Stable Factor IX Expression and Sustained Reductions in Factor IX Use 8 Years After Gene Therapy with CSL220 (Formerly AMT-060) in Adults with Hemophilia B

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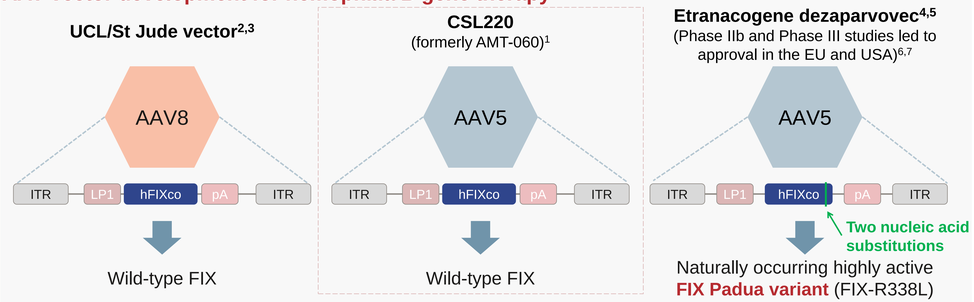
Abstract: 3578

BACKGROUND

- CSL220 (formerly AMT-060) is an adeno-associated virus serotype 5 (AAV5) vector, encoding a codon-optimized, wild-type human factor IX (FIX) gene, driven by a liver-specific promoter[1]

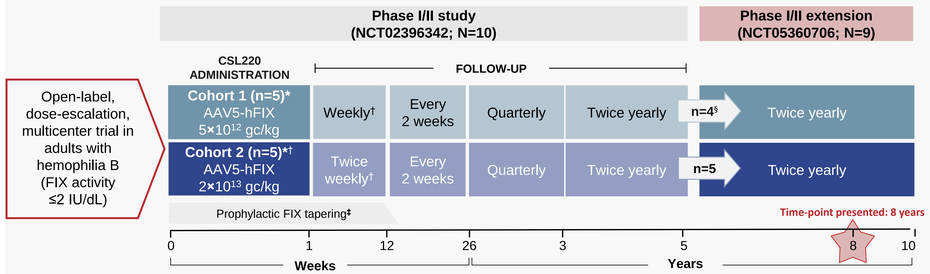
AAV vector development for hemophilia B gene therapy



FIX, factor IX; hFIXco, codon optimized human factor IX; ITR, inverted terminal repeat; LP1, liver promoter 1; pA, poly A; UCL, University College London.

- CSL220 has an identical vector sequence to etranacogene dezaparvovec, except it does not have the activity-enhancing two nucleotide change in the human FIX coding sequence as in the Padua variant[1,4–7]

CSL220 Phase I/II and extension trial design



*Data Monitoring Committee evaluated safety data for 24 hours after first two patients before dosing of the next patient; †Cohort 2 dosing was initiated after the completion of Cohort 1 dosing and review of initial safety data by the Data Monitoring Committee; ‡Prophylactic FIX tapering generally occurred between Weeks 6–12 if FIX activity was ≥2.0 IU/dL in at least two consecutive visits. Investigators could taper prophylaxis later than 12 weeks at their discretion but included the requirement to document that the participant could maintain a FIX activity level ≥2.0 IU/dL; §One patient in Cohort 1 who remained on FIX prophylaxis enrolled into the extension study. FIX, factor IX; gc, genome copies.

Phase I/II study outcomes[1]

- The majority of patients (9/10) were FIX prophylaxis free after administration of CSL220
- Mean (standard deviation [SD]) FIX activities at 5 years post-treatment with CSL220 were 6.5 (0.3) IU/dL in Cohort 1 (n=2) and 6.6 (2.0) IU/dL in Cohort 2 (n=4)
- CSL220 had a positive safety profile and resulted in clinically important stable increases in FIX activity
- The Cohort 2 dose (2×10^{13} gc/kg) was chosen for further clinical development[8]

OBJECTIVE

- **Examine the long-term efficacy and safety of CSL220, a gene therapy for hemophilia B**

METHODS

- Patients who successfully completed all assessments in the 5-year Phase I/II study, were enrolled into the open-label extension study
- Outcomes measured included adverse event characterization, endogenous FIX activity, exogenous FIX consumption, annualized bleeding rate (ABR; all bleeds, treated and untreated), spontaneous bleeds, and traumatic bleeds
- We report the third year of follow-up in the extension study; representing 8 years after CSL220 administration

RESULTS

Patient disposition and characteristics

- Overall, four participants from Cohort 1 (including one who remained on FIX prophylaxis) and five participants from Cohort 2 enrolled in the extension study

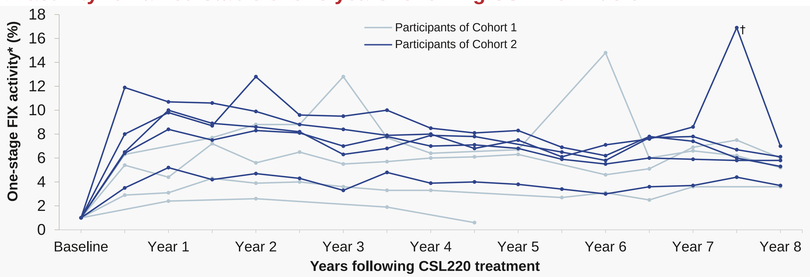
	Cohort 1 (N=4)	Cohort 2 (N=5)[1,2]
Age,* median (min–max), years	69 (35–72)	35 (33–46)
Weight, median (min–max), kg	84.5 (71.2–89.1)	84.0 (71.4–96.0)
HIV-positive status, n	1	0
Prior hepatitis C infection, n	4	2
Pre-existing Anti-AAV5 positive,† n	2	0

*Age at screening prior to CSL220 administration; †Assessed using luciferase-based assay.[9] AAV5, adeno-associated virus serotype 5; HIV, human immunodeficiency virus.

No new safety events were identified during the eighth-year post-infusion

- No new treatment-related adverse events were identified during Year 8; including no FIX inhibitors, thromboembolic events, new or recurrent cancer, or transaminase elevations

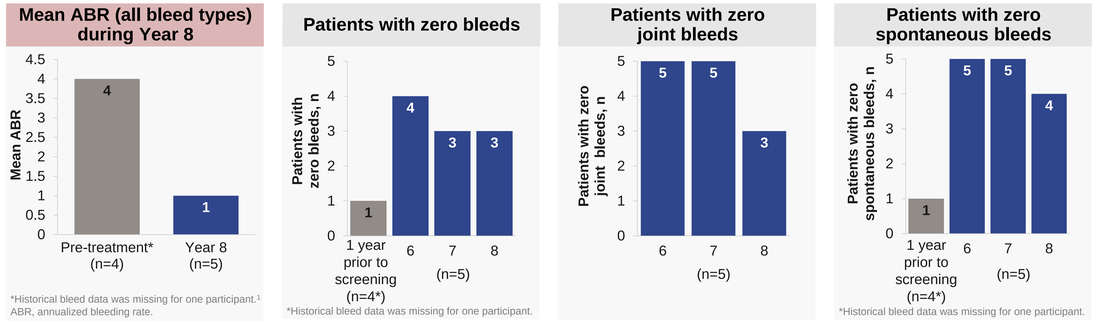
FIX activity remained stable over 8 years following CSL220 infusion



*FIX activity, using one-stage activated partial thromboplastin time assay (HemosIL® SynthASil reagent). Only uncontaminated (blood sampling that did not occur within five half-lives of exogenous FIX use) values were included. Baseline FIX based on participants' historical hemophilia B severity. †Potentially contaminated by exogenous FIX, query open. FIX, factor IX.

- FIX activity, mean (SD) and median (range) were 4.9 (1.2) IU/dL and 5.2 (3.6–6.0) IU/dL, respectively, in Cohort 1 (n=3, excluding the patient who remained on prophylaxis), and 5.6 (1.2) IU/dL and 5.8 (3.7–7.0) IU/dL, respectively, in Cohort 2 (n=5)

Bleeding protection was sustained for up to 8 years post-infusion in Cohort 2



*Historical bleed data was missing for one participant.[1] ABR, annualized bleeding rate.

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- At 8 years post-CSL220 infusion:
  - Mean (SD) ABR was 1.0 (1.8, n=5) for Cohort 2
  - Mean (SD) annualized spontaneous bleeding rate was 0.4 (0.9, n=5) in Cohort 2
  - One patient experienced a traumatic bleed in Cohort 1, as did one patient in Cohort 2

Exogenous FIX consumption was low, and no patient returned to continuous prophylaxis in Year 8

	Cohort 1 (N=4) 5×10^12 gc/kg				Cohort 2 (N=5)[1,2] 2×10^13 gc/kg				
Participant	1	2†	3	4	1	2	3	4	5
Number of FIX infusions*	13	29†	0	0	0	0	13	0	2
Annualized exogenous FIX use,* IU/year	53,451	68,781†	0	0	0	0	55,373	0	6139

*Excluding invasive procedures. †Participant 2 started FIX prophylaxis in the Phase I/II study and remained on prophylaxis throughout follow-up. FIX, factor IX; gc, genome copies.

Cohort 1: three patients remained free of prophylaxis at 8 years post-treatment; one participant continued FIX prophylaxis*

Cohort 2: all five (100%) patients remained free of prophylaxis in the 8 years following CSL220 therapy

- Mean (SD) annualized FIX consumption during Year 8 (excluding surgeries and the patient who remained on FIX prophylaxis) was 17,817.1 (30,860.1) IU/year (or 189.5 [328.3] IU/kg/year) in Cohort 1 (n=3) and 12,302.4 (24,223.6) IU/year (or 149.3 [300.0] IU/kg/year) in Cohort 2 (n=5)

CONCLUSIONS

- **Factor expression durability is a key consideration in the decision-making process about gene therapy for patients and physicians[10]**
- **With only one amino acid difference in the expressed FIX protein, CSL220 is the precursor of etranacogene dezaparvovec, which was the first gene therapy approved for the treatment of hemophilia B[1,4–7]**
- **This 8-year follow-up after CSL220 administration provides continued evidence for the durability, stability, and safety of FIX expression after AAV5-based gene therapy for the treatment of hemophilia B**

REFERENCES & ACKNOWLEDGMENTS

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