on advisory boards for CSL Behring and BioMarin, R. Klamroth Grant/Research support from: Bayer, BioMarin, CSL Behring, Novo Nordisk, Octapharma, Consultant for: Bayer, BioMarin, CSL Behring, Chugai, Novo Nordisk, Octapharma, Pfizer, Takeda/Shire, Biotest, Grifols, Roche and Sobi, Speaker Bureau of: Bayer, BioMarin, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Takeda/Shire, Biotest, Grifols, Roche/Chugai and Sobi, P. van der Valk Grant/Research support from: Bayer, Consultant for: Speaker fee from CSL Behring. Paid to the institution, R. Wang Employee of: CSL Behring, W. Seifert Employee of: CSL Behring, P. Monahan Employee of: CSL Behring, F. Leebeek Grant/Research support from: unrestricted research grants from CSL Behring, Shire/Takeda, Sobi and uniQure, Consultant for: CSL Behring, Shire/Takeda, Biomarin and uniQure, of which the fees go to Erasmus University Rotterdam. FL was a Data Safety Monitoring Board member of a study sponsored by Roche.

OR04 | Regular prophylaxis with a plasma-derived von Willebrand factor/factor VIII concentrate is effective for reducing nosebleeds in children and adults with von Willebrand disease

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Introduction: Prophylaxis with a von Willebrand factor (VWF) is recommended for von Willebrand disease (VWD) with a history of frequent and severe bleeds. Bleeding from the nose is one of the most common types of bleeding in VWD. The WIL-31 study demonstrated the efficacy of prophylaxis with a plasma-derived VWF/factor VIII (pdVWF/FVIII) concentrate containing VWF and FVIII in a 1:1 activity ratio (wilate®) in adults and children with VWD of all types. The efficacy of prophylaxis during WIL-31 in reducing nosebleeds in people with VWD, compared with previous on-demand treatment is described.

Methods: WIL-31 (NCT04052698) was a prospective, non-controlled, international, multicentre phase 3 trial that enrolled male/female patients, aged ≥6 years with VWD type 1 (VWF:RCo < 30 IU/dL), type 2 (except 2N) or type 3. Prior to WIL-31, all patients had received on-demand treatment with a VWF concentrate during a 6-month, prospective, observational, run-in study (WIL-29); patients who experienced at least six bleeding episodes, excluding menstrual bleeds, of which ≥2 were treated with a VWF concentrate, could enter WIL-31. Patients in WIL-31 received prophylaxis with pdVWF/FVIII 2–3 × per week at 20–40 IU/kg for 12 months. Nosebleeds during WIL-29/-31 were described, and mean ABRs compared.

Results: There were 173 breakthrough bleeds during WIL-31, of which nosebleeds were the most common (89/173; 51.4%). Nosebleeds occurred in 26/33 (79%) patients during on-demand treatment versus 16/33 (48%) during prophylaxis. The mean number of spontaneous nosebleeds per patient during prophylaxis was 2.1 (overall population), 2.3 (6—11 years), 1.2 (12—16 years) and 2.2 (≥17 years). The mean nose ABR reduced by 76% during prophylaxis versus on-demand treatment. This was consistent across age groups (74%—77%) but not across VWD types, with mean nose ABR reductions of 48% (type 1), 89% (type 2) and 80% (type 3). During prophylaxis, a higher number of type 3 patients, compared with type 1 and type 2, experienced nosebleeds (12 vs. 3 vs. 1). 80.9% (72/89) of nosebleeds were treated with pdVWF/FVIII, 86.1% (62/72) of which required only a single infusion; two required concomitant treatment with tranexamic acid.

Discussion/Conclusion: Prophylaxis with pdVWF/FVIII was effective at reducing nosebleeds in VWD across all age groups and to a greater extent in types 2 and 3 patients.

Disclosure of Interest: A. Boban Grant/Research support from: Octapharma, Speaker Bureau of: Amgen, Astra Zeneca, Bayer, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi, Swixx, Takeda, R. Sidonio Jr Grant/Research support from: Genentech, Octapharma, Takeda, Speaker Bureau of: Genentech, Takeda, Octapharma, Guardian Therapeutics, Bayer, Novo Nordisk, UniQure, Biomarin, Spark, Pfizer, L. Dubey: None declared, K. Vilchevska: None declared, A. Inati Grant/Research support from: Novartis, Bausch Health Forma/ Novo Nordisk, Agios, Octapharma, Vifor, Roche, GBT/Pfizer, Speaker Bureau of: Roche, Forma, Novartis, Takeda, Pfizer, Novo Nordisk, C. Khayat Speaker Bureau of: Octapharma, CSL Behring

OR05 | Stable expression of factor VIII over 5 years following adeno-associated viral vector-mediated gene transfer in participants with severe haemophilia a using a novel human factor VIII variant

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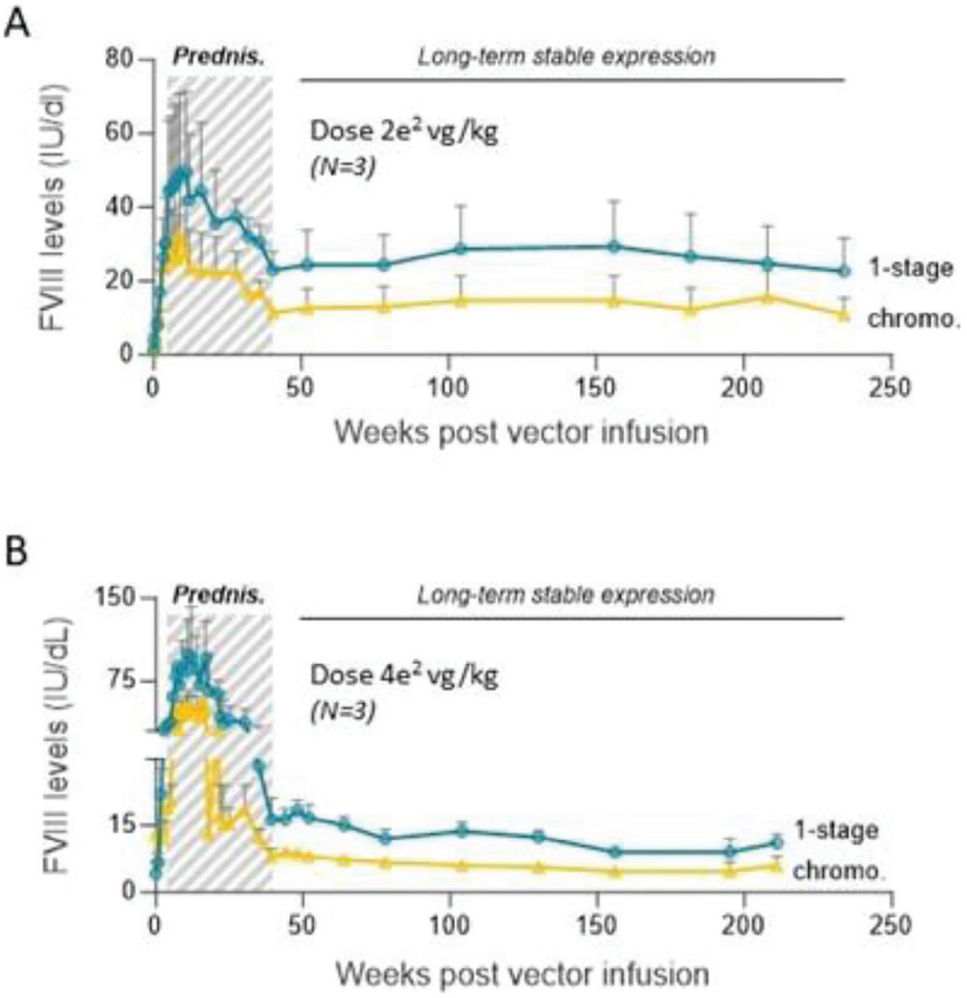
Introduction: GO-8 (ClinicalTrials.gov: NCT03001830) is a study of liver-directed adeno-associated virus (AAV) gene therapy for severe haemophilia A (SHA) using a factor VIII (FVIII) variant containing a 17 amino-acid peptide comprising six N-linked glycosylation motifs from the human FVIII B-domain (AAV-HLP-hFVIII-V3).

Methods: In a multi-centre, open-label, phase I/II clinical trial, we assessed the safety and efficacy of escalating doses of AAV-HLP-hFVIII-V3 pseudotyped with an AAV8 capsid in adults with SHA (FVIII activity ≤1%). Participants received prophylactic immunosuppression to reduce the risk of vector-related transaminase elevation. The primary endpoints were safety, and efficacy assessed by FVIII activity (FVIII: C).

Results: As of May 31 2023, 12 participants were enrolled into one of four vector doses: 6×10^{11} vector genomes (vg)/kg *t* ($n = 1$), 2×10^{12} vg/kg ($n = 3$), 4×10^{12} vg/kg ($n = 3$), or 6×10^{12} vg/kg ($n = 5$). The most common vector-related adverse event was elevation in liver aminotransferase levels, which occurred in 10 of 12 participants within 12 months. Mean chromogenic FVIII: C levels at 12 months after gene therapy were 3 IU/dL in the 6×10^{11}vg/kg cohort, 13 ± 9 IU/dL (range: 2–19 IU/dL) in the 2×10^{12}vg/kg cohort, 8 ± 1 IU/dL in the 4×10^{12} vg/kg cohort (range: 7–9 IU/dL) and 22 ± 34 IU/dL in the 6×10^{12} vg/kg cohort (range 1–82 IU/dL). Transgene expression was stably maintained over a median follow-up of 3 years (range: 2–5 years) from the level achieved 1-year post-infusion, best illustrated by the data from the 2×10^{12} and 4×10^{12} vg/kg cohorts. Nine of the 12 participants remained off prophylaxis post-gene therapy. Median (mean) annualised FVIII consumption reduced from 4097 IU/kg (4657) per year at baseline to 61 IU/kg (1186), that was significant (One sample *t*-test $p = 0.0009$). No FVIII inhibitors or thrombotic events were reported for the duration of the study.

Discussion/Conclusion: A single infusion of AAV-HLP-hFVIII-V3 resulted in stable FVIII expression over a follow-up period of up to 5 years in participants with SHA. A high rate of liver aminotransferase elevation following gene transfer impacted transgene expression. However, nine of the 12 participants were able to discontinue FVIII prophylaxis over the duration of the study, resulting in a significant reduction in FVIII concentrate usage.

Image:



Disclosure of Interest: None declared

OR06 | Human liver biopsy analysis reveals lower RNA transcription may contribute to a decline in FVIII levels following AAV5-hFVIII-SQ gene therapy

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Introduction: Valoctocogene roxaparvovec (AAV5-hFVIII-SQ), an approved gene therapy (GT) for severe haemophilia A (HA), uses an adeno-associated virus vector serotype 5 (AAV5) to deliver a B-domain-deleted factor VIII (FVIII-SQ) cDNA driven by a liver-selective promoter. We obtained liver biopsies (Bx) from clinical trial participants post-GT to investigate FVIII expression variability and decline mechanisms.

Methods: In this optional sub-study of the phase 3, single-arm, open-label GENEr8-1 trial (NCT03370913) assessing 6×10^{13} vg/kg valoctocogene roxaparvovec in males with severe HA (FVIII ≤1 IU/dL), liver Bx were collected from 12 participants 2.1–4.1 years (yrs) post-dosing. Standard-of-care Bx in response to transient transaminitis were collected from two additional participants 0.3–1.1 yrs post-GT. Exclusion criteria were any liver ultrasound findings that precluded safe Bx. Primary endpoints were to examine liver histopathology, assess transduction efficiency, and quantify episomal forms of vector DNA and transgene expression. Droplet digital PCR was used to quantify DNA and RNA in hepatocytes.

Results: Of the 14 Bx collected, two were from individuals with respective peak FVIII activity of 45.1 and 27.4 IU/dL at weeks 12 and 33, which both declined to <3 IU/dL at the time of Bx (2.7 and 3.3 yrs). The remaining 12 Bx were from participants with measurable FVIII activity (13.8–86.9 IU/dL; FVIII > 3 IU/dL) at Bx (2.7–2.9 yrs). In the two individuals with FVIII < 3 IU/dL, circular full-length vector genome levels were 1.5 and 2.2 vg/diploid cell; FVIII-SQ RNA transcript levels were 0.2 and 1.7 transcripts/ng RNA. In the 12 participants with FVIII > 3 IU/dL, mean ± standard deviation (SD) circular full-length vector genome levels were 4.1 ± 2.1 (range, 1.9–7.8) vg/diploid cell; mean ± SD FVIII-SQ RNA transcript levels were 92.9 ± 47.7 (range, 15.8–152.9) transcripts/ng RNA. The two individuals with FVIII < 3 IU/dL had a significantly lower RNA/DNA ratio than the 12 with FVIII > 3 IU/dL ($P = 0.004$).

Discussion/Conclusion: Participants had similar vector DNA levels; however, the two individuals with <3 IU/dL FVIII had lower RNA levels. Decline in FVIII over time may be due to reduced transcription of episomal vector DNA to RNA in hepatocytes. Ongoing histopathology and molecular studies will assess additional factors contributing to expression variability and transient transaminitis.

Disclosure of Interest: A. Ismail Shareholder of: BioMarin Pharmaceutical Inc., Employee of: BioMarin Pharmaceutical Inc., B. Yates Shareholder of: BioMarin Pharmaceutical Inc., Employee of: BioMarin Pharmaceutical Inc., K. Jayaram Shareholder of: BioMarin Pharmaceutical Inc., Employee of: BioMarin Pharmaceutical Inc., G. Kenet Grant/Research support from: Genentech and Pfizer, Consultant for: BioMarin Pharmaceutical Inc., Novo Nordisk, Sanofi US Services, Bayer, CSL Behring, Genentech, and Sobi, Inc., J. Mason: None declared, J. Mahlangu Grant/Research support from: BioMarin Pharmaceutical Inc., CSL Behring, F Hoffmann-La Roche, Novartis, Novo Nordisk, Pfizer, Sanofi, and Spark Therapeutics, Consultant for: BioMarin Pharmaceutical Inc., CSL Behring, F Hoffmann-La Roche, Novo Nordisk, and Spark Therapeutics, Employee of: University of the Witwatersrand, Speaker Bureau of: F Hoffmann-La Roche, ISTH, Novo Nordisk, Pfizer, Sanofi, Takeda, WFH, and Springer, A. Dunn Grant/Research support from: BioMarin Pharmaceutical Inc., Novo Nordisk, Sanofi, and Takeda, Consultant for: CSL Behring, Roche, uniQure, and The National Hemophilia Foundation and World Federation of Hemophilia USA, S. Shapiro Grant/Research support from: Bayer, Chugai/Roche, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Shire, Sobi, and Takeda, Consultant for: Bayer, Chugai/Roche, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Shire, Sobi, and Takeda, Speaker Bureau of: Bayer, Chugai/Roche, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Shire, Sobi, and Takeda, M. Wang Consultant for: Bayer, BioMarin Pharmaceutical Inc., Bioverativ, Catalyst Biosciences, CSL Behring, Genentech, Novo Nordisk, and Takeda, Speaker Bureau of: Bayer, BioMarin Pharmaceutical Inc., Bioverativ, Catalyst Biosciences, CSL Behring, Genentech, Novo Nordisk, and Takeda, F. Peyvandi Consultant for: BioMarin Pharmaceutical Inc., Roche, Sanofi, Sobi, and Takeda, Speaker Bureau of: Grifols and Roche, A. Giermasz Grant/Research support from: BioMarin Pharmaceutical Inc., Bioverativ/Sanofi, Genentech/Roche, Sangamo Therapeutics, and uniQure, Consultant for: ATHN, Bayer, BioMarin Pharmaceutical Inc., Bioverativ/Sanofi, Genentech/Roche,

Novo Nordisk, Pfizer, Sangamo Therapeutics, Sanofi Genzyme, and uniQure„ Speaker Bureau of: Bioverativ/Sanofi and Genentech/Roche, R. Kazmi Consultant for: BioMarin Pharmaceutical Inc. and CSL Behring, N. Key Consultant for: BioMarin Pharmaceutical Inc., Genentech USA, Novo Nordisk AS, and CSL Behring, T. Robinson Shareholder of: BioMarin Pharmaceutical Inc., Employee of: BioMarin Pharmaceutical Inc., S. Fong Shareholder of: BioMarin Pharmaceutical Inc., Employee of: BioMarin Pharmaceutical Inc.

OR07 | Efficacy and safety of concizumab prophylaxis in haemophilia A or B with and without inhibitors: 56-week cut-off results of the phase 3 explorer7 and explorer8 studies

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Introduction: Concizumab is an anti-tissue factor pathway inhibitor (TFPI) monoclonal antibody in development as a once-daily subcutaneous prophylaxis for haemophilia A/B with and without inhibitors (HAwI/HBwI and HA/HB). The efficacy and safety of concizumab in patients with HAwI/HBwI and HA/HB were assessed in the phase 3 explorer7 (NCT04083781) and explorer8 (NCT04082429) trials, respectively. Primary and confirmatory analysis cut-off (32-week) results were previously presented; 56-week cut-off results are shown here.

Methods: Male patients (≥12 years) with HAwI/HBwI and HA/HB comprised the four arms of the trials. Arm 1 received concizumab after 24 weeks of on-demand treatment; arms 2–4 received concizumab from the study onset. The dosing regimen consisted of a 1.0 mg/kg loading dose (Day 1), then a daily dose of 0.20 mg/kg (Day 2+), with potential adjustment to 0.15 or 0.25 mg/kg based on concizumab plasma concentration after 4 weeks. The 56-week cut-off was defined as when all patients in concizumab arms 2–4 had completed a 56-week visit or permanently discontinued treatment. Bleeding episodes were analysed using the full analysis set of patients (arms 1–4) on treatment, excluding periods on ancillary therapy, from the start of the new concizumab dosing regimen until the 56-week cut-off (explorer7/explorer8), or on the initial concizumab dosing regimen for patients not exposed to the new dosing regimen (explorer7).

Results: The 56-week cut-off analyses of bleeding episodes comprised patients in arms 1–4 exposed to concizumab (i.e., including patients from arm 1 who switched to concizumab prophylaxis after 24 weeks of on-demand treatment). It contained 76 patients with HAwI, 51 patients with HBwI (explorer7), 80 patients with HA, and 64 patients with HB (explorer8). Median annualised bleeding rate (interquartile range) for treated spontaneous and traumatic bleeding episodes on concizumab prophylaxis was 0.7 (0.0–3.0) for HAwI, 1.1 (0.0–3.2) for HBwI, 1.7 (0.0–4.5) for HA, and 2.8 (0.0–6.4) for HB. No thromboembolic events were reported from restart of the trials until the 56-week cut-off of either trial.

Discussion/Conclusion: Concizumab-exposed patients maintained a low bleeding rate with a favourable safety profile after >1 year of exposure.

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OR08 | Emicizumab prophylaxis for the treatment of infants with severe haemophilia A without factor VIII inhibitors: primary analysis of the HAVEN 7 study

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Introduction: Venous access presents a significant challenge in infants with haemophilia A (IwHA) requiring prophylaxis. Subcutaneous emicizumab enables prophylaxis from birth, reducing bleed risk. The HAVEN 7 (NCT04431726) primary analysis evaluates emicizumab prophylaxis over ≥52 weeks (wks) in IwHA.

Methods: IwHA in the Phase 3b, open-label study were aged ≤12 months (m) without factor (F)VIII inhibitors. They received emicizumab 3 mg/kg maintenance dose every 2 wks (Q2W) for 52 wks, continuing emicizumab for 7 years' planned follow-up. Endpoints include efficacy (negative binomial regression model-based annualised bleed rates [ABR] for treated, all, treated spontaneous, and treated joint bleeds), safety, pharmacokinetics, anti-emicizumab antibodies (ADAs), FVIII inhibitors, and biomarkers (biomarker results are not detailed here, but will be included in the event of an associated presentation).

Results: At data cut-off (22 May, 2023), 55 male IwHA had received emicizumab for ≥52 wks (54.5% previously minimally treated [≤5 exposure days, EDs], and 45.5% previously untreated [PUP]). Median (range) age: 4 m (9 days−11 m 30 days) at enrolment; 29 (12−39) m at cut-off. Median (range) treatment duration: 100.3 (52−118) wks.

Mean ABRs (95% confidence interval) for treated, all, and treated joint bleeds were 0.4 (0.30–0.63), 2.0 (1.49−2.66), and 0.0 (0.01–0.09), respectively. Overall, 207 bleeds occurred in 46 IwHA (83.6%), 87.9% of which were traumatic. Of the 207 total bleeds, 42 bleeds in 25 IwHA were treated, all traumatic. Thirty (54.5%) IwHA had zero treated bleeds, and no IwHA had >3 treated bleeds. No intracranial haemorrhage occurred. One IwHA was up-titrated (Day 374) to 3 mg/kg weekly per investigator request based on locally assessed decreasing emicizumab levels. Nine IwHA (16.4%) had ≥1 treatment-related adverse event (AE), all Grade 1 injection-site reaction. No AE led to emicizumab change/withdrawal. No deaths/thrombotic events/thrombotic microangiopathies occurred. Mean steady-state emicizumab concentrations were 57−66 μg/mL, above those with the same regimen in HAVEN 2/3 (46−48 μg/mL). No IwHA developed ADAs. Two PUPs developed confirmed inhibitors after three and ten FVIII EDs, respectively.

Discussion/Conclusion: This analysis suggests that emicizumab is efficacious and well tolerated in IwHA without FVIII inhibitors.

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OR09 | 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

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Introduction: Etranacogene dezaparvovec (formerly AMT-061) is the first approved gene therapy for haemophilia B in the EU and US. The HOPE-B pivotal phase 3 clinical trial (NCT03569891) demonstrated superior bleed protection compared to FIX prophylaxis up to 24 months post treatment with ongoing follow-up from Year 2 onward. Here, we report efficacy and safety during Years 1–3.

Methods: In this pivotal phase 3 open-label, single-arm trial, adult male patients (pts) with severe or moderately severe haemophilia B, with or without preexisting adeno-associated virus serotype 5 (AAV5) neutralising antibodies, received a single dose of etranacogene dezaparvovec (2×10^{13} gc/kg, an AAV5 vector containing factor IX [FIX] Padua R338L transgene under the control of the liver-specific LP-1 promoter) following ≥6-month lead-in period of FIX prophylaxis.

Results: Of 54 pts receiving etranacogene dezaparvovec, 52 completed 36 months' follow-up. Mean annualized bleeding rate (ABR) for all bleeds during Months 7–36 was reduced by 64% versus lead-in (1.52 and 4.17, respectively; $P = 0.0004$). Mean ± SD endogenous FIX activity was sustained at 41.5 IU/dL ± 21.7 ($n = 50$), 36.7 IU/dL ± 19.0 ($n = 50$), and 38.6 IU/dL ± 17.8 ($n = 48$) at Years 1, 2 and 3 post-treatment, respectively. At 3 years posttreatment, 51 pts (94%) remained free of continuous FIX prophylaxis; mean annualized FIX consumption decreased by 96% versus lead-in ($P < 0.0001$). One pt's FIX levels eventually declined to 2%–5%; his bleeding phenotype returned, and he resumed prophylaxis per protocol at Month 30 post-treatment.

All pts experienced at least one adverse event (treatment-emergent AE), with no serious AEs related to treatment (one case of hepatocellular carcinoma [HCC] and one death were reported before Year 2 and unrelated to treatment). A total of 38/54 (70%) pts experienced 96 treatment-related AEs. The most common AE was increased alanine transaminase (ALT). Nine pts (16.7%) received reactive corticosteroids for mean ± SD 81.4 ± 28.6 days. No new deaths, HCC, or late treatment-related ALT elevations were reported during Year 3.

Discussion/Conclusion: A single dose of etranacogene dezaparvovec provides long-term FIX Padua expression and superior bleed protection compared to prophylaxis, with a favourable safety profile over 3 years post administration.

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OR10 | Safety and efficacy of valoctocogene roxaparvovec in participants with active and prior FVIII inhibitors: Preliminary results from GENEr8-INH, a phase 1/2 study

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Introduction: Valoctocogene roxaparvovec is a gene therapy licensed in the EU and US for individuals with severe haemophilia A (sHA) without adeno-associated virus serotype 5 (AAV5) antibodies and factor VIII (FVIII) inhibitors. We present interim results for the first individuals treated with active or prior inhibitors.

Methods: GENEr8-INH (NCT04684940) is a phase 1/2 trial evaluating safety and efficacy of valoctocogene roxaparvovec (6×10^{13} vg/kg) in anti-AAV5–negative sHA participants and active (part A) or prior (part B) FVIII inhibitors. Prophylactic corticosteroid (CS) started on day 15 (part A) and day 1 (part B). Primary outcome was treatment-related adverse events (AEs). Secondary outcomes included change from baseline in FVIII activity, change in FVIII inhibitor titter (part A) or recurrence (part B), change in annualized prophylactic or on-demand HA therapy, and annualized treated bleeds. As emicizumab use was permitted, a chromogenic assay with bovine reagents was used for FVIII and FVIII inhibitor assessment. Two participants enrolled in part A and B; expansion is dependent on data monitoring committee evaluation (week 12).

Results: Participants 1 and 2 in part A (PAP1 and PAP2) received emicizumab for >2 years prior to enrolment. Their inhibitor titter, 3.8 and 2.2 BU/mL at screening, peaked by 12 weeks post-infusion. Inhibitors declined in PAP1 but rose after an AE of elevated alanine aminotransferase (ALT) that was treated with increased CS. For PAP2, inhibitors declined from 20.1 BU/mL (week 9) to <0.6 BU/mL (week 32). At this time, FVIII activity peaked (41.7 IU/dL) and FVIII B-domain–deleted antigen was 26.0 ng/mL. In part B, participants 1 and 2 (PBP1 and PBP2) had prior immune tolerance induction therapy and inhibitor titters <0.6 BU/mL at screening. FVIII activity for PBP1 and PBP2 reached 26.2 and 247.8 IU/dL, respectively. In the available 32-week follow-up, inhibitor titters did not recur. The most common AEs were non-serious ALT elevations (PAP1, PBP1 and PBP2) and grade 1 non-serious AEs related to CS use (moon face, acne, and weight gain). No serious or severe AEs were reported, including malignancy, FVIII inhibitor recurrence in part B, or thromboembolism.

Discussion/Conclusion: To date, valoctocogene roxaparvovec has a similar safety profile in participants regardless of inhibitor status. Interim efficacy results are encouraging.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.