CR17

Long-term factor VIII expression with reduced bleeding following gene transfer for hemophilia A: follow-up on the dirloctocogene samoparvovec (SPK-8011) Phase I/II trial

Stacy E. Croteau,[*1] M. Elaine Eyster,[2] Huyen Tran,[3] Margaret V. Ragni,[4] Benjamin J. Samelson-Jones,[5] Lindsey George,[5] Spencer Sullivan,[6] John E.J. Rasko,[7] Jill Moormeier,[8] Pantep Angchaisuksiri,[9,10] Jerome Teitel,[11] Gili Kenet,[12] Tung Wynn,[13] Kristen Jaworski,[14] Amy MacDougall,[14] Savina Jaeger,[14] Trupti Trivedi,[14] Federico Mingozzi,[14] Tiffany Chang,[14] Gallia Levy[14]

Presenting author

[1]Department of Pediatrics, Harvard Medical School, and the Division of Hematology and Oncology, Boston Children's Hospital, Boston, MA, USA; [2]Department of Medicine, Division of Blood and Vascular Disorders, Penn State Milton S. Hershey Medical Center, Hershey, PA, USA; [3]Australian Centre for Blood Diseases, Monash University, Melbourne, Victoria, Australia; [4]Department of Medicine, University of Pittsburgh, Pittsburgh, PA, USA; [5]Division of Hematology and the Raymond G. Perelman Center for Cellular and Molecular Therapeutics, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [6]Mississippi Center for Advanced Medicine, Madison, MS, USA; [7]Department of Cell and Molecular Therapies, Royal Prince Alfred Hospital, and the Gene and Stem Cell Therapy Program, Centenary Institute, Faculty of Medicine and Health, University of Sydney, Camperdown, NSW, Australia; [8]Department of Medicine, UMKC School of Medicine, Kansas City, MO, USA; [9]Department of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [10]University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, USA; [11]St Michael's Hospital Hemophilia Treatment Centre, University of Toronto, Toronto, Canada; [12]Israel National Hemophilia Center and Thrombosis Institute, Sheba Medical Center, Tel Hashomer, Israel; [13]Division of Hematology & Oncology, Department of Pediatrics, University of Florida, Gainesville, FL, USA; [14]Spark Therapeutics, Inc., Philadelphia, PA, USA

Summary and Conclusions

We report updated efficacy and safety for people with hemophilia A (HA) enrolled in the Phase I/II trial of dirloctocogene samoparvovec gene therapy

N=24

No major safety signals were reported after a single infusion of dirloctocogene samoparvovec, and the timing of transient ALT (liver enzyme) increases were consistent with the presumed capsid immune response

After up to 5 years of follow-up, sustained year-to-year factor VIII expression (with a majority of participants achieving levels in the mild HA range) and reductions in bleeding rate and factor consumption were observed in participants following a single infusion of dirloctocogene samoparvovec

These results support the investigation of the safety and efficacy of dirloctocogene samoparvovec gene therapy in a larger population of people with HA

Background

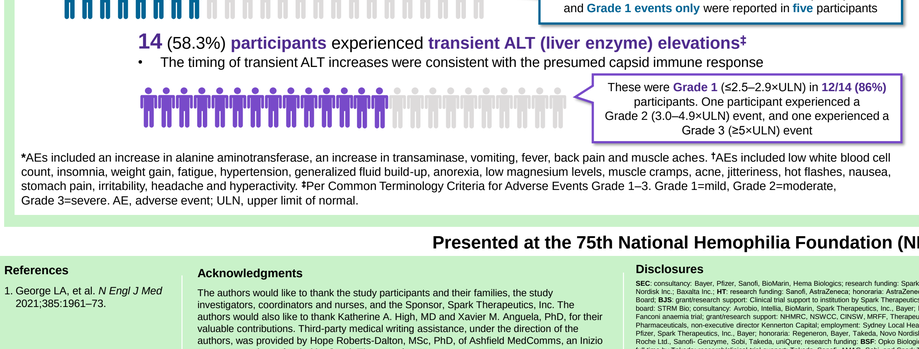
Dirloctocogene samoparvovec (SPK-8011) is an investigational gene therapy that uses a modified adeno-associated viral vector to deliver a factor VIII gene to liver cells. It is designed to provide sustained factor VIII expression to prevent bleeding in people with hemophilia A (HA).[1]

Previously published Phase I/II dirloctocogene samoparvovec trial (NCT03003533/NCT03432520) results indicate a 92% (95% confidence interval [CI]: 89–94%) reduction in annualized bleed rate and 96% (95% CI: 96–97%) reduction in annualized factor VIII infusion rate after a median follow-up of 33.4 months (data cut-off: May 3, 2021). No safety concerns were reported.[1]

The aim of this study was to provide an update on the efficacy and safety of an infusion of dirloctocogene samoparvovec after 5 years of follow-up.

Methods

Figure 1. Study design: a Phase I/II, open-label, multicenter, non-randomized trial



*SPK200 was the vector capsid. IV, intravenous; vg/kg, vector genomes per kilogram of bodyweight.

Results

Median observation time: 191 (range: 2–285) weeks

No major safety signals were reported, and the timing of transient ALT (liver enzyme) increases were consistent with the presumed capsid immune responses

Figure 2. Adverse events at data cut-off: October 04, 2022

No factor VIII inhibitors or thrombotic events were reported

28 adverse events related to **dirloctocogene samoparvovec** were reported in **13** (54.2%) **participants***

1 serious adverse event (Grade 2 ALT [liver enzyme] elevation) resulted in elective hospitalization for intravenous corticosteroids. The remaining 12 participants experienced mild/moderate events

26 adverse events related to **immunomodulatory therapy** were reported in **8** (33.3%) **participants†**

Grade 1 and 2 events were reported in **three** participants, and **Grade 1 events only** were reported in **five** participants

14 (58.3%) **participants** experienced **transient ALT (liver enzyme) elevations‡**

- The timing of transient ALT increases were consistent with the presumed capsid immune response

These were **Grade 1** (≤2.5–2.9×ULN) in **12/14 (86%)** participants. One participant experienced a Grade 2 (3.0–4.9×ULN) event, and one experienced a Grade 3 (≥5×ULN) event

*AEs included an increase in alanine aminotransferase, an increase in transaminase, vomiting, fever, back pain and muscle aches. †AEs included low white blood cell count, insomnia, weight gain, fatigue, hypertension, generalized fluid build-up, anorexia, low magnesium levels, muscle cramps, acne, jitteriness, hot flashes, nausea, stomach pain, irritability, headache and hyperactivity. ‡Per Common Terminology Criteria for Adverse Events Grade 1–3. Grade 1=mild, Grade 2=moderate, Grade 3=severe. AE, adverse event; ULN, upper limit of normal.

With up to 5 years of follow-up, a single infusion of dirloctocogene samoparvovec resulted in durable factor VIII expression, with a majority of participants expressing levels within the mild HA range, alongside an 82–99% reduction in annualized bleed rate and a 99.6% reduction in factor consumption

Figure 3. Factor VIII activity ≥1 year after a single infusion of dirloctocogene samoparvovec (includes 18 participants with ≥1 year of follow-up)

16 participants (88.9%) showed **sustained factor VIII activity**, with a majority in the mild HA range

2 participants (11.1%) **lost factor VIII expression within the first year*** and were excluded from this analysis

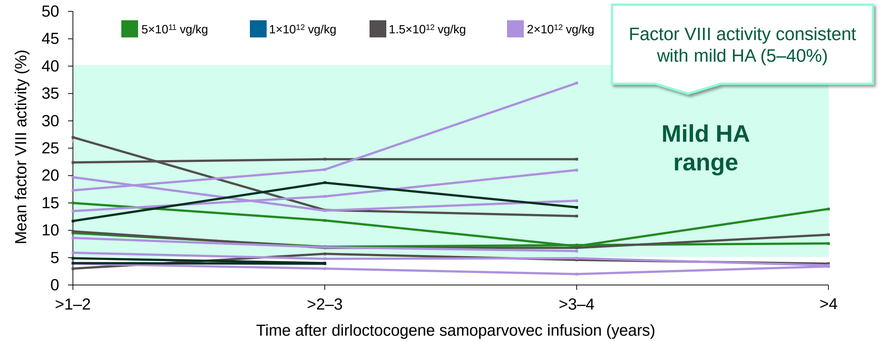


Figure 4. Mean† annualized bleed rate (ABR) before and after‡ dirloctocogene samoparvovec infusion (includes 22 participants with any duration of follow-up)

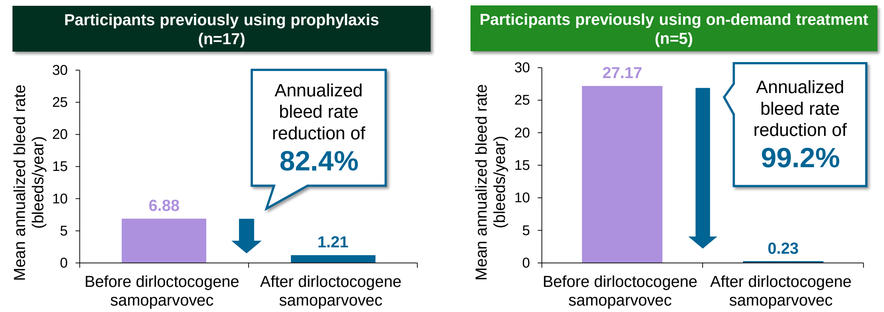
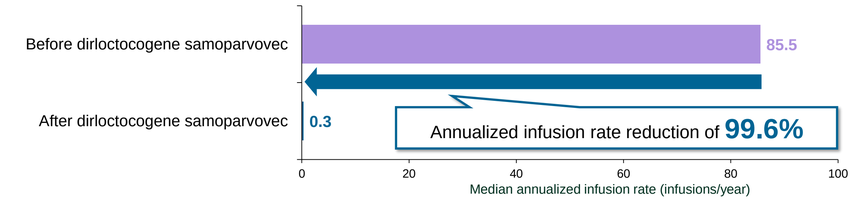


Figure 5. Median annualized factor consumption before and after dirloctocogene samoparvovec infusion (includes 22 participants with any duration of follow-up)



*Following a presumed capsid immune response. †Model-based mean calculated via negative binomial regression. ‡At data cut-off (October 04, 2022). Both ABR and AIR (after infusion) summaries exclude the first 28 days of follow-up. ABR, annualized bleed rate; AIR, annualized infusion rate; HA, hemophilia A; vg/kg, vector genomes per kilogram of bodyweight.

Presented at the 75th National Hemophilia Foundation (NHF) Annual Bleeding Disorders Conference | August 17–19, 2023

References

1. George LA, et al. *N Engl J Med* 2021;385:1961–73.

Acknowledgments

The authors would like to thank the study participants and their families, the study investigators, coordinators and nurses, and the Sponsor, Spark Therapeutics, Inc. The authors would also like to thank Katherine A. High, MD and Xavier M. Anguela, PhD, for their valuable contributions. Third-party medical writing assistance, under the direction of the authors, was provided by Hope Roberts-Dalton, MSc, PhD, of Ashfield MedComms, an Inizio company, and was funded by Spark Therapeutics, Inc.

Disclosures

SEC: consultancy: Bayer, Pfizer, Sanofi, BioMarin, Hema Biologics; research funding: Spark Therapeutics, Inc., Genentech, Inc., Sanofi; honoraria: Bayer, Pfizer; membership on an entity's Board of Directors or advisory committees: ATHN, Hemophilia Alliance, THSNA; **MEE**: employment: Penn State Hershey Medical Center; research funding: Spark Therapeutics, Inc., F. Hoffmann-La Roche Ltd.; Novo Nordisk Inc.; Baxalta Inc.; **HT**: research funding: Sanofi, AstraZeneca; honoraria: AstraZeneca, CSL Behring; speaker's bureau: Pfizer, Takeda; **MVR**: grant/research support: Biomarin, Sanofi, Spark Therapeutics, Inc., Takeda; consultancy: honoraria: BeBio, Takeda, Biomarin, TPG (Hemab Therapeutics); membership on an entity's board of directors or advisory committees: FWGBD, Blood Advances Editorial Board; **BJS**: grant/research support: Clinical trial support to institution by Spark Therapeutics, Inc., Pfizer; sponsored research support: Accugen; consultancy: Genentech, Inc., Biomarin; honoraria: Pfizer; membership on an entity's board of directors or advisory committees: GeneVentiv, Amarna; patents and royalties: Accugen, Cabaletta; employment: The University of Pennsylvania; **LG**: scientific advisory board: STRM Bio; consultancy: Avrobio, Intellia, BioMarin, Spark Therapeutics, Inc., Bayer; licensing fees: Ask Bio Therapeutics; **SS**: consultancy: CSL, Genentech, Inc., Octapharma, Pfizer; membership on an entity's board of directors or advisory committees: Make-A-Wish Mississippi, employment: Mississippi Center for Advanced Medicine; **JEJR**: shareholder: shareholdings with Rarecyte, Woke; DSMB for Fanconi anaemia trial; grant/research support: NHMRC, NSWCC, CINSW, MRFF, Therapeutic Innovation Australia, philanthropic foundations; supply of material (MTA) or consultancy or honoraria: Rarecyte, Novartis, Bluebird Bio, Spark Therapeutics, Inc., Cynata, Pfizer, CRISPRTx; membership on an entity's board of directors or advisory committees: co-Founder AAVrec Bio, non-executive director Woke Pharmaceuticals, non-executive director Kennerton Capital; employment: Sydney Local Health District at Royal Prince Alfred Hospital; **JM**: employment: University Health Physicians, University of Missouri-Kansas City; **PA**: employment: Ramathibodi Hospital; **JT**: consultancy: Regeneron, Bayer, Takeda, Novo Nordisk, Pfizer, F. Hoffmann-La Roche Ltd., Sanofi, BioMarin, Vega Therapeutics; research funding: Pfizer, Spark Therapeutics, Inc., Bayer; honoraria: Regeneron, Bayer, Takeda, Novo Nordisk, Pfizer, F. Hoffmann-La Roche Ltd., Sanofi; membership on an entity's board of directors or advisory committees: Pfizer; **GK**: employment: Sheba Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Israel; consultancy: ASC therapeutics, Bayer, Biomarine, Novo Nordisk, Pfizer, F. Hoffmann-La Roche Ltd., Sanofi- Genzyme, Sobi, Takeda, uniQure; research funding: **BSF**: Opko Biologics, Pfizer, F. Hoffmann-La Roche Ltd., Shire; honoraria: Bayer, BioMarin, BPL, CSL, Pfizer, Novo Nordisk, Roche, Sanofi-Genzyme, Sobi, Spark Therapeutics, Inc., Takeda, Uniquore; scientific advisory board: PedNet foundation; **TW**: Spouse was employed by Novartis full time until October 2022 and is now employed full time by Takeda; research/clinical trial support: Takeda, Sanofi, AMAG, Sobi, and Spark Therapeutics, Inc.; **TT**: employment: Spark Therapeutics, Inc., equity: F. Hoffmann-La Roche Ltd.; **FM**: employment: Spark Therapeutics, Inc., equity: F. Hoffmann-La Roche Ltd.; **TC**: shareholder: F. Hoffmann-La Roche Ltd.; employment Spark Therapeutics, Inc; **GL**: shareholder: F. Hoffmann-La Roche Ltd.; employment: Spark Therapeutics, Inc. Board of Directors (non-voting).