Expression of SGCA and Safety Following Treatment With Patidistrogene Bexoparvovec in Patients With LGMD2D/R3: Results From a Phase 1b Study

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Background

- Limb-girdle muscular dystrophy subtype 2D/R3 (LGMD2D/R3) is caused by pathogenic variants in the α-sarcoglycan (*SGCA*) gene leading to progressive muscle loss (**Figure 1**)[1]
- Patidistrogene bexoparvovec (SRP-9004) is an investigational recombinant adeno-associated virus rhesus 74 serotype-based gene therapy designed to deliver full-length *SGCA* transgene and optimally express functional α-sarcoglycan protein (α-SG) in patients diagnosed with LGMD2D/R3[2]
- Study SRP-9004-102 (DISCOVERY; NCT01976091) is a multicenter, open-label, phase 1b study evaluating the effects of patidistrogene bexoparvovec on α-SG expression and safety in ambulatory and non-ambulatory patients with LGMD2D/R3[2]

Figure 1 *α-SG, a component of sarcoglycan complex, stabilizes DAPC and sarcolemma*[3]

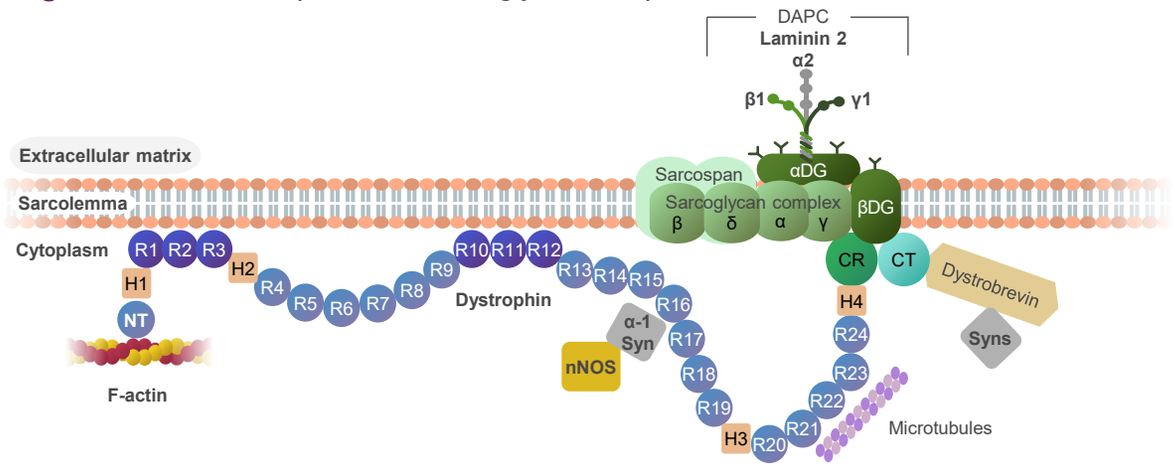


Image adapted from Elangkovan N, Dickson G. *J Neuromuscul Dis.* 2021;8(suppl 2):S303-S316.
α-SG, α-sarcoglycan protein; CR, cysteine-rich; CT, carboxy-terminus; DAPC, dystrophin-associated protein complex; DG, dystroglycan; F-actin, filamentous actin; H, hinge; nNOS, neuronal nitric oxide synthase; NT, N-terminus; R, spectrin-like repeat; syn, syntrophin.

Objective

To report 60-day α-SG expression and 90-day safety findings from the phase 1b, multi-site, open-label DISCOVERY trial (NCT01976091)

Methods

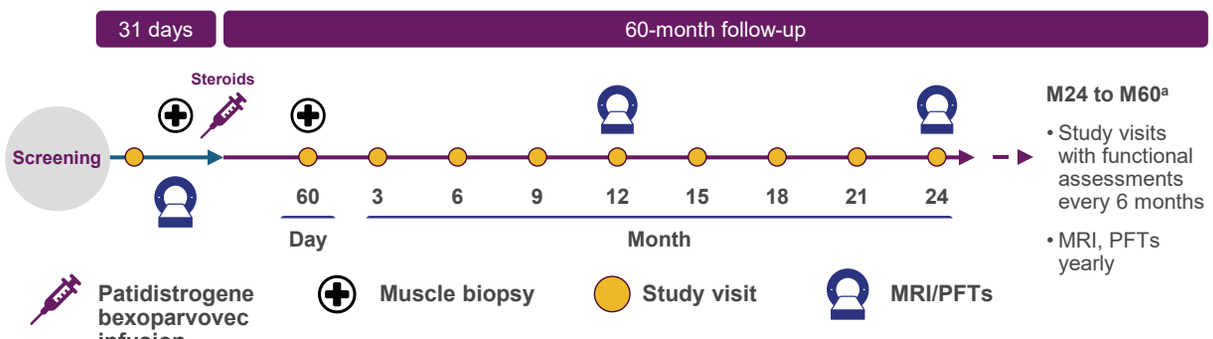
Study design

- Eligible patients
  - Male or female
  - Aged 4-20 years if ambulatory or ≥4 years if non-ambulatory
  - Had 1 homozygous or 2 heterozygous pathogenic and/or likely pathogenic *SGCA* DNA variant as documented prior to screening
- Participants received a single infusion of patidistrogene bexoparvovec (7.41×10^{13} vg/kg) (**Figure 2**)

Outcomes

- The primary endpoint was safety, including incidence of adverse events (AEs) and of treatment-emergent AEs (TEAEs)
- Secondary endpoints included change from baseline to day 60 in α-SG expression as measured by percent positive fibers (PPF), percent fluorescent intensity (PFI) using immunofluorescence (IF) staining,[4] and western assay
- Vector genome copies per nucleus were analyzed by using a validated droplet digital polymerase chain reaction method
- Changes in serum creatine kinase (CK) levels were also analyzed up to 90 days

Figure 2 *Study design*



[a]The study was terminated; therefore, any follow-up visits are at the discretion of the patient and PI after closure of the study up to 12 months post D1 infusion.
D, day; M, month; MRI, magnetic resonance imaging; PFT, pulmonary function test; PI, principal investigator.

Results

Baseline characteristics

- A total of 4 patients were enrolled; 3 patients were ambulatory (mean [standard deviation; SD] age, 11 [0] years) and 1 patient was non-ambulatory (51 [−] years) (**Supplemental Table 1**)
- In the ambulatory group, 2 patients (66.7%) were female; the non-ambulatory patient was male
- The mean (SD) weight was 51.8 (15.7) kg for the ambulatory patients and 68.9 (−) kg for the non-ambulatory patient

Safety

- In total, 4 (100%) participants had TEAEs, but most were grade 1 or 2
- There were 2 treatment-related serious AEs (SAEs):
  - 1 ambulatory 11-year-old patient with grade 3 (severe) hepatotoxicity, which resolved with corticosteroids
  - 1 non-ambulatory 51-year-old male patient with grade 5 (fatal) acute hepatic failure 77 days after dosing (**Supplemental Table 2; Supplemental Figure 1**)
- At 60 days, all patients had mostly mild to moderate treatment-related TEAEs, including nausea, fatigue, hepatotoxicity, and increased transaminases
  - In the 3 ambulatory patients, these mostly resolved within 90 days of onset
- There were no AEs leading to discontinuation (**Table 1**)

Table 1 *Summary of adverse events*

Parameter, n (%)	Ambulatory (n=3)	Non-ambulatory (n=1)	Overall (N=4)
TEAEs[a]	3 (100)	1 (100)	4 (100)
SAEs	1 (33.3)	1 (100)	2 (50)
Treatment-related TEAEs	3 (100)	1 (100)	4 (100)
Treatment-related SAEs	1 (33.3)	1 (100)	2 (50.0)

[a]TEAEs are defined as all AEs that had occurred on or after the study drug administration date. AEs are coded using MedDRA version 28.0. Cutoff date: June 27, 2025. AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Biological efficacy outcomes

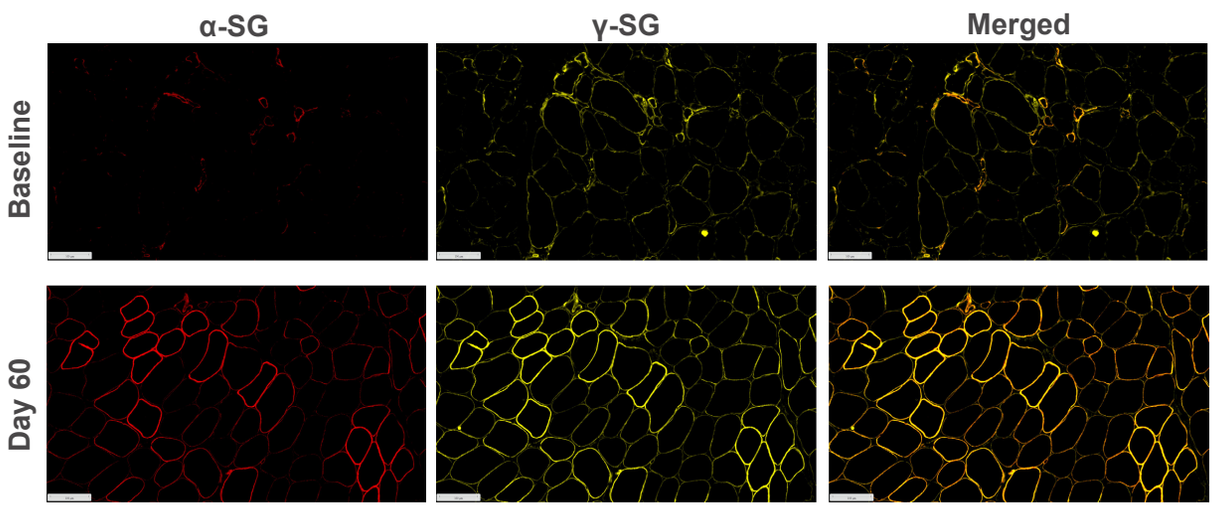
- Overall α-SG expression was consistent at day 60 (N=4): mean (SD) change in PPF was 15.6% (13.2%) and 14.7% (15.4%) for western assay
  - The mean (SD) change from baseline in PPF was 19.5 (13.0) and 3.9 (−) for the ambulatory and non-ambulatory cohorts, respectively (**Table 2**)
  - The mean (SD) change from baseline for western assay was 20.0 (13.7) for the ambulatory cohort and -1.3 (−) for the non-ambulatory cohort (**Table 2**)
- The mean (SD) number of vector genome copies per nucleus was 11.0 (5.7) at day 60
- Representative images of α-SG expression from an ambulatory patient are shown in **Figure 3**

Table 2 *Biological efficacy outcomes*

Cohort	Time point	Transduction at day 60: Vector genome copies per nucleus[a] Mean (SD) [Min-max]	α-SG protein expression at day 60: IF, PPF % Mean (SD) [Min-max]	IF, PFI % Mean (SD) [Min-max]	Western assay % NC mean (SD) [Min-max]
Ambulatory	Baseline (n=3)	0 (0) [0 to 0]	9.4 (16.3) [0 to 28.2]	19.7 (26.5) [0 to 49.7]	17.1 (12.8) [6.7 to 31.4]
	Day 60 (n=3)	12.3 (6.2) [8.1 to 19.4]	28.9 (29.3) [11.1 to 62.6]	77.3 (11.9) [63.8 to 86.1]	37.1 (25.9) [21.0 to 67.0]
	Mean change from baseline (n=3)	**12.3 (6.2) [8.1 to 19.4]**	**19.5 (13.0) [11.0 to 34.5]**	**57.7 (38.4) [14.0 to 86.1]**	**20.0 (13.7) [10.1 to 35.6]**
Non-ambulatory	Baseline (n=1)	0 (–) [0 to 0]	31.3 (–) [31.3 to 31.3]	55.5 (–) [55.5 to 55.5]	30.9 (–) [30.9 to 30.9]
	Day 60 (n=1)	7.2 (–) [7.2 to 7.2]	35.1 (–) [35.1 to 35.1]	54.5 (–) [54.5 to 54.5]	29.7 (–) [29.7 to 29.7]
	Mean change from baseline (n=1)	7.2 (–) [7.2 to 7.2]	3.9 (–) [3.9 to 3.9]	-1.0 (–) [-1.0 to -1.0]	-1.3 (–) [-1.3 to -1.3]

[a]Baseline results were below limit of quantification.
α-SG, α-sarcoglycan; IF, immunofluorescence; PFI, percent fluorescent intensity; PPF, percent positive fibers; SD, standard deviation.

Figure 3 *Representative immunofluorescent images of α-sarcoglycan and γ-sarcoglycan expression and membrane localization from an ambulatory patient*



Selected images showing immunofluorescence staining expression at baseline and day 60. Scale bar is 100 µm. α-SG, α-sarcoglycan protein; γ-SG, γ-sarcoglycan protein.

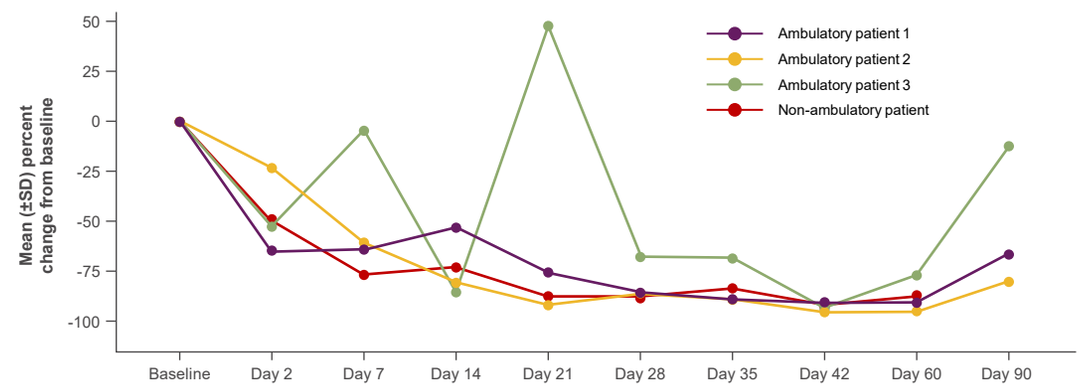
Restoration of DAPC

- To evaluate the effect of patidistrogene bexoparvovec on sarcoglycan complex restoration within the dystrophin-associated protein complex (DAPC), colocalization of the α-SG and γ-SG subunits was measured by IF PPF of biopsied muscle tissue (**Figure 3**)
- From baseline to day 60, the percentage of fibers with colocalized expression of α-SG and γ-SG increased for both cohorts (**Supplemental Figure 2**)

Serum CK reduction

- The mean (SD; min-max) percent change from baseline to day 90 in CK levels was −53.1% (36.0%; −80.9% to −12.4%) in ambulatory patients (**Figure 4**)

Figure 4 *Mean percent change in serum CK values*



Baseline values, U/L		Baseline	Day 2	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 60	Day 90
Ambulatory, mean (SD)	3,593.0 (2,974.0)										
Non-ambulatory, mean (SD)	1,392.0 (−)										
Ambulatory mean		0	−47.1	−43.1	−73.1	−40.1	−80.1	−82.3	−93.1	−87.7	−53.1
Ambulatory, n		3	3	3	3	3	3	3	3	3	3
Non-ambulatory mean		0	−49.9	−77.0	−73.6	−87.8	−88.0	−83.9	−92.3	−87.2	
Non-ambulatory, n		1	1	1	1	1	1	1	1	1	

CK, creatine kinase; SD, standard deviation.

Conclusions

- Expression of full-length α-SG, restoration of the DAPC, and CK reduction levels indicate patidistrogene bexoparvovec elicits a biological cascade in muscle likely to lead to clinical benefit
- The fatal acute hepatic failure event in this trial was similar to other fatal hepatic events observed with adeno-associated virus -based gene therapies across multiple indications[5]
- Events such as acute liver failure serve as a reminder of the critical importance of hepatic monitoring and early intervention following gene therapy administration. Prophylactic use of sirolimus prior to gene therapy is being evaluated in other gene therapy programs to reduce the incidence of acute liver injury
- The SRP-9004 program is currently paused

Acknowledgments and Disclosures

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References

1. Griffin DA, et al. *Hum Gene Ther*. 2021;32(7-8):390-404. **2.** ClinicalTrials.gov identifier: NCT01976091. Updated June 15, 2023. Accessed February 17, 2026. https://clinicaltrials.gov/study/NCT01976091. **3.** Elangkovan N, Dickson G. *J Neuromuscul Dis*. 2021;8(suppl 2):S303-S316. **4.** Connolly AM, et al. Poster presented at: 30th Annual International Congress of the World Muscle Society; October 7-11, 2025; Vienna, Austria. Poster 734LBP. **5.** *Nat Biotechnol*. 2020;38(8):910.

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Supplemental Table 1 *Baseline characteristics*

Parameter	Ambulatory (n=3)	Non-ambulatory (n=1)
Age at enrollment, years		
Mean (SD)	11 (0)	51 (−)
Min-max	11-11	51-51
Sex, n (%)		
Male	1 (33.3)	1 (100)
Female	2 (66.7)	0
Ethnicity, n (%)		
Not Hispanic or Latino	3 (100)	1 (100)
Race, n (%)		
White or Caucasian	2 (66.7)	1 (100)
Asian	1 (33.3)	0
Baseline weight, kg		
Mean (SD)	51.8 (15.7)	68.9 (−)
(Min-max)	35.7-67.0	68.9-68.9
BMI, kg/m^2		
Mean (SD)	22.7 (4.2)	19.9 (−)
(Min-max)	19.4-27.5	19.9-19.9

SD, standard deviation.

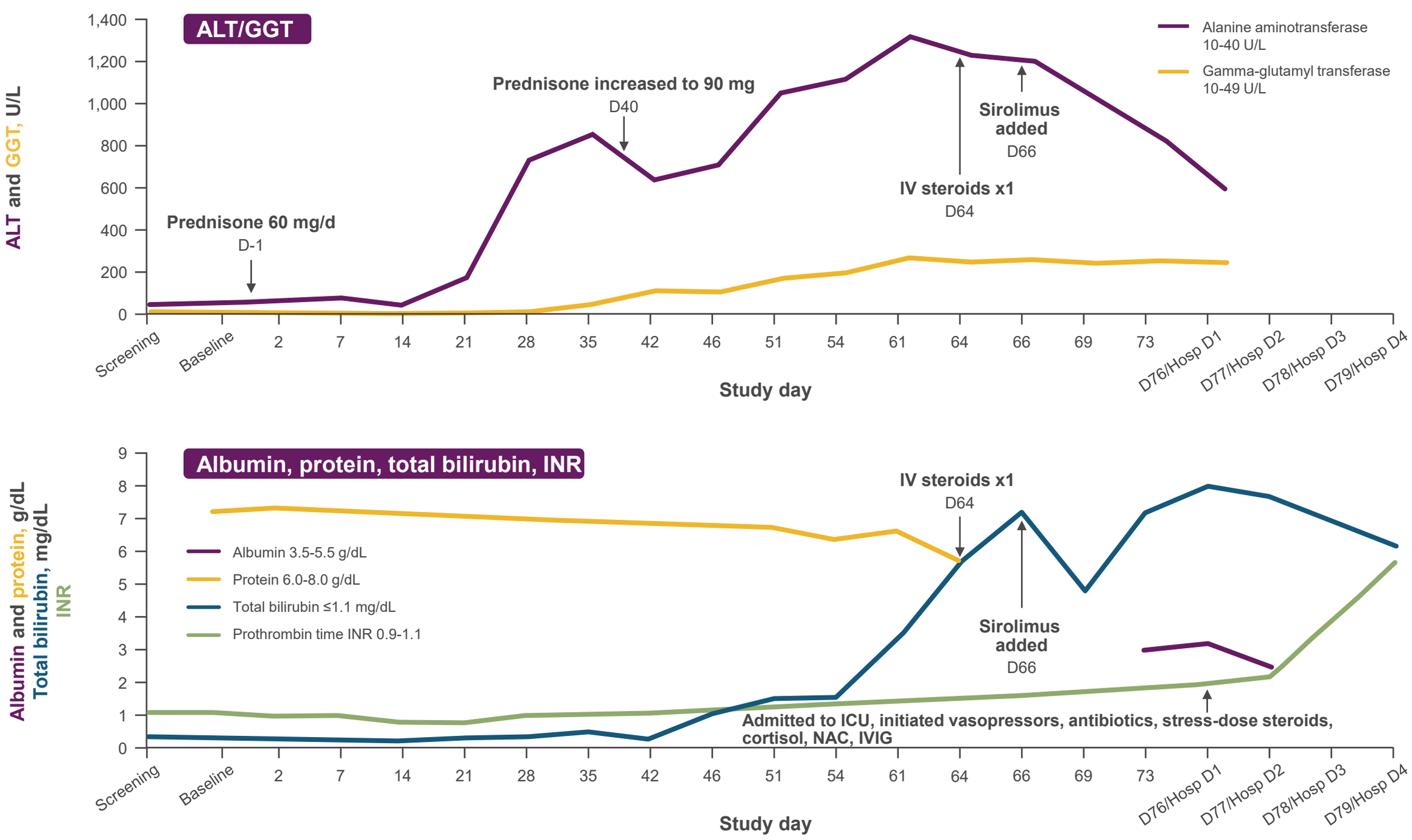
Acute liver failure fatality

- This non-ambulatory 51-year-old male patient was diagnosed with LGMD2D/R3 at age 16 and had been non-ambulatory for approximately 2 years
- No baseline respiratory support had been provided, and he was steroid naïve
- His medical history included 2 pulmonary embolisms (2016, 2021), and he had had hypogonadism since 2010
- Concomitant medications included testosterone since 2010 and apixaban since 2021

Supplemental Table 2 *Acute liver failure case study*

Time	Events
~11 weeks post dosing	Patient was hospitalized for acute liver injury (ALI) and treated with intravenous steroids and other immunomodulatory therapies
Post-ALI therapies	Liver enzymes improved, but synthetic liver function subsequently worsened, as evidenced by low albumin and prolonged international normalized ratio, with accompanying thrombocytopenia
~12 weeks post dosing	Liver failure and patient death. Liver failure was assessed as related to patidistrogene bexoparvovec

Supplemental Figure 1 *Acute liver failure: liver function tests*



ALT, alanine aminotransferase; D, day; GGT, gamma-glutamyl transferase; hosp, hospitalization; ICU, intensive care unit; INR, international normalized ratio; IV, intravenous; IVIG, intravenous immunoglobulin; NAC, n-acetylcysteine.

Supplemental Figure 2 *DAPC restoration*

DAPC, dystrophin-associated protein complex; IF, immunofluorescence; PPF, percent positive fibers; SD, standard deviation.

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