Favorable Complement Profile of AAVrh10: Clinical Monitoring Experience From Three Gene Therapy Studies Across Two Programs

Aubert G.[1], Khan A.[1], Rosales X.[1], See Tai S.[1], Adler E.[1], Crystal R.[2]

[1]Lexeo Therapeutics, Inc., New York, NY, USA; [2]Weill Cornell Medicine, New York, NY, USA

BACKGROUND

- Adeno-associated virus (AAV) vector gene therapy has emerged as a promising therapy for a range of genetic disorders; however, advances have been hindered by immunologic responses that can impact their safety and efficacy[1–3]
- Globally, the seroprevalence of antibodies against wild-type AAV is approximately 40–80%; therefore, patients may possess neutralizing antibodies that could bind the AAV capsids and trigger complement-mediated inflammation and cell damage[1,2]
- High doses of AAV may induce complement activation by binding to C1q on cell surfaces, initiating the classical pathway via cleavage of C4 and C2 to form C3 convertase, C5 convertase, and the eventual assembly of the membrane attack complex (sC5b-9)[3]
- Complement activation via component binding to the AAV capsid may trigger inflammatory responses, including thrombotic microangiopathy, thrombocytopenia, or capillary leak syndrome[4–6]
- Safety concerns related to complement activation have been reported in studies of the US Food and Drug Administration-approved gene therapy onasemnogene abeparvovec, as well as in ongoing clinical trials of other investigational AAV-based gene therapies.[4–6] As such, a systematic understanding of complement activation in AAV trials is essential to enhance safety monitoring and inform the development of effective risk mitigation strategies
- In this study, prospective complement monitoring was implemented across two clinical programs evaluating systemic AAVrh10 in Friedreich ataxia cardiomyopathy (FA-CM) and plakophilin 2-arrhythmogenic cardiomyopathy (PKP2-ACM) to assess systemic immune activation following vector administration

METHODS

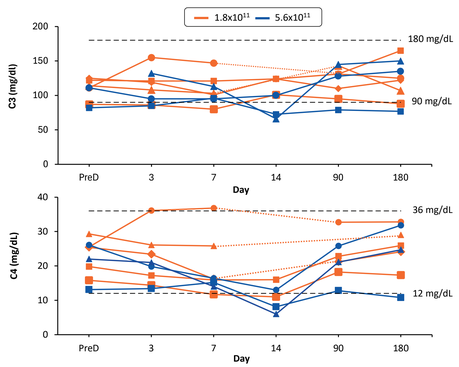
- Complement levels are being evaluated in three ongoing clinical studies that utilize the AAVrh10 vector
- Two studies are investigating AAVrh10-hFXN gene therapy in FA-CM at doses of $1.8x10^{11}$, $5.6x10^{11}$, or $1.2x10^{12}$ gc/kg: an investigator sponsored study at Weill Cornell Medical College (WCM; NHLBI HL151355), and the multi-site Lexeo Therapeutics-sponsored SUNRISE-FA study (NCT05445323)[7,8]
- Both studies:
  - Include adult patients (18–65 years) with a confirmed genetic diagnosis of Friedreich ataxia with evidence of cardiomyopathy and who have neutralizing anti-AAVrh10 below the protocol-defined threshold
  - Use corticosteroids as immunosuppression for 3 months following dosing
  - Include monitoring of complement components C3 and C4 during the early post-dosing period, with extended longitudinal follow-up in the WCM study
- The third study, Lexeo Therapeutics-sponsored HEROIC-PKP2 (NCT06109181), evaluates AAVrh10-hPKP2 gene therapy in PKP2-ACM at doses of $2x10^{13}$ and $6x10^{13}$ gc/kg[8,9]
- This study:
  - Includes adult patients (18–65 years) with a clinical diagnosis of arrhythmogenic cardiomyopathy with a pathogenic or likely pathogenic variant in PKP2 who have neutralizing anti-AAVrh10 below the protocol-defined threshold
  - Uses prednisone and sirolimus for 3 months following dosing
  - Monitors complement markers (C3, C4, sC5b-9, CH50, Factor I, Factor H, and ADAMTS13) from screening to Day 28
- Prednisone was administered to patients in the WCM, SUNRISE-FA, and HEROIC-PKP2 studies at 40 mg QD from Week 1 to Week 8, with a tapering by Week 12 in the HEROIC-PKP2 study and Week 14 in the WCM and SUNRISE-FA studies. Sirolimus was administered for 12 weeks in HEROIC-PKP2 only, with a target trough level of 4–8 ng/mL
- Data are summarized descriptively, with laboratory reference ranges included

RESULTS

C3 and C4 after AAVrh10-hFXN in FA-CM

- Two patients with FA-CM in the WCM study (N=8) showed a concurrent decrease in C3 and C4 below normal ranges on Day 14 at a dose of $5.6x10^{11}$ gc/kg (Figure 1); a third patient had values below the normal range at Day 7 at a dose of $1.8x10^{11}$ gc/kg
- Decreases in C3 and C4 were minimal and transient by Day 90, and were generally sustained at 90 days post-immunosuppression (Day 180)

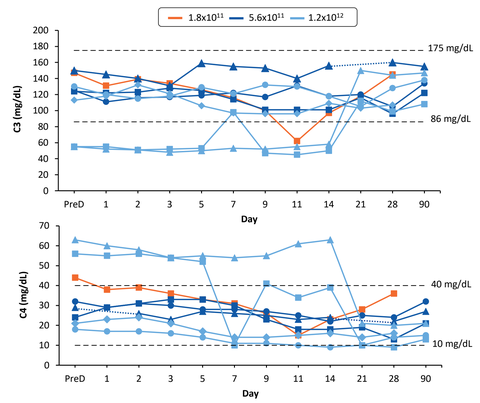
Figure 1. C3 and C4 up to 180 days after AAVrh10-hFXN gene therapy in FA-CM: WCM study



Line markers represent individual patients per dose group. Dashed black lines indicate lower and upper normal reference ranges, determined by the laboratories that conducted the assays. Dotted colored lines represent interpolations connecting missing patient data.

- One patient with FA-CM in the SUNRISE-FA study (N=8) showed a decrease in C3 below the normal range at Day 11 at a dose of $1.8x10^{11}$ gc/kg, and returned to the normal range by Day 14 (Figure 2)
  - Two patients had C3 and C4 levels below and above the normal reference ranges, respectively, at PreD; complement factors were within normal ranges by Day 21

Figure 2. C3 and C4 up to 90 days after AAVrh10-hFXN gene therapy in FA-CM: SUNRISE-FA study



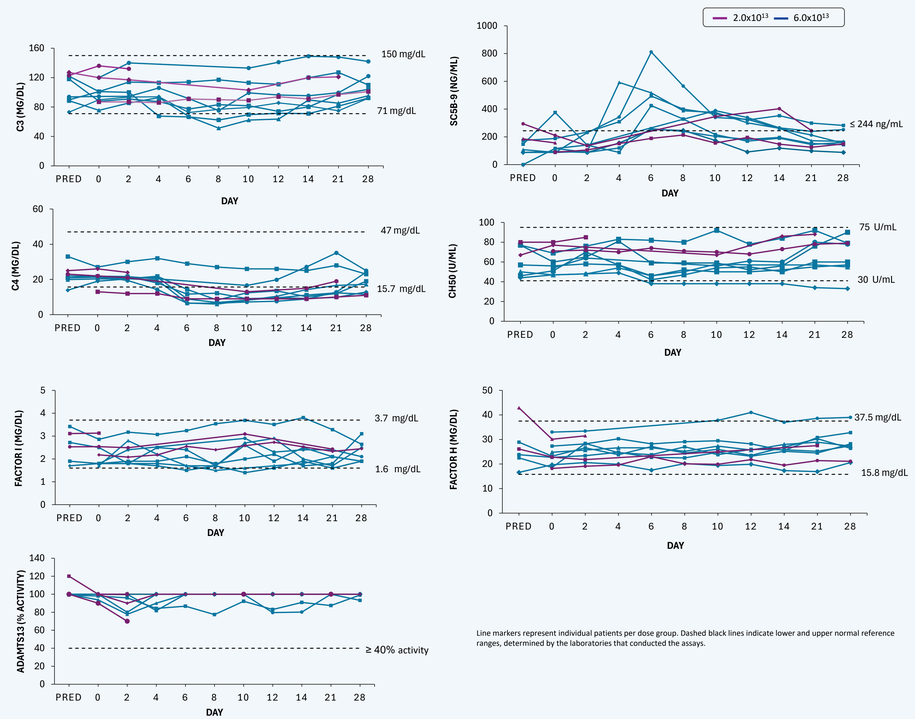
Line markers represent individual patients per dose group. Dashed black lines indicate lower and upper normal reference ranges, determined by the laboratories that conducted the assays. Dotted colored lines represent interpolations connecting missing patient data.

- Overall, findings were not associated with thrombocytopenia or other clinically significant laboratory abnormalities; patients returned to normal ranges without intervention
- No clinically significant changes in complement values were observed in any other patients during the monitoring period following AAVrh10-hFXN administration

Complement markers after AAVrh10-hPKP2 in PKP2-ACM

- Low dose ($2x10^{13}$ gc/kg) and high dose ($6x10^{13}$ gc/kg) cohorts in the HEROIC-PKP2 study (N=10) showed similar complement profiles, with early, transient, non-sustained changes across activation markers (sC5b-9, C3, C4, CH50), more pronounced and variable in the higher-dose cohort, with subsequent recovery toward baseline (Figure 3)
- Complement regulatory proteins (Factor H, Factor I) remained stable across both dose levels, consistent with intact pathway regulation
- ADAMTS13 activity remained well above clinically relevant thresholds in both cohorts, with no signal of endothelial or prothrombotic risk
- Across complement activation markers, functional assays, regulatory proteins, and ADAMTS13, the data are consistent with transient complement engagement with recovery and no evidence of clinically meaningful complement dysregulation, sustained complement deficiency, or downstream thrombotic risk

Figure 3. Complement markers up to 28 days after AAVrh10-hPKP2 gene therapy in PKP2-ACM



Line markers represent individual patients per dose group. Dashed black lines indicate lower and upper normal reference ranges, determined by the laboratories that conducted the assays.

ABBREVIATIONS

AAVrh10, adeno-associated virus rh10; **ADAMTS13**, A disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; **C1q**, complement component 1q; **C2**, complement component 2; **C3**, complement component 3; **C4**, complement component 4; **C5**, complement component 5; **CH50**, total hemolytic complement; **gc**, genome copies; **hFXN**, human frataxin; **hPKP2**, human plakophilin-2; **PreD**, pre-dosing; **QD**, once daily; **sC5b-9**, membrane attack complex.

REFERENCES

1. Salabarria S, et al. *J Clin Invest*. 2024;134(1):e173510. 2. Kropf E, et al. *Hum Gene Ther*. 2024;35(13–14):425–438. 3. Wang J-H, et al. *Signal Transduct Target Ther*. 2024;9(1):78. 4. Camelo CG, et al. *Gene Ther.* 2025;10.1038/s41434-025-00545-6. Online ahead of print. 5. Dreghici RD, et al. *Neuromuscul Disord.* 2022;32(Suppl. 1):S98. 6. Rocket Pharmaceuticals, Inc. Rocket Pharmaceuticals Provides Update on Phase 2 Clinical Trial of RP-A501 for Danon Disease [press release]. May 27, 2025. Accessed June 27, 2025. https://ir.rocketpharma.com/news-releases/news-release-details/rocket-pharmaceuticals-provides-update-phase-2-clinical-trial-rp. 7. Angeli F, et al. Poster presented at American College of Cardiology Annual Meeting; March 29–31, 2025; Chicago, IL. 8. Lexeo Therapeutics. (2024) Corporate Overview. Data on File. 9. Aubert G, et al. Poster presented at American College of Cardiology Annual Meeting; March 29–31, 2025; Chicago, IL.

KEY TAKEAWAYS

1. AAV remains the preferred platform in gene therapy due to the high specificity in gene delivery and low pathogenicity; however, approved and investigational AAV-based gene therapies have been hindered by safety concerns associated with complement activation.[1,3,4–6]
2. Across three clinical trials, patients were systemically administered with AAVrh10 doses of $1.8x10^{11}$ to $6x10^{13}$ gc/kg and received immunosuppression with corticosteroids and/or sirolimus; complement biomarkers demonstrated only transient, non-sustained changes with recovery, preserved functional activity and regulatory control, and no evidence of clinically meaningful complement dysregulation or downstream thrombotic risk.
3. To date, limited changes in complement activation have been observed with close laboratory and clinical monitoring concurrent with gene therapy administration, which suggests a favorable complement profile for the AAVrh10 vector.

MORE INFORMATION

To **learn more**, visit:
www.lexeotx.com

DISCLOSURES & DISCLAIMERS

Greg Aubert, Aashir Khan, Xiomara Q. Rosales, Sandi See Tai, and Eric Adler are employees and stockholders of Lexeo Therapeutics, Inc. Ron Crystal is a shareholder and board observer of Lexeo Therapeutics, Inc.

The data in Figure 3 represent an updated analysis of complement markers for AAVrh10-hPKP2 gene therapy in PKP2-ACM relative to analyses presented at the CGT 2nd Annual Meeting in 2025.

ACKNOWLEDGMENTS

Medical writing support was provided by Jacob Huffman, PhD, of BOLDSCIENCE®, Inc. and was funded by Lexeo Therapeutics, Inc. Editorial support was provided in accordance with Good Publication Practice guidelines (https://www.ismpp.org/gpp-2022).