Emicizumab Prophylaxis in Infants with Severe Hemophilia A Without Factor VIII Inhibitors: Results from the Primary Analysis of the HAVEN 7 Study

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Presented at the 65th ASH Annual Meeting | December 9–12, 2023

Background

- Starting prophylaxis early in life should be the standard of care[1]
- However, many infants with severe HA do not receive prophylaxis until ≥1 year of age, owing to the **challenges of FVIII administration**:[2–4]
  - Venous access issues
  - CVAD-associated risks
- Emicizumab can be administered subcutaneously from HA diagnosis, enabling **early initiation of prophylaxis**, and **may mitigate risks of**:[5–9]
  - Untreated spontaneous and traumatic bleeding, which accrues damage
  - Intracranial hemorrhages, of which there is a substantial risk in the first year of life
  - FVIII inhibitor development, due to reduced use of FVIII products

MASAC recommendation:

*"Infants should be considered for prophylaxis with emicizumab **at any time after birth** given the increased risk of intracranial hemorrhage prior to initiation of FVIII prophylaxis[10]"*

The primary analysis of **HAVEN 7** (NCT04431726) evaluates the efficacy, safety, PK (and PD, reported in Poster 1238) of emicizumab in infants ≤12 months of age with severe HA without FVIII inhibitors

CVAD, central venous access device; F, factor; HA, hemophilia A; PD, pharmacodynamics; PK, pharmacokinetics.

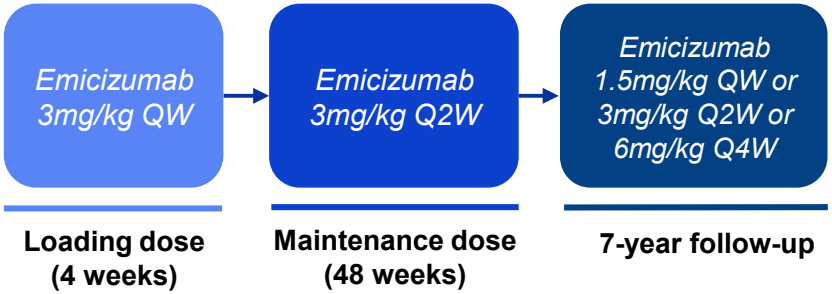
1. Srivastava A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia 2020;26(Suppl 6):1–158; 2. Lung R, et al. Haemophilia 2023;29:498–504; 3. Wiley RE, et al. Haemophilia 2019;25:433–40; 4. Valentino LA, et al. Haemophilia 2004;10:134–46; 5. Hemlibra® (emicizumab) EMA approval, https://www.ema.europa.eu/en/medicines/human/EPAR/hemlibra, Accessed November 2023; 6. FDA prescribing information emicizumab, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761083s002s004lbl.pdf, Accessed November 2023; 7. Warren BB, et al. Blood Adv 2020;4:2451–9; 8. Zwagemaker A-F, et al. Blood 2021;138:2853–73; 9. Gouw SC, et al. Blood 2013;121:4046–55; 10. National Hemophilia Association 2022; MASAC Document #268.

Study design

- At data cut-off, **55 participants** were exposed to emicizumab for a median (range) duration of **100.3 (52–118) weeks***
- **Key inclusion criteria:**
  - PUPs or MTPs† from **birth to ≤12 months of age** with **severe HA without FVIII inhibitors**
  - No evidence of ICH at enrollment

- Endpoints included:
  - **Efficacy:** ABRs for treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds
  - **Safety:** AEs, AESIs including TEs and TMAs, immunogenicity including ADAs and FVIII inhibitors
  - **PK:** Plasma trough emicizumab concentrations
  - **PD:** Biomarker data, reported in Poster 1238

A Phase IIIb, multi-center, open-label study of emicizumab in infants aged ≤12 months with severe HA without FVIII inhibitors

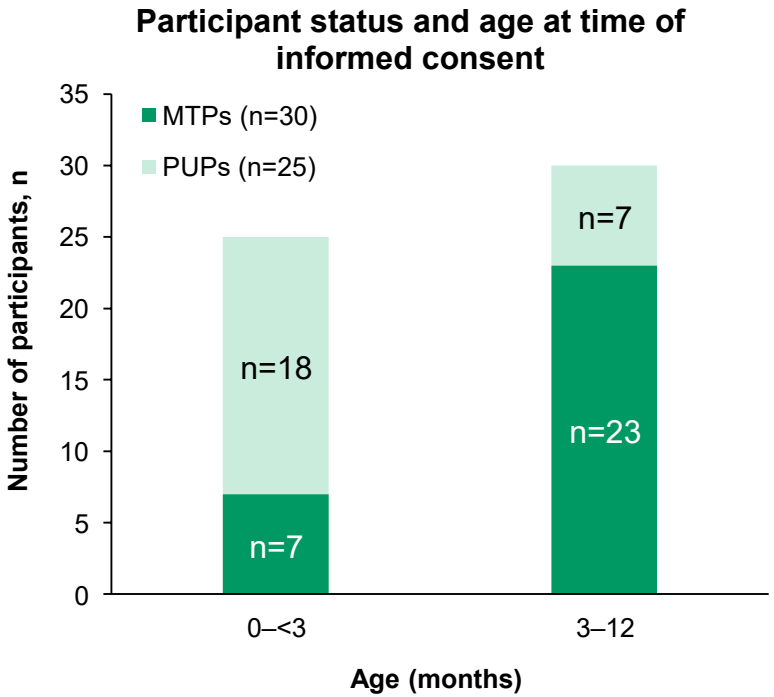


- Primary analysis clinical cut-off date: May 22, 2023
- Future analyses over the 7-year long-term follow-up period will include, but will not be limited to, safety, and joint health outcomes assessed by MRI

*Treatment exposure is defined as the last dose of study medication minus the date of the first dose plus one day. †Defined as a participant with ≤5 exposure days to FVIII. Recruitment was completed on May 20, 2022, with 55 participants. ABR, annualized bleeding rate; ADAs, anti-drug antibodies; AE, adverse event; AESI, adverse event of special interest; F, factor; HA, hemophilia A; ICH, intracranial hemorrhage; MRI, magnetic resonance imaging; MTP, minimally treated participant; PD, pharmacodynamics; PK, pharmacokinetics; PUP, previously untreated participant; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; TE, thrombotic event; TMA, thrombotic microangiopathy.

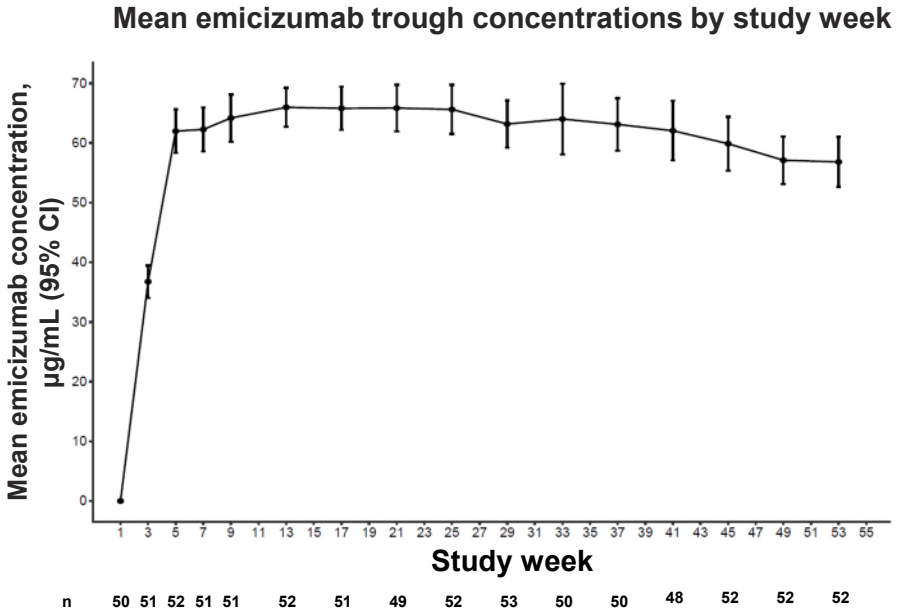
Baseline characteristics

	Emicizumab (N=55)
Age at informed consent, months	
Mean (SD)	5.0 (3.9)
Median	4.0
Range	9 days–11 months 30 days
Age group, n (%)	
0–<3 months	25 (45.5)
3–12 months	30 (54.5)
Prior treatment status, n (%)	
MTP*	30 (54.5)
PUP	25 (45.5)
Historical bleeding episodes prior to first dose of emicizumab†	
Participants with ≥1 bleed, n (%)	36 (65.5)
Total number of bleeds, n	77
Spontaneous, n (%)	25 (32.5)
Traumatic, n (%)	19 (24.7)
Procedural/surgical, n (%)	33 (42.9)
Family history of HA, n (%)	41 (74.5)
Family history of FVIII inhibitors	7 (12.7)



*Defined as a participant with ≤5 exposure days to FVIII. †The reporting period was variable across the 36 participants who had ≥1 bleed prior to receiving emicizumab, with the median (min, max) age at time of first historical treated or untreated bleed being 1 (0, 49) week(s).
HA, hemophilia A; F, factor; MTP; minimally treated participant; PUP, previously untreated participant; SD, standard deviation.

Effective emicizumab trough concentrations were achieved and sustained in infants



Emicizumab trough concentrations by study week

- Following loading doses, mean (95% CI) trough concentrations were **62.0 (58.3–65.6) µg/mL** at Week 5
- Steady-state trough concentrations of **~57–66µg/mL** were higher than those in older people with HA on the same dosing regimen in the HAVEN 1–4 studies (46.7µg/mL)[1]
  - Injection site may have played a role, as 80% of loading dose administrations were in the thigh, which has been associated with a trend for higher exposure than abdomen or upper arm administrations[2]

Emicizumab trough concentrations by age

- Mean steady-state trough concentrations **increased slightly with age** until approximately 6 months of age, whereupon trough concentrations were maintained at ≥60µg/mL
- Mean FIX and FX concentrations were **not impacted by emicizumab treatment**

For the participant whose dose was up-titrated, only data before up-titration are included.
CI, confidence interval; F, factor; HA, hemophilia A.

1. Retout S, et al. Clin Pharmacokinet 2020;59:1611–25;
2. Kotani N, et al. Clin Pharmacol Drug Devel 2019;8:702–12.

No new safety signals were identified at primary analysis

	Emicizumab (N=55)
Total number of AEs, n	631
Participants with ≥1 AE, n (%)	55 (100)
AE with fatal outcome	0 (0)
AE leading to withdrawal from treatment	0 (0)
AE leading to dose modification/interruption	0 (0)
AE of Grade ≥3	17 (30.9)
AE related to treatment	9 (16.4)*
SAEs	16 (29.1)†
AEs of special interest, n (%)	
Systemic hypersensitivity reactions and anaphylactic / anaphylactoid reactions	1 (1.8)‡
Thromboembolic event	0 (0)
Thrombotic microangiopathy	0 (0)

No ICHs were reported

No AEs led to withdrawal or dose modification or interruption

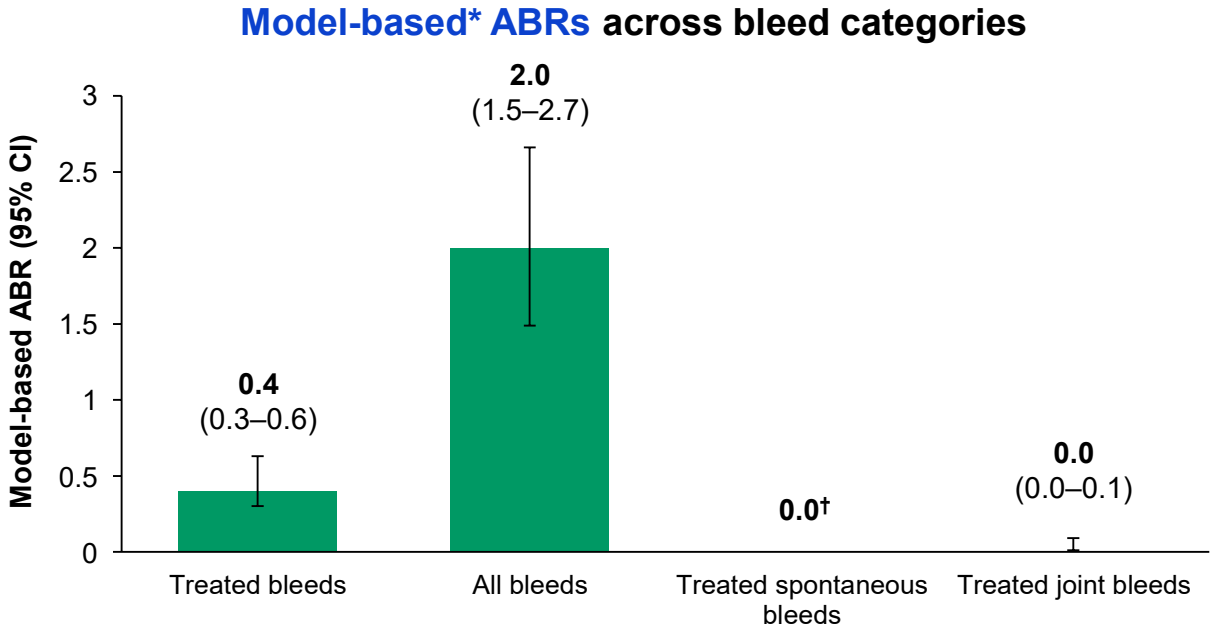
All treatment-related AEs were **Grade 1 ISRs**

No SAEs were considered treatment-related; most were infant specific (respiratory-related and head-injury events) and considered serious due to required or prolonged hospitalization†

There was one anaphylactic reaction, confirmed to be due to egg allergy and deemed **unrelated to emicizumab**‡

*All treatment-related AEs were Grade 1 local injection-site reactions. †Sixteen participants reported 30 SAEs; none were considered emicizumab related and all considered serious due to hospitalization. SAEs included: fall (n=4); head injury (n=4); bronchiolitis, bronchitis, pneumonia, tonsillitis, mouth hemorrhage, tongue hemorrhage (n=2 for each); ear infection, laryngitis, upper respiratory tract infection, urinary tract infection, viral infection, eyelid contusion, post-procedural fever (liver biopsy), post-procedural hemorrhage (tonsillectomy), skin laceration, tongue injury (n=1 for each). ‡One Grade 2 anaphylactic reaction due to an egg allergy was reported in one participant; this event resolved and was considered not related to emicizumab. AE, adverse event; ICH, intracranial hemorrhage; ISR, injection-site reaction; SAE, serious adverse event.

Emicizumab demonstrated consistent efficacy across bleeding endpoints



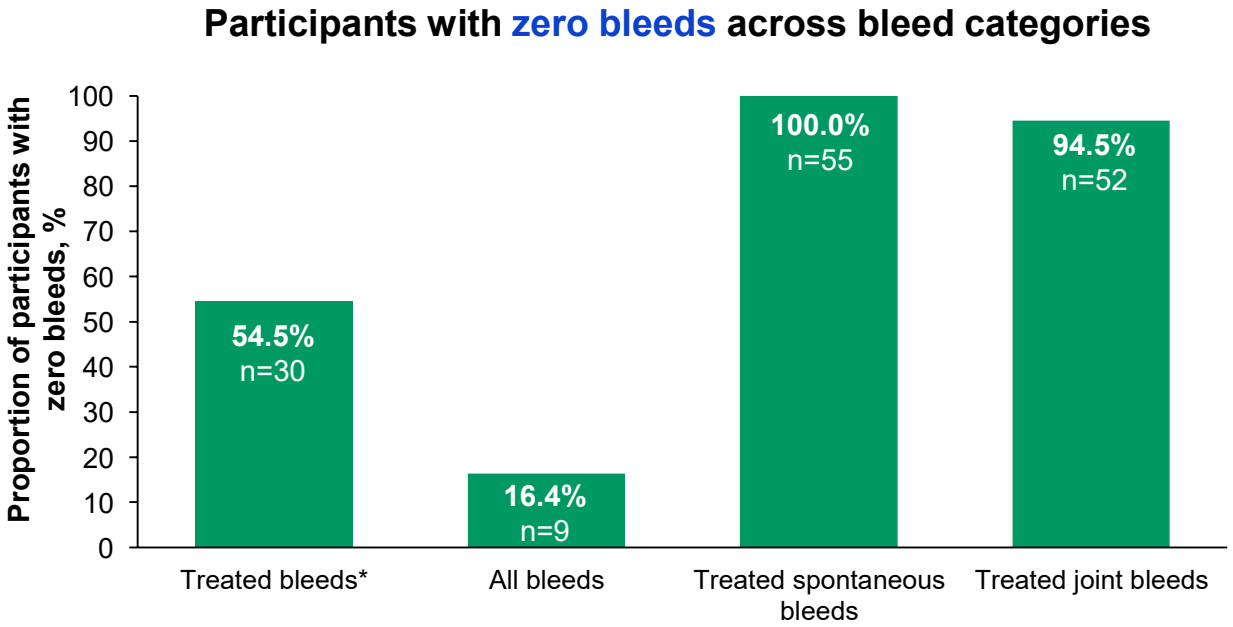
Median (range) follow-up: 101.9 (52.6–119.7) weeks (N=55)

Median (range) age at analysis: 29 (12–39) months (N=55)

All treated bleeds were categorized as **traumatic**‡

*Model-based ABRs were assessed with aid of a negative binomial regression model. †ABR could not be estimated via the negative binomial regression model as no treated spontaneous bleeds were observed in the study; as a result, a value of 0.0 is reported instead. ‡Bleeds were categorized as traumatic if parents/caregivers recorded a bleed with a known or believed reason for the bleed. ABR, annualized bleeding rate; CI, confidence interval.

Emicizumab demonstrated consistent efficacy across bleeding endpoints



No participant had >3 treated bleeds

Thirty-seven participants (67.3%) had **0–3 all bleeds**

Emicizumab dose was **up-titrated** to 3mg/kg QW in **one participant,** per investigator request based on decreasing emicizumab levels (locally assessed)†

Median (range) age at analysis: 29 (12–39) months and median (range) follow-up: 101.9 (52.6–119.7) weeks (N=55). *All 42 treated bleeds in 25 participants were traumatic. †Emicizumab level was confirmed retrospectively by central assessment to be 6.6 µg/mL at the lowest. The participant experienced three treated bleeds before up-titration (Day 374) and two untreated bleeds after up-titration until clinical cut-off date (328 days later); all bleeds were traumatic. Emicizumab level in this participant one week after up-titration was 22.7 µg/mL, and ranged from 46.6–62.4 µg/mL in samples collected between Weeks 3 and 13 post up-titration. The participant tested negative for ADAs at all timepoints before and after up-titration (baseline, Week 5, 17, 29, 41, and 53, as well as up-titration Week 1 and 5). ADA, anti-drug antibody; QW, every week.

Immunogenicity to emicizumab and FVIII

All 55 participants were evaluable for immunogenicity; **none tested positive for ADAs to emicizumab***

On study, 27 participants did not have any FVIII EDs. In the **28 participants with ≥1 FVIII ED(s)**

- Median (min, max) on-study FVIII ED(s) was 1 (0, 10), with a mean (SD) of 1.8 (3.3) doses
- On-study FVIII EDs were similar between PUPs (median [min, max]: 1 [0, 10], n=14) and MTPs (median [min, max]: 0 [0, 10], n=14)

Following FVIII exposure, 24 participants were tested for **FVIII inhibitors**,† with **two testing positive**; both were PUPs aged 0–3 months at enrollment

- **Low FVIII inhibitor rate** in HAVEN 7 (3.6%) may be a consequence of **reduced FVIII usage** in participants treated with emicizumab; however, many participants are still within the FVIII exposure risk period for inhibitors[1]

Participant 1‡

- **No family history of FVIII inhibitors**
- Confirmed for FVIII inhibitors on **Day 603 (6.9CBU/mL)** and **Day 681 (1.5CBU/mL)**
- Experienced **three non-consecutive EDs with standard half-life FVIII** for traumatic bleed management

Participant 2§

- **Family history of FVIII inhibitors**
- Tested positive for FVIII inhibitors on **Day 428 (28.4 CBU/mL)** and confirmed post CCOD on **Day 532 (9.0 CBU/mL)**
- Experienced **10 non-consecutive EDs with extended half-life FVIII** for bleed treatment and surgical procedures

*ADAs were measured at weeks 1, 5, 17, 29, 41, and 53; and during long-term follow-up in the case of clinical suspicion. †Participants were tested for FVIII inhibitors following ≥3 EDs, or two consecutive doses, of FVIII. ‡A PUP (<1 month old) with large F8 deletion receiving five doses of standard half-life FVIII (500 IU; two doses on Day 333 and 404, one dose on Day 405) for treatment of two traumatic mouth bleeds. §A PUP (1 month old) with intron 22 inversion with a traumatic mouth bleed (Day 279) treated with 350 IU extended half-life FVIII and negative for inhibitors. On Days 414–422, seven non-consecutive EDs of preventative extended half-life FVIII were provided for adenotonsillectomy, ranging from 500 IU to 2550 IU. Tonsillectomy resumed (Day 425), accompanied by a post-procedural bleed treated with extended half-life FVIII (Day 425: 500 IU, 1200 IU, 250 IU; Day 426: 250 IU) and rFVIIa (Days 427–434).
ADA, anti-drug antibody; CBU, chromogenic Bethesda unit; CCOD, clinical cut-off date; ED, exposure day; F, factor; PUP, previously untreated participant; rFVIIa, recombinant activated factor VII.

1. Gouw SC, et al. Blood 2013;121:4040–55.

PD data are reported in **Poster 1238**

Conclusions

- Effective mean trough concentrations of emicizumab were **achieved and maintained**
- In line with the safety profile of emicizumab in clinical trials,[1–6] **no new safety signals** were observed, and **no ICH** occurred
- Model-based ABRs were consistently low, all participants had **zero treated spontaneous bleeds**
- Up to CCOD, **no participant** developed **ADAs**, and **FVIII EDs were low**, resulting in 3.6% of participants developing *de novo* FVIII inhibitors

This primary analysis of HAVEN 7 indicates that emicizumab is **efficacious and well tolerated in infants with severe HA** without FVIII inhibitors; future analyses over the 7-year follow-up period will describe the **natural history** of children with HA initiating emicizumab soon after birth, including **joint health outcomes**

ABR, annualized bleeding rate; ADA, anti-drug antibody; CCOD, clinical cut-off date; ED, exposure day; F, factor; HA, hemophilia A; PD, pharmacodynamics; ICH, intracranial hemorrhage.

1. Oldenburg J, et al. N Engl J Med 2017;377:809–18; 2. Mahlangu J, et al. N Engl J Med 2018;379:811–22; 3. Pipe SW, et al. Lancet Haematol 2019;6:E295–305; 4. Yang R, et al. Res Prac Thromb Haemostas 2022;6:e12670; 5. Négrier C, et al. Lancet Haematol 2023;10:e168–77; 6. Young G, et al. Blood 2019;124:2127–38.

Acknowledgments

- The patients and their families
- The study investigators:
  - Dr C. Barnes, Dr T. Carter, Dr J. Curtin (**Australia**); Dr C. Male (**Austria**); Dr V. Labarque, Dr A. Van Damme (**Belgium**); Dr L. Oliveira (**Brazil**); Dr M. Carcao, Dr R. Klaassen (**Canada**); Dr R. Nuñez, Dr R. Berrueco, Dr V. Jimenez Yuste (**Spain**); Dr H. Chambost, Dr R. d'Oiron, Dr A. Harroche (**France**); Dr C. Escuriola-Ettingshausen, Prof. Dr J. Oldenburg, Dr M. Olivieri, Dr I. Wieland (**Germany**); Dr G. Kenet (**Israel**); Dr F. Peyvandi, Dr M. Schiavulli, Dr A. Coppola, Dr G. Castaman (**Italy**); Prof. Dr K. Fijnvandraat (**Netherlands**); Dr F. Achini (**Switzerland**); Prof. Dr K. Kavakli, Dr C. Albayrak, Dr B. Antmen, Dr S. Aytac (**Turkey**); Dr D. Gosrani, Dr D. Hart, Dr F. Pinto (**UK**); Dr S. Ahuja, Dr S. Carpenter, Dr S. Croteau, Dr G. Young, Dr C. Knoll, Dr K. Maher, Dr M. Wang, Dr S. Pipe, Dr A. Blair, Dr A. Rafique, Dr N. Rodriguez, Dr A. Shapiro (**USA**); Prof. Dr J. Mahlangu (**South Africa**)
- The study coordinators and nurses
- The sponsor, F. Hoffmann-La Roche Ltd

Third-party medical writing assistance, under the direction of the authors, was provided by Jen Evans, BSc, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd

Disclosures

S.W.P: scientific advisory board member: GeneVentiv, Equilibra Bioscience; grants/contracts: Siemens; consultancy: Apcintex, ASC Therapeutics, Bayer, BioMarin, CSL Behring, HEMA Biologics, Freeline, LFB, Novo Nordisk, Pfizer, Regeneron/Intellia, Genentech, Inc./F. Hoffmann-La Roche Ltd, Sanofi, Takeda, Spark Therapeutics, uniQure.
P.C: Entity's Board of Directors member: HAVEN 7 trial steering committee; member of the UK Haemophilia Centre Doctors' Organisation, which received a research grant from F. Hoffmann-La Roche Ltd.
C.D: employment: F. Hoffmann-La Roche Ltd.
G.K: Grants/research funding: BSF, Pfizer, F. Hoffmann-La Roche Ltd, Tel Aviv University, Sheba research authorities; consultancy: ASC Therapeutics, Bayer, BioMarin, Novo Nordisk, Pfizer, F. Hoffmann-La Roche Ltd, Sobi, Sanofi-Genzyme, Takeda, uniQure; honoraria: Bayer, BioMarin, BPL, CSL Behring, Pfizer, Novo Nordisk, F. Hoffmann-La Roche Ltd, Sanofi-Genzyme, Spark Therapeutics; Data Safety Monitoring Board/advisory board: ASC Therapeutics, BioMarin, Pfizer, Novo Nordisk, uniQure, F. Hoffmann-La Roche Ltd, Sanofi-Genzyme, Sobi, Spark Therapeutics; leadership role: PedNet Research foundation.
C.S and **M.B**: employment and stockholders: F. Hoffmann-La Roche Ltd.
V.J-Y: grants/contracts: F. Hoffmann-La Roche Ltd, Novo Nordisk, Sobi, Takeda, Grifols, Bayer, Pfizer, Octapharma, CSL Behring; consultancy: F. Hoffmann-La Roche Ltd, Novo Nordisk, Sanofi, Sobi, Takeda, Grifols, Bayer, Pfizer, Spark Therapeutics, BioMarin, Octapharma, CSL Behring; honoraria: F. Hoffmann-La Roche Ltd, Novo Nordisk, Sanofi, Sobi, Takeda, Grifols, Bayer, Pfizer, Spark Therapeutics, BioMarin, Octapharma, CSL Behring.
F.P: advisory boards: Sanofi, Sobi, Takeda, F. Hoffmann-La Roche Ltd, BioMarin; educational meetings: Grifols, F. Hoffmann-La Roche Ltd.
G.Y: grants/contracts: Genentech, Inc., Grifols, Takeda; royalties/licenses: Viatris; consultancy: Bayer, BioMarin, CSL Behring, Genentech, Inc./F. Hoffmann-La Roche Ltd, LFB, Novo Nordisk, Pfizer, Sanofi, Spark Therapeutics, Takeda; honoraria: Bayer, BioMarin, CSL Behring, Genentech, Inc./F. Hoffmann-La Roche Ltd, Novo Nordisk, Pfizer, Sanofi, Spark Therapeutics, Takeda; speakers bureau: BioMarin, Genentech, Inc., Hema Biologics, Sanofi, Spark Therapeutics.
J.O: research funding: Bayer, Biotest, CSL Behring, Octapharma, Pfizer, Swedish Orphan Biovitrum, Takeda; consultancy/speakers bureau/honoraria/advisory board/travel expenses: Bayer, Biogen Idec, BioMarin, Biotest, Chugai Pharmaceutical Co., Ltd, CSL Behring, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, F. Hoffmann-La Roche Ltd, Sanofi, Spark Therapeutics, Swedish Orphan Biovitrum, Takeda.
M.E.M: consultancy: Bayer, CSL Behring, Novo Nordisk, F. Hoffmann-La Roche Ltd, Octapharma, Pfizer, Sanofi, Sobi, Kedrion, Grifols, BioMarin, Catalyst, uniQure, and LFB; honoraria: Bayer, CSL Behring, Novo Nordisk, F. Hoffmann-La Roche Ltd, Octapharma, Pfizer, Sobi, Kedrion, Grifols, BioMarin, Spark Therapeutics.
K.K: consultancy/honoraria: F. Hoffmann-La Roche Ltd, Novo Nordisk, Takeda, Pfizer; research funding: F. Hoffmann-La Roche Ltd, Pfizer.
A.K, M.N and **M.L**: employment and stockholders: F. Hoffmann-La Roche Ltd. **T.C**: employment: Spark Therapeutics, which is part of the Roche group and holds stock in F. Hoffmann-La Roche Ltd.
K.F: unrestricted research grants: CSL Behring, Sobi, Novo Nordisk; consultancy: F. Hoffmann-La Roche Ltd, Sanofi, Sobi, Novo Nordisk.