A-23-07426

The Phase 3 RESILIENT Study in Spinal Muscular Atrophy

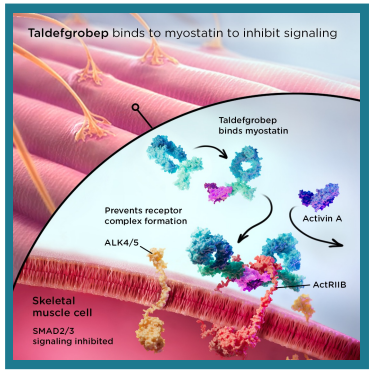
Lindsey Lee Lair[1], Irfan Qureshi[1], Clifford Bechtold[1], Ricardo Garvao[1], Susan Durham[1], Daniel Campbell[1], Jackie Marin[1], Vlad Coric[1] • [1]Biohaven Pharmaceuticals, Inc.

INTRODUCTION

- Spinal muscular atrophy (SMA) is a progressive, debilitating genetic condition that results from a homozygous deletion or mutation in the survival motor neuron (*SMN1*) gene, leading to diminished levels of survival motor neuron (SMN) protein.[1,2]
- It is estimated that the incidence of SMA, a rare disease, is approximately 1 in every 10,000 births worldwide.[3]
- SMA historically has been subdivided into 3 main types that have pediatric onset (types 1-3) and 2 less common types—1 with adult onset (type 4) and another with antenatal onset (type 0). However, traditional classifications that rely on age and motor function do not capture the phenotypic changes that occur in patients exposed to the new disease-modifying therapies.[3]
- SMN upregulators, with mechanisms of action directly relating to SMN protein expression, are the disease-modifying agents currently approved for treatment of SMA. These therapies rescue neuronal cell death but do not target muscle.[4-6]
- As such, SMN upregulators are effective in helping patients achieve milestones and improving survival; however, functional deficits and significant quality-of-life impairment still remain.[6-8]

Figure 1

Taldefgrobep Mechanism of Action



- Myostatin is a negative regulator of muscle growth and is secreted primarily by skeletal muscle cells.[9]
- When administered along with SMN upregulators in murine SMA models, pharmacologic inhibition of myostatin has shown promise for increasing muscle mass and function, beyond the use of SMN regulators alone.[1,2,10]
- Taldefgrobep alfa (BHV-2000) is a bivalent, humanized, anti-myostatin adnectin modified with a human IgG1 Fc tail to prolong its half-life in circulation.[4,11] **Figure 1.**
- Taldefgrobep is differentiated by both binding mature myostatin dimer and blocking the signaling of the ActRIIB pathway.[4]
- Two randomized, phase 1 studies conducted in healthy adults (n=179) and phase 1b/2 and phase 2/3 randomized, double-blind, placebo-controlled studies in pediatric patients with neuromuscular disease (n=180) support the well-established safety of taldefgrobep.[4]
- Here, we report the design of RESILIENT, a global, prospective, randomized, double-blind, phase 3, placebo-controlled study (NCT05337553) that will investigate the efficacy and safety of taldefgrobep as an adjunctive therapy along with SMN upregulators in patients with SMA.[4,12]

METHODS

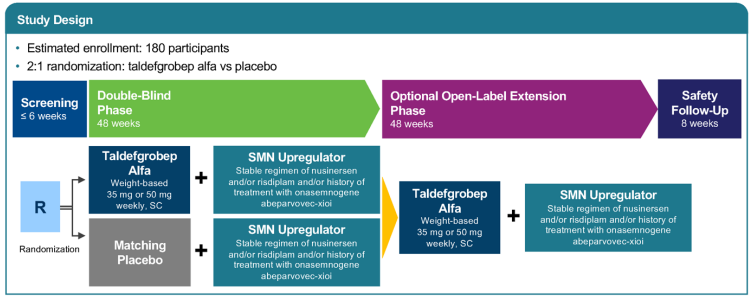
STUDY DESIGN

- RESILIENT's design includes a screening period of up to approximately 6 weeks before participants are randomly assigned 2:1 to receive taldefgrobep or placebo in a 48-week, double-blind phase. **Figure 2.**
- After completing the double-blind phase, eligible participants have the option to enroll in an open-label extension in which they will receive taldefgrobep for 48 weeks before being assessed for an additional 8 weeks in a safety follow-up period.
- Approximately 180 participants are anticipated for enrollment.

Figure 2

Phase 3 RESILIENTStudy Design

48-Week, Double-Blind, Placebo-Controlled Study in Pediatric and Adult Patients With Spinal Muscular Atrophy



- Participants receive 35.0 mg or 50.0 mg of taldefgrobep subcutaneously (SC), based on their weight.
- Taldefgrobep is administered once weekly, and injection sites (arm, thigh, or abdomen) rotate throughout the study.
- After the baseline visit, participants attend visits at the site clinic approximately every 12 weeks, preferably in the morning.
- Participants remain on the stable regimen of their SMN upregulator (including nusinersen and/or risdiplam and/or onasemnogene abeparvovec-xioi) that they received prior to study enrollment.

ELIGIBILITY & PRIMARY OUTCOME

- Given the high unmet need and changing treatment paradigms, Biohaven is utilizing a patient-centric approach by including a broad patient population, without limiting or restricting participation on the basis of ambulatory status, background therapy, or SMA type.
- Accordingly, RESILIENT includes both ambulant and nonambulant patients with any SMA type who are 4-21 years of age and currently stable on SMN upregulators.
- Participant inclusion and exclusion criteria are highlighted in **Figure 3**.

Figure 3

Population and Primary Outcome

Population

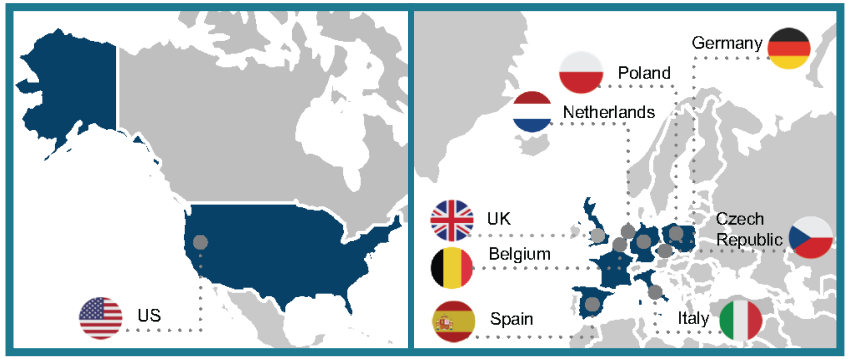
- 4-21 years of age
- Body weight of ≥ 15 kg
- Diagnosis of 5q autosomal recessive SMA as well as SMN2 copy number confirmed by genetic testing
- Ambulant or nonambulant
- Currently stable on risdiplam and/or nusinersen for ≥ 6 months and/or history of onasemnogene abeparvovec-xioi for > 2 years and expected to remain on the same regimen throughout the study
- No prior anti-myostatin therapies
- No history of spinal fusion or major surgeries within 6 months prior to screening or planned during the study. Note: nonsurgical adjustments (such as MAGEC rods) allowed during study
- No implanted shunt for cerebral spinal fluid drainage or implanted central nervous system catheter
- No need for invasive or noninvasive ventilation for daytime treatment to maintain respiratory sufficiency (use during daytime naps or overnight is allowed)

Primary Outcome: change in 32-item Motor Function Measure total score from baseline to week 48

- The RESILIENT study is currently recruiting patients with SMA, with a goal of enrolling patients from Belgium, the Czech Republic, Germany, Italy, the Netherlands, Poland, Spain, the UK, and the US. Patients are being recruited from approximately 60 sites globally. **Figure 4.**

Figure 4

Enrollment



CONCLUSIONS

- SMA is a debilitating, progressive, rare genetic disease characterized by deficient SMN protein, resulting in motor neuron loss and muscular atrophy.
- SMN upregulators have advanced the care of patients with SMA. However, although these agents rescue neuronal cell death, they do not target muscle. Despite such treatment, patients still experience significant functional deficits and impaired quality of life.
- Taldefgrobep alfa (BHV-2000), a myostatin inhibitor that directly lowers myostatin and also blocks downstream signaling, has shown promise for increasing muscle mass and function when administered in conjunction with SMN upregulators. Studied in 179 healthy adults and more than 180 pediatric participants with neuromuscular disease to date, taldefgrobep has a well-established safety profile.
- RESILIENT is a global, prospective, randomized, double-blind, placebo-controlled, phase 3 study (NCT05337553) that is investigating the efficacy and safety of taldefgrobep as an adjunctive therapy along with SMN upregulators in patients with SMA.

Abbreviations: MAGEC, magnetic expansion control; SC, subcutaneously; SMA, spinal muscular atrophy; SMN, survival motor neuron.

Disclosures: CB: employed by and holds stock/stock options in Biohaven; **DC:** employed by and holds stock/stock options in Biohaven; **IQ:** employed by and holds stock/stock options in Biohaven; **JM:** employed by and holds stock/stock options in Biohaven; **LL:** employed by and holds stock/stock options in Biohaven; **RG:** employed by and holds stock/stock options in Biohaven; **SD:** employed by and holds stock/stock options in Biohaven; **VC:** employed by and holds stock/stock options in Biohaven.

Acknowledgments
We extend sincere appreciation to the investigative sites, patients, and families who dedicated time and shared experiences to support this work. We also thank Eubio for providing editorial support, funded by Biohaven, Ltd.

References: 1. Long KL, 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.** Mercuri E, Sumner CJ, Muntoni F. Spinal muscular atrophy. *Nat Rev Dis Primers.* 2022;8(1):52. **4.** Data on File. Biohaven Pharmaceuticals. 2023. **5.** Helderman-van den Enden ATM, Straathof CSM, Aartsma-Rus A, et al. Becker muscular dystrophy patients with deletions around exon 51; a promising outlook for exon skipping therapy in Duchenne patients. *Neuromuscul Disord.* 2010;20(4):251-254. **6.** Darras BT, Masson R, Mazurkiewicz-Bełdzińska M, et al; for the FIREFISH Working Group. Risdiplam-treated infants with type 1 spinal muscular atrophy versus historical controls. *N Engl J Med.* 2021;385(5):427-435. **7.** Finkel RS, Mercuri E, Darras BT, et al; for the ENDEAR Study Group. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N Engl J Med.* 2017;377(18):1723-1732. **8.** Day JW, Howell K, Place A, et al. Advances and limitations for the treatment of spinal muscular atrophy. *BMC Pediatr.* 2022;22(1):632. **9.** Abati E, Manini A, Pietro Comi G, Corti S. Inhibition of myostatin and related signaling pathways for the treatment of muscle atrophy in motor neuron diseases. *Cell Mol Life Sci.* 2022;79(7):374. **10.** 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. **11.** Suh J, Lee YS. Myostatin inhibitors: panacea or predicament for musculoskeletal disorders? *J Bone Metab.* 2020;27(3):151-165. **12.** A study to evaluate the efficacy and safety of taldefgrobep alfa in participants with spinal muscular atrophy (RESILIENT). Updated May 1, 2023. Accessed May 4, 2023. https://www.clinicaltrials.gov/ct2/show/NCT05337553.