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Taldefgrobep Alfa: Preclinical and Clinical Data Supporting the Phase 3 RESILIENT Study in Spinal Muscular Atrophy

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BACKGROUND

- Spinal muscular atrophy (SMA) is a debilitating, progressive, genetic condition that results from a homozygous deletion or mutation in the survival of motor neuron gene *SMN1*, leading to diminished levels of survival motor neuron (SMN) protein and associated weakness and motor neuron loss.[1,2] SMN upregulators have been approved to treat SMA. Despite their use, however, many patients continue to experience weakness that impairs function and quality of life.[1]
- When administered in combination with SMN upregulators in murine models of SMA, pharmacologic myostatin inhibition has shown promise for increasing muscle mass and function.
  - In one SMA murine model, the presence of both SMN restoration and a myostatin inhibitor increased gastrocnemius muscle mass by 50%, tibialis anterior muscle mass by 38%, and muscle fiber size by 35%. Other muscular and neuronal improvements, such as those seen in hanging wire grip test performance and neuromuscular junction maturation and innervation, were also observed.[2]
  - In another SMA murine model, treatment with the SMN upregulator SMN-C1 and an antibody that inhibits myostatin activation resulted in improvements in muscle mass and function, including significant improvements in plantarflexor maximal torque.[1,3]
- Taldefgrobep alfa (BHV-2000) is differentiated by both targeting the myostatin pathway to directly inhibit free myostatin and blocking key downstream receptor signaling.[4]
- Extensive nonclinical studies and a well-established safety profile in patients with neuromuscular disease support taldefgrobep's continued development.[5]

OBJECTIVE

- To review preclinical and clinical data on taldefgrobep and provide an overview of the phase 3 global, randomized, double-blind, placebo-controlled RESILIENT trial in SMA.

CONCLUSIONS

- In preclinical studies using an SMA murine model, the combination of taldefgrobep and SMN-C1 demonstrated improvements in muscle size and function, compared to the use of SMN-C1 alone.
- Preclinical outcomes and data from safety analyses across 2 clinical studies involving a total of 180 pediatric participants with neuromuscular disease (including a phase 1b/2 open-label extension, in which 41 participants received taldefgrobep for up to 228 weeks) support conducting the global, prospective, randomized, double-blind, placebo-controlled phase 3 RESILIENT study (NCT05337553) in participants with SMA.[5]
- RESILIENT, designed to evaluate the efficacy and safety of taldefgrobep, is currently enrolling ambulatory and nonambulatory participants aged 4-21 years who have SMA (of any type) and are receiving SMN-upregulating therapies.

Disclosures: CB: employed by and holds stock/stock options in Biohaven; **LL**: employed by and holds stock/stock options in Biohaven; **IQ**: employed by and holds stock/stock options in Biohaven; **SD**: employed by and holds stock/stock options in Biohaven; **DC**: employed by and holds stock/stock options in Biohaven; **JM**: employed by and holds stock/stock options in Biohaven; **KC**: no disclosures to report; **VC**: employed by and holds stock/stock options in Biohaven.

References: 1. Long KK, O'Shea KM, Khairallah RJ, et al. Specific inhibition of myostatin activation is beneficial in mouse models of SMA therapy. *Hum Mol Genet.* 2019;28(7):1076-1089. **2.** Zhou H, Meng J, Malerba A, et al. Myostatin inhibition in combination with antisense oligonucleotide therapy improves outcomes in spinal muscular atrophy. *J Cachexia Sarcopenia Muscle.* 2020;11(3):768-782. **3.** Zhao X, Feng Z, Ling KKY, et al. Pharmacokinetics, pharmacodynamics, and efficacy of a small-molecule SMN2 splicing modifier in mouse models of spinal muscular atrophy. *Hum Mol Genet.* 2016;25(10):1885-1899. **4.** Suh J, Lee YS. Myostatin inhibitors: panacea or predicament for musculoskeletal disorders? *J Bone Metab.* 2020;27(3):151-165. **5.** A study to evaluate the efficacy and safety of taldefgrobep alfa in participants with spinal muscular atrophy (RESILIENT). Updated January 19, 2022. Accessed January 23, 2022. https://www.clinicaltrials.gov/ct2/show/NCT05337553 **6.** Evrysdi. Prescribing information. Genentech, Inc.; 2022. Accessed December 21, 2022. https://www.gene.com/download/pdf/evrysdi_prescribing.pdf **7.** Spinraza. Prescribing information. Biogen; 2020. Accessed December 21, 2022. https://www.spinrazahcp.com/content/dam/commercial/spinraza/hcp/en_us/pdf/spinraza-prescribing-information.pdf

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METHODS

Preclinical studies

- Two different studies of SMA murine models using SMNΔ7 mice evaluated taldefgrobep in combination with the SMN upregulator SMN-C1. SMN-C1 was delivered at varied dosages, in addition to vehicle; wild-type mice were also included as controls.
- In the first study (RK050216), the experimental group of 9 mice received taldefgrobep from postnatal day 24 (PND24) through PND52. After subjects received low-dose SMN-C1 from PND1 to PND24, high-dose SMN-C1 was provided from PND24 to PND52; 10 SMA control mice received SMN-C1 with the same dosing schedule.
- In the second preclinical study (RK100115), taldefgrobep was given from PND21 to PND42 in an experimental group of 20 mice, while low-dose SMN-C1 was provided from PND2 to PND62; 15 SMA control mice received SMN-C1 with the same dosage schedule.
- Multiple outcomes related to body weight, muscle weight, and/or muscle structure and function were evaluated.

Clinical studies

- Two randomized phase 1 studies have been conducted in healthy adults to evaluate safety, pharmacokinetics, and/or pharmacodynamics or other parameters for taldefgrobep.
  - One study evaluated taldefgrobep dosing, and the other study evaluated subcutaneous injection of taldefgrobep in the abdomen, arm, or thigh.
- A phase 1b/2 randomized, double-blind, placebo-controlled study evaluated the safety, tolerability, and pharmacokinetics of taldefgrobep in pediatric participants with neuromuscular disease who were receiving corticosteroids.
  - A 24-week double-blind phase was followed by a 48-week open-label phase (with all participants receiving taldefgrobep) and a 228-week open-label extension period.
- A phase 2/3 randomized, double-blind, placebo-controlled study evaluated the efficacy, safety, and tolerability of taldefgrobep in pediatric participants with neuromuscular disease who were receiving corticosteroids.
  - Taldefgrobep was administered weekly in low-dose (7.5 mg or 15 mg) and high-dose (35 mg or 50 mg) groups, with specific dosing based on body weight.
  - A 48-week double-blind phase was followed by a 48-week open-label phase in which participants received either high- or low-dose taldefgrobep.

RESULTS

PRECLINICAL STUDIES

- At PND52 in the first preclinical study (RK050216), masseter muscle function appeared to be similar across treatment groups, but the combination of taldefgrobep and high-dose SMN-C1 was associated with improved plantarflexor muscle function ($P<.05$; **Figure 1**) and a nonsignificant trend toward higher gastrocnemius muscle weight ($P=.08$), compared to SMN-C1 alone.
  - Additionally, muscle fiber type composition and cross-sectional area overall were similar across groups, but there was a nonsignificant trend toward increased plantarflexor muscle fiber mean cross-sectional area in SMA mice that received the combination treatment vs SMN-C1 treatment alone ($P=.14$).
- In the second preclinical study in SMA mice (RK100115), the addition of taldefgrobep to low-dose SMN-C1 was associated with the following results, compared to SMN-C1 alone:
  - Increased body weight at PND48 ($P<.05$) and increased gastrocnemius muscle weight at PND62 ($P<.05$)
  - Improvements across several metrics of gastrocnemius muscle performance (**Figure 2**) and contraction/relaxation kinetics at PND48 and/or at PND62 ($P<.05$)
  - Improved maximal torque in the masseter muscle at 150 Hz at PND62 ($P<.05$), with nonsignificant trends toward improved maximal force normalized to body weight ($P=.11$) and maximum rate of relaxation at 150 Hz ($P=.05$)
  - Increased mean muscle fiber cross-sectional area at PND48 ($P<.05$) and type IIb muscle fiber cross-sectional area at PND48 ($P<.05$), in addition to restoration of type IIa atrophic muscle fibers at both PND48 and PND62 ($P<.05$; **Figure 3**)

Figure 1.
Plantarflexor muscle function in the RK050216 study at PND52.

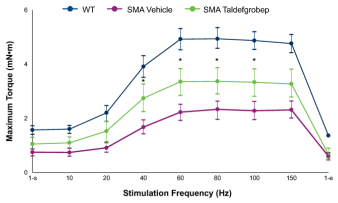


Figure 2.
Gastrocnemius muscle function in the RK100115 preclinical study: muscle performance at PND48.

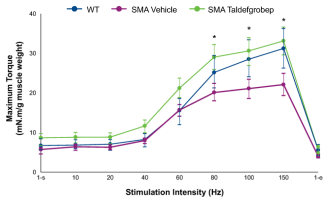
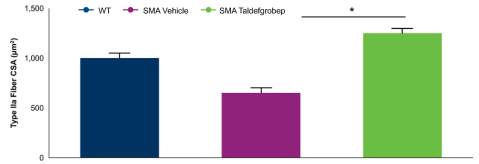


Figure 3.
Type IIa muscle fiber cross-sectional areas at PND48 in the RK100115 preclinical study.



*P<.05 for taldefgrobep-treated SMA mice vs vehicle-treated SMA mice in Figures 1, 2 and 3.

CLINICAL STUDIES

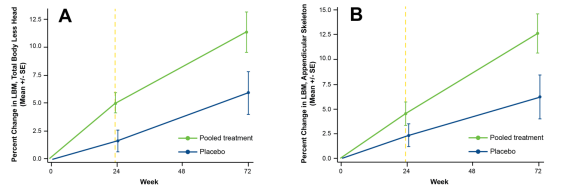
Phase 1b/2 and phase 2/3 clinical studies

- A total of 359 individuals have received taldefgrobep in studies to date, including 179 healthy adults and 180 pediatric participants with neuromuscular disease.
- In healthy adults, phase 1 analyses revealed suppression of free myostatin in the serum that increased in a dose-dependent manner with taldefgrobep; taldefgrobep exposure was comparable across the subcutaneous injection sites.
- Additionally, magnetic resonance imaging findings in healthy adults showed that taldefgrobep was associated with an increased percent change in right thigh muscle volume compared to baseline.
- Dual x-ray absorptiometry findings in the phase 1b/2 study of pediatric participants with neuromuscular disease indicated that the percent increases in lean body mass over the study period were numerically larger in the pooled taldefgrobep treatment group than in the placebo group.
  - Changes in lean body mass and lean body mass index through week 72 are shown in **Figure 4** for the placebo and pooled taldefgrobep treatment groups; participants on placebo switched to taldefgrobep treatment at week 24.

Safety with taldefgrobep

- In the randomized portion of the phase 2/3 study of pediatric participants with neuromuscular disease, which included 55 participants in the taldefgrobep low-dose group, 55 participants in the taldefgrobep high-dose group, and 56 participants in the placebo group (**Table 1**):
  - Adverse events (AEs) were reported in 48 (87.3%), 49 (89.1%), and 46 (82.1%) participants, respectively.
  - There were no taldefgrobep-related discontinuations or deaths.
  - One fatality was reported in a patient in the high-dose taldefgrobep group (1.8%), which involved cardiac arrest following cardiac ablation and was deemed unrelated to the study drug, per the investigator; this AE was also associated with discontinuation of the study drug in this patient.
  - One serious AE of hyperbilirubinemia in the high-dose taldefgrobep group was considered to be related to taldefgrobep.
  - The most frequently reported AEs that were deemed to be related to the study drug involved injection site reactions, which were mostly mild.
- In the randomized portion of the phase 1b/2 study of pediatric participants with neuromuscular disease, which included 32 participants in the taldefgrobep group and 11 participants in the placebo group:
  - AEs were reported in 29 (90.6%) and 9 (81.8%) participants, respectively, with serious AEs in 1 (3.1%; spinal compression fracture) and 1 (9.1%; skull fracture) patient in each treatment group, respectively; no severe AEs, AEs leading to discontinuation of the study drug, or related serious AEs were reported in any participants in either group during this period.
  - AEs reported in ≥15% of participants in the taldefgrobep group during this period included headache, pyrexia, nasopharyngitis, upper respiratory tract infection, injection site bruising, and vomiting.
- In the studies of pediatric participants with neuromuscular disease:
  - Participants receiving taldefgrobep showed numerically greater percent increases in lean body mass than did those given placebo.
  - Taldefgrobep was considered to be well-tolerated, with an acceptable safety profile.

Figure 4.
Percent change from baseline in lean body mass (LBM): (A) total body less head and (B) appendicular skeleton



Taldefgrobep was associated with lean body mass increases of 11.2% and 12.3% in the total body less head and the appendicular skeleton, respectively, by week 72. The yellow dotted line refers to the timepoint at which subjects initially receiving placebo switched to taldefgrobep.

Table 1.
Adverse events reported in studies of pediatric participants with neuromuscular disease, across the phase 2/3 study (randomization period and whole study) and among those receiving taldefgrobep across the whole phase 1b/2 study.

	AEs reported in the randomized period of the phase 2/3 study, n (%)			AEs in participants who received ≥1 dose of taldefgrobep in the phase 2/3 study, n (%)		AEs in participants who received ≥1 dose of taldefgrobep in the phase 1b/2 study, n (%)
	Low-dose taldefgrobep (n=55)	High-dose taldefgrobep (n=55)	Placebo (n=56)	Low-dose taldefgrobep (n=69)	High-dose taldefgrobep (n=68)	Whole study analysis (N=43)
Serious AEs	2 (3.6)	4 (7.3)	3 (5.4)	2 (2.9)	4 (5.9)	6 (14.0)
Related serious AEs	0	1 (1.8)	0	0	1 (1.5)	0
AEs leading to discontinuation of study drug	0	1 (1.8)*	0	0	1 (1.5)*	0
Deaths	0	1 (1.8)*	0	0	1 (1.5)*	0
Related AEs	22 (40.0)	24 (43.6)	18 (32.1)	23 (33.3)	28 (41.2)	27 (62.8)
Severe AEs	1 (1.8)	3 (5.5)	2 (3.6)	1 (1.5)	4 (5.9)	5 (11.6)
AEs in ≥15% of participants in any group of the phase 2/3 study						
Nasopharyngitis	13 (23.6)	13 (23.6)	13 (23.2)	15 (21.7)	13 (19.1)	16 (37.2)
Injection site erythema	11 (20.0)	12 (21.8)	8 (14.3)	11 (15.9)	16 (23.5)	12 (27.9)
Pyrexia	9 (16.4)	8 (14.5)	8 (14.3)	12 (17.4)	10 (14.7)	13 (30.2)
Diarrhea	10 (18.2)	4 (7.3)	3 (5.4)	10 (14.5)	6 (8.8)	13 (30.2)
Cough	8 (14.5)	7 (12.7)	10 (17.9)	9 (13.0)	8 (11.8)	13 (30.2)
Headache	14 (25.5)	10 (18.2)	9 (16.1)	15 (21.7)	11 (16.2)	16 (37.2)
Injection site reactions	19 (34.5)	20 (36.4)	14 (25.0)	20 (29.0)	24 (35.3)	25 (58.1)
Hypersensitivity/ allergic reactions	19 (34.5)	20 (36.4)	19 (33.9)	22 (31.9)	21 (30.9)	21 (48.8)
Immunogenicity (antidrug antibody)	6 (10.9)	5 (9.1)	1 (3.7)	Not applicable	Not applicable	1 (2.3)

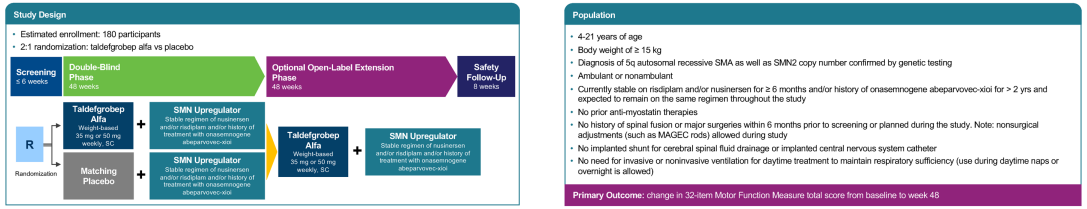
*Represents one participant. Considered by the investigator to be unrelated to study treatment, as the participant experienced a cardiac arrest following cardiac ablation.

PHASE 3 RESILIENT

The phase 3 RESILIENT study

- Preclinical and clinical data support the development of taldefgrobep as a possible treatment for SMA. RESILIENT is now underway to evaluate the efficacy and safety of taldefgrobep in ambulatory and nonambulatory participants 4-21 years of age who have SMA (of any type) and are receiving SMN-upregulating therapies.[5]
- In RESILIENT, participants are randomized 2:1 to receive either taldefgrobep according to weight-based dosing plus standard of care or placebo with standard of care (**Figure 6**).
- RESILIENT is recruiting participants with SMA, with a goal of enrolling participants from Belgium, the Czech Republic, Germany, Italy, the Netherlands, Poland, Spain, the UK, and the US. Participants are being recruited from approximately 60 sites globally.

Figure 6.
Phase 3 RESILIENT study design, population, and primary outcome.[6,7]



AE, adverse event; LBM, lean body mass; MAGEC, magnetic expansion control; PND, postnatal day; SC, subcutaneous; SMA, spinal muscular atrophy; SMN, survival motor neuron; WT, wild-type.