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Expression of SGCB and Safety Following Bidridistrogene Xeboparvovec Treatment in Patients With LGMD2E/R4: Results From the EMERGENE Phase 3 Study

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Background

- Limb-girdle muscular dystrophy subtype 2E/R4 (LGMD2E/R4) is caused by pathogenic variants in the β-sarcoglycan gene (*SGCB*), leading to β-sarcoglycan protein (β-SG) deficiency and destabilizing the dystrophin-associated protein complex (DAPC) and the sarcolemma (**Figure 1**)[1-3]
- Bidridistrogene xeboparvovec, an investigational recombinant adeno-associated virus rhesus isolate serotype 74 (rAAVrh74) vector that delivers the full-length *SGCB* transgene (**Figure 2**), has shown functional gains or stabilization with manageable safety in early-phase studies[4,5]
- Study SRP-9003-301 (EMERGENE, NCT06246513) is a global, multicenter, open-label, phase 3 study evaluating the effects of bidridistrogene xeboparvovec on β-SG expression and safety in ambulatory and non-ambulatory patients with LGMD2E/R4[6]

Figure 1 *β-SG, a Component of Sarcoglycan Complex, Stabilizes DAPC and Sarcolemma*[7]

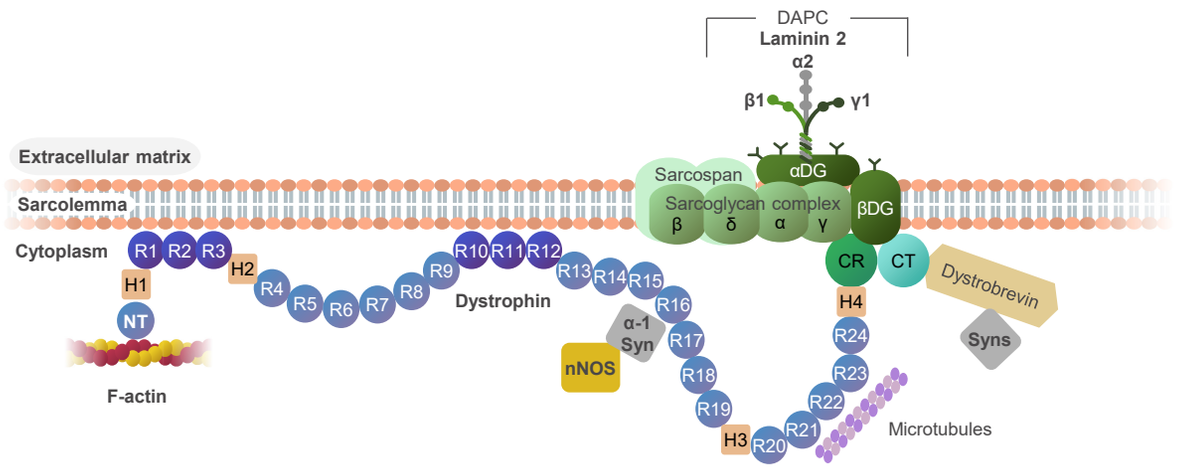
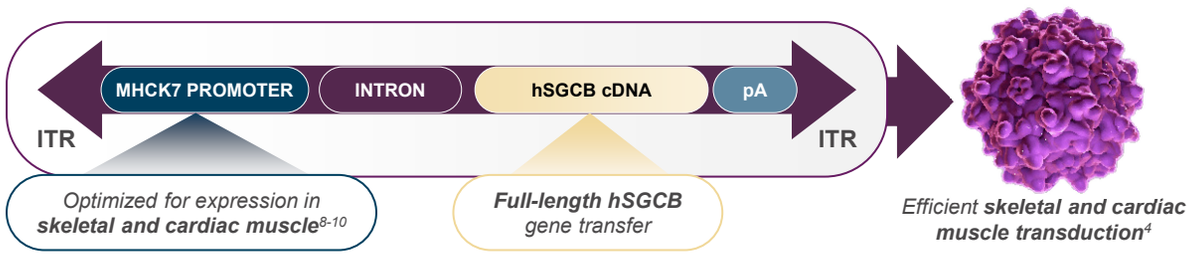


Image adapted from Elangkovan N, Dickson G. *J Neuromuscul Dis.* 2021;8(suppl 2):S303-S316. β-SG, β-sarcoglycan protein; CR, cysteine-rich; CT, carboxy-terminus; DAPC, dystrophin-associated protein complex; DG, dystroglycan; F-actin, filamentous actin; H, hinge; nNOS, neuronal nitric oxide synthase;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

Figure 2 *Overview of Bidridistrogene Xeboparvovec*



cDNA, complementary DNA; hSGCB, human β-sarcoglycan; ITR, inverted terminal repeat; MHCK7, myosin heavy-chain creatine kinase 7; pA, polyadenylation; rAAVrh74, recombinant adeno-associated virus rhesus isolate serotype 74.

Objective

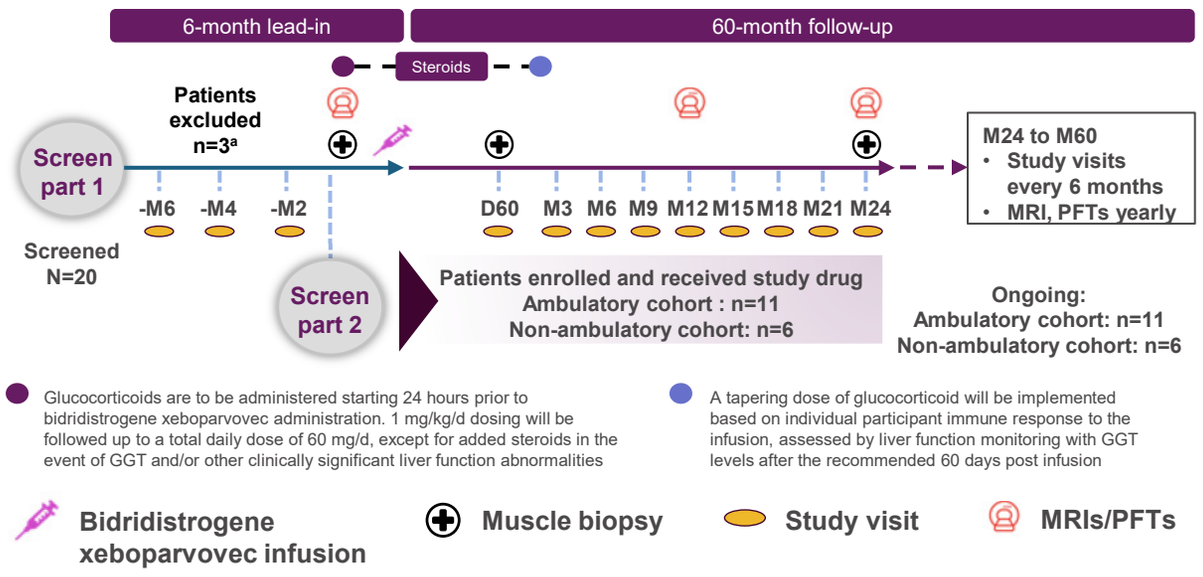
To evaluate 60-day β-SG expression and 90-day safety (data cutoff date: March 20, 2025) from EMERGENE in an ongoing, open-label, single-arm, phase 3 study

Methods

Study design

- Eligible male or female patients were aged ≥4 years with 1 homozygous or 2 heterozygous pathogenic and/or likely pathogenic *SGCB* DNA variant as documented prior to screening
- Participants received a single infusion of bidridistrogene xeboparvovec (7.41×10^{13} vg/kg) (**Figure 3**)

Figure 3 *Study Design, Patient Flow, and Study Endpoints*



[a]Excluded due to screen failures.
D, day; GGT, gamma-glutamyl transferase; M, month; MRI, magnetic resonance imaging; PFT, pulmonary function test.

Outcomes

- Primary endpoint: mean change from baseline (CFBL) to day 60 in β-SG expression, measured by percent positive fibers (PPF) using immunofluorescence (IF) staining in ambulatory participants (**Supplemental Methods**)
- Secondary endpoints: CFBL in β-SG expression at day 60, measured by percent fluorescent intensity (PFI) and Western blot in ambulatory and non-ambulatory patients
  - CFBL in β-SG expression at day 60 was also measured by PPF for patients in the non-ambulatory cohort
- Safety and change in serum creatine kinase (CK) levels were also analyzed for both cohorts

Results

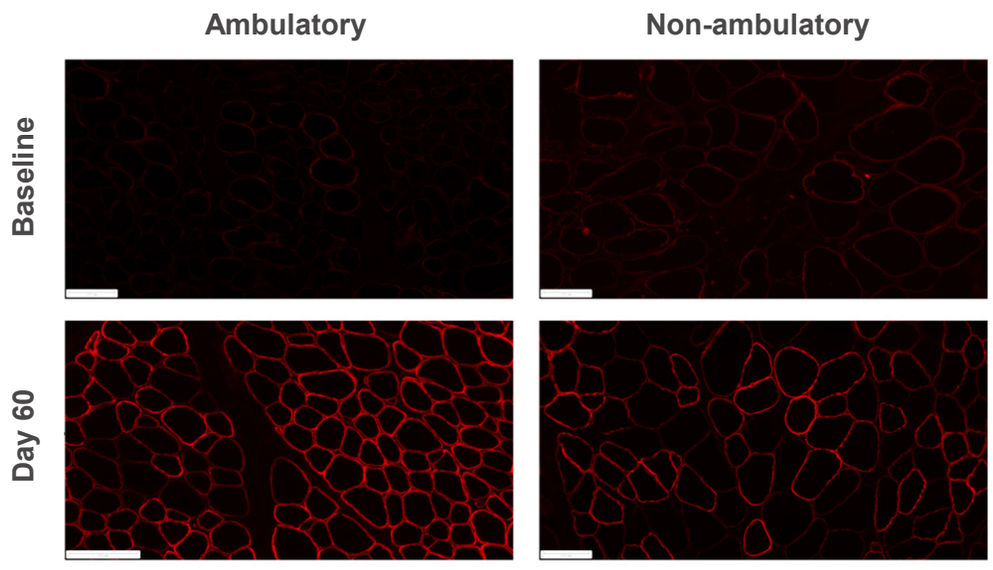
Baseline characteristics

- A total of 20 patients were assessed for eligibility; of the 17 patients who met eligibility criteria, 11 patients were enrolled in cohort 1 (ambulatory; 6 males) and 6 patients were enrolled in cohort 2 (non-ambulatory; all females) (**Figure 3**)
- The mean age (standard deviation [SD]) at baseline was 12.7 (4.71) years for cohort 1 and 25.8 (15.94) years for cohort 2 (**Supplemental Table 1**)
- The mean (SD) weight was 48.6 (20.52) kg and 54.0 (11.19) kg and CK values were 5,246.9 (4,832.44) U/L and 1,204.2 (468.49) U/L for cohorts 1 and 2, respectively, at baseline (**Supplemental Table 1**)

Biological efficacy outcomes

- The **primary endpoint** (mean [SD] CFBL to day 60 PPF in β-SG expression) was met (**Table 1**):
  - Ambulatory cohort: 43.4% (29.9%); *P*<0.001
  - Non-ambulatory cohort: 23.9% (14.2%); *P*<0.02

Figure 4 *Representative Immunofluorescent Images of β-Sarcoglycan Expression and Membrane Localization*



Images show immunofluorescence staining reflecting mean percent positive fibers expression for both ambulatory and non-ambulatory cohorts at baseline and day 60. Scale bar is 100 µm.

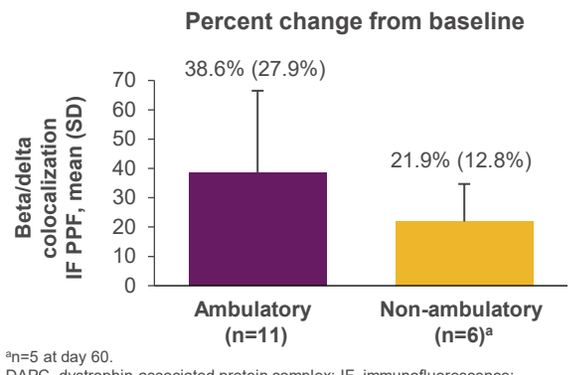
Restoration of DAPC

- To evaluate the effect of bidridistrogene xeboparvovec on sarcoglycan complex restoration within the DAPC, colocalization of the β-SG and δ-SG subunits was measured by IF PPF of biopsied muscle tissue
- At day 60, the PPF for both β and δ increased in patients of both cohorts (**Figure 5**)

Serum CK reduction

- Mean (SD; min, max) percent CFBL to day 60 CK levels were as follows: −88.8% (10.9%; −99.6% to −66.8%) in ambulatory and −92.4% (4.5%; −97.1% to −86.7%) in non-ambulatory cohorts (**Figure 6**)

Figure 5 *DAPC Restoration*



[a]n=5 at day 60.
DAPC, dystrophin-associated protein complex; IF, immunofluorescence; PPF, percent positive fibers; SD, standard deviation.

Figure 6 *Serum CK Values*

Baseline values, U/L														
Ambulatory, mean (SD)	5,246.9 (4,832.44)													
Non-ambulatory, mean (SD)	1,204.2 (468.49)													
Ambulatory mean	0	−28.36	−8.71	−71.5	−78.62	−79.96	−84.16	−86.26	−88.78	−92.74	−90.38	−36.67	−50.52	−64.81
Ambulatory, n	11	10	11	11	11	11	11	11	11	1	1	11	8	4
Non-ambulatory mean	0	−15.38	−64.07	−77.26	−81.83	−85.44	−87.5	−91.49	−92.39			−82.04	−76.14	−83.44
Non-ambulatory, n	6	6	6	6	6	6	6	5	6			6	3	2

CK, creatine kinase; SD, standard deviation.

Table 1 *Primary, Secondary, and Exploratory Biological Efficacy Outcomes*

Cohort	Timepoint	β-SG protein expression: IF PPF, % mean (SD) [median]	β-SG protein expression: IF PFI, % mean (SD) [median]	β-SG protein expression: Western, % NC mean (SD) [median]	Transduction: ddPCR, copies/ nucleus mean (SD) [median]
Ambulatory	Baseline (n=11)	15.44 (19.75) [4.65]	23.26 (7.83) [25.08]	19.80 (8.16) [18.42]	0 (0) [0]
	Change from baseline (n=11)	**43.38 (29.92) [50.28][a] *P*<0.001**	**18.23 (11.23) [18.78][b] *P*<0.001**	**33.58 (31.28) [24.98][b] *P*<0.01**	**5.96 (2.43) [6.36][c]**
Non-ambulatory	Baseline (n=6)	7.80 (13.56) [0.11]	15.30 (12.31) [20.04]	23.11 (7.75) [23.45]	0 (0) [0]
	Change from baseline (n=6)	**23.90 (14.24)[d] [28.75][b] *P*<0.02**	**21.81 (14.04)[d] [21.75][b]**	**12.99 (10.56) [17.29][b]**	**4.98 (2.43) [4.95][c]**

[a]Primary endpoint. [b]Secondary endpoint. [c]Exploratory endpoint. [d]n=5.
β-SG, β-sarcoglycan; ddPCR, droplet digital polymerase chain reaction; IF, immunofluorescence; NC, normal control; PFI, percent fluorescent intensity; PPF, percent positive fibers; SD, standard deviation.

Safety

- The overall safety of bidridistrogene xeboparvovec was manageable with appropriate monitoring, with no notable differences between cohorts
- The most common treatment-related treatment-emergent adverse events (TEAEs) were nausea (70.6%), decreased appetite (47.1%), vomiting (41.2%), upper abdominal pain (29.4%), and fatigue (29.4%) (**Supplemental Table 2**)
- At data cutoff (March 20, 2025), 7 patients (41.2%) had TEAEs associated with acute liver injury:
  - Ambulatory: 5 (grade 2/3), of which 1 patient (non-serious) remained ongoing at data cutoff
  - Non-ambulatory: 2 (grade 1)
- Following data cutoff, 4 additional patients were reported to have experienced TEAEs (grade 1) associated with acute liver injury
- There were no treatment-related deaths or acute liver injuries reported

Conclusions

- These findings demonstrate robust expression of β-SG at 60 days post treatment along with restoration of other component proteins of the sarcoglycan complex in both ambulatory and non-ambulatory patients
- The safety and tolerability results were consistent with previous results and were observed up to 90 days post treatment
- These findings indicate that bidridistrogene xeboparvovec treatment induces a biological cascade likely to predict clinical benefit

Acknowledgments & Disclosures

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Disclosures: AMC: Served on an advisory board for Edgewise Therapeutics and for Sarepta Therapeutics, Inc., unrelated to this work. Served as principal investigator of studies sponsored by Biohaven, Edgewise Therapeutics, Novartis, and Scholar Rock. Served as a Data Safety and Monitoring Board member for Avidity Biosciences and Octapharma. **CGL:** Participated in advisory boards for Biogen, Catalyst, Dyne, Novartis, and Sarepta Therapeutics, Inc. **CMP:** Participated in advisory boards and served as a consultant for Biogen, Genentech/Roche, Novartis Gene Therapies, Sarepta Therapeutics, Inc., and Scholar Rock. Served as a speaker for Biogen. Served as principal investigator of studies sponsored by Astellas, Biogen, Biohaven, CSL Behring, FibroGen, Novartis Gene Therapies, Pfizer, PTC, Sarepta Therapeutics, Inc., and Scholar Rock. **JDM:** Participated in advisory boards for Amicus, Astellas, Lupin, Sanofi, Sarepta Therapeutics, Inc., and Spark. Received funding for research from Boehringer Ingelheim, Sanofi, Sarepta Therapeutics, Inc., and Spark. **KGC:** Received speaker/advisory board honoraria from Alexion, Alnylam, Amicus Therapeutics, argenx, Biogen, CSL Behring, Ipsen, Janssen Pharmaceuticals, Lupin, Pfizer, Roche, Sanofi Genzyme, and UCB and research funding from CSL Behring, Roche, and Vertex. **GC:** Participated in advisory boards and served as a consultant for Italfarmaco, Roche, and Sarepta Therapeutics, Inc. Served as a speaker for Sarepta Therapeutics, Inc. Served as principal investigator of studies sponsored by Atamyo, Roche, Sarepta Therapeutics, Inc., and Scholar Rock. **JLDB:** Received speaker/advisory board honoraria from Alexion, Alnylam, Amicus Therapeutics, argenx, Biogen, CSL Behring, Janssen Pharmaceuticals, Roche, Sanofi Genzyme, and UCB. **SEM:** Participated in advisory boards for Novartis and Sarepta Therapeutics, Inc. and served as a consultant for Avidity Biosciences. Received funding for research from Dyne, Genentech/Roche, Pfizer, and Sarepta Therapeutics, Inc. **HS**, **WH**, **AE**, **AH**, and **LRR-K**: Employees of Sarepta Therapeutics, Inc., and may own stock/options in the company.

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Supplemental Methods

Immunofluorescence image analysis

- Immunofluorescence image analysis involved staining cryosectioned biopsy tissues (10-12 µm) with Alexa Fluor 488 for laminin, Alexa Fluor 647 for β-sarcoglycan (β-SG), Alexa Fluor 555 for δ-sarcoglycan (δ-SG), and DAPI (4′,6-diamidino-2-phenylindole) for nuclei
- The slides were scanned using the Aperio VERSA scanner, annotated in HALO, and analyzed with the HALO Muscle Fiber FL module
- The algorithm quantified total fibers and membrane-specific β-SG and δ-SG expression and calculated metrics such as percent positive membranes, membrane stain intensity, and percent fluorescent intensity (PFI) for β-SG and δ-SG

Western assay

- The Western assay was performed in alignment with Good Laboratory Practice standards according to a validated method
- Biopsy samples were homogenized and total protein extracts were loaded at a concentration of 0.25 mg/mL, along with a 7-point standard curve (0.125-8.0 pg/µL recombinant human β-SG protein (Abcam Inc., Waltham, MA, USA); a capillary-based Simple Western assay was performed on the Protein Simple Jess system (Bio-techne, Minneapolis, MN, USA)
- Three levels of quality control samples were prepared with a recombinant protein, a negative control, and a positive control. The positive control was composed of a pool of muscle samples with no histopathologic evidence of neuromuscular disease. β-SG protein was detected using a custom monoclonal primary antibody (Abcam Inc., Waltham, MA, USA) and visualized using a horseradish peroxidase-conjugated secondary antibody and luminol-peroxide substrate
- The analysis was conducted using the integrated Compass for Simple Western Software (Bio-techne, Minneapolis, MN, USA), and for each β-SG band, the area under the curve was determined
- The slope equation of the linear regression of the standard curve points was used to extrapolate the β-SG content of the quality control, positive control, negative control, and samples
- The β-SG content was reported as the percentage of the positive control sample, representative of a normal control muscle

Muscle biodistribution droplet digital polymerase chain reaction assay

- Testing was performed using a validated droplet digital polymerase chain reaction (ddPCR) method
- DNA was isolated from muscle biopsy samples using a Qiagen DNeasy Blood and Tissue Kit (Qiagen, Venlo, The Netherlands). Isolated DNA was stored in water at −80°C
- Samples were diluted further in nuclease-free water for testing. The ddPCR assay utilized 2 primer/probe sets (Integrated DNA Technologies, Coralville, IA, USA) whose sequences are specific for the myosin heavy-chain creatine kinase 7 (MHCK7) promoter sequence of SRP-9003 and the human myogenin gene. Plasmid containing the MHCK7 promoter sequence and commercially available human genomic DNA (BioChain Institute, Newark, CA, USA) were used as a positive control. The negative controls for the assay were nuclease-free water and a DNA isolation environmental negative control containing no tissue/analyte
- Following plate setup, droplets were generated using the Bio-Rad QX200 Automated Droplet Generator (Bio-Rad Laboratories, Hercules, CA, USA). Next, the reaction was amplified using a thermal cycler according to the manufacturer's recommendation. The plate was then read using the Bio-Rad QX200 Droplet Reader
- The concentration of both MHCK7 vector genomes and human genomic DNA was determined per reaction well by the Quantasoft ddPCR program following manual gating of droplets positive and negative for both assay targets
- The number of vector genome copies per nucleus in each sample was calculated by dividing the concentration of MHCK7 vectors by the concentration of human myogenin copies in each reaction and multiplying by 2 (number of myogenin copies per diploid genome)

Statistical methods

- The sample size for cohort 1 (ambulatory patients) was determined based on statistical considerations
- For the primary endpoint and secondary expression endpoints for patients in cohort 1, assuming approximately 10% of missing data and using a 1-sample *t* test at the 2-sided α=0.05 level, a sample size of approximately 10 ambulatory patients will have at least 91% power to detect a standardized change from baseline to day 60 of 1.5 (minimum for immunofluorescence percent positive fibers, immunofluorescence percent fluorescent intensity, and Western assay based on prior data) using a hierarchical testing procedure
- For cohort 2 (non-ambulatory participants), the sample size is based on feasibility

Supplemental Table 1 *Baseline Characteristics*

Parameter	Ambulatory (n=11)	Non-ambulatory (n=6)
Age at baseline, years		
Mean (SD)	12.7 (4.71)	25.8 (15.94)
Range	5-21	13-50
Sex, n (%)		
Male	6 (54.5)	0
Female	5 (45.5)	6 (100)
Ethnicity, n (%)		
Hispanic or Latino	0	0
Not Hispanic or Latino	11 (100)	6 (100)
Race, n (%)		
White	7 (63.6)	5 (83.3)
Asian	0	1 (16.7)
Other/multiple	4 (36.4)	0
Baseline weight, kg		
Mean (SD)	48.6 (20.52)	54.0 (11.19)
Range	17-77	38-71
Baseline creatine kinase, U/L		
Mean (SD)	5,246.9 (4,832.44)	1,204.2 (468.49)
Range	1,611-16,500	332-1,653

SD, standard deviation.

Supplemental Table 2 *Most Common Treatment-Related TEAEs (n≥5)*

System organ class preferred term, n (%)	Ambulatory (n=11)	Non-ambulatory (n=6)	Overall (n=17)
Any treatment-related TEAEs	10 (90.9)	5 (83.3)	15 (88.2)
Gastrointestinal disorders			
Nausea	8 (72.7)	4 (66.7)	12 (70.6)
Vomiting	6 (54.5)	1 (16.7)	7 (41.2)
Abdominal pain upper	4 (36.4)	1 (16.7)	5 (29.4)
General disorders and administration site conditions			
Fatigue	3 (27.3)	2 (33.3)	5 (29.4)
Metabolism and nutrition disorders			
Decreased appetite	5 (45.5)	3 (50.0)	8 (47.1)

TEAE, treatment-emergent adverse event.

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