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The Phase 3 RESILIENT Study in Spinal Muscular Atrophy

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CONCLUSIONS

1. SMA is a debilitating, progressive, rare genetic disease characterized by deficient SMN protein, resulting in motor neuron loss and muscular atrophy.
2. 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.
3. 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. Previously studied in 179 healthy adults and more than 180 pediatric participants with neuromuscular disease, taldefgrobep has a well-established safety profile.
4. 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 participants with SMA.

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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, Inc.

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Presented at the
American Academy of Neurology
2024 Annual Meeting
April 13-18, 2024
Denver, Colorado, USA

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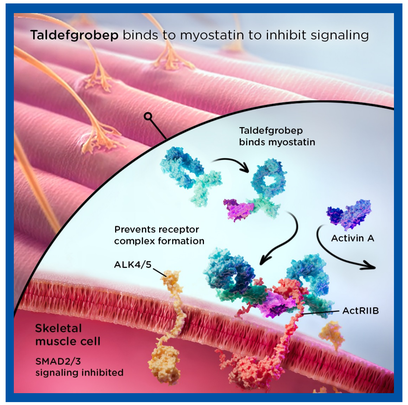
INTRODUCTION

- Spinal muscular atrophy (SMA) is a debilitating genetic condition caused by homozygous deletion or mutation in the survival motor neuron (*SMN1*) gene. Affected individuals experience diminished levels of survival motor neuron (SMN) protein and progressive deterioration of muscle function.[1,2,3]
- A rare disease, SMA has an estimated incidence of approximately 1 in every 11,000 births in the US.[4]
- Historically, SMA has been classified into 3 main types with pediatric onset (types 1-3) and 2 less common types—one with adult onset (type 4) and another with antenatal onset (type 0). However, traditional classifications based on age and motor function do not capture the phenotypic changes that occur in patients treated with SMN upregulators.[4]
- SMN upregulators are the disease-modifying agents currently approved for treatment of SMA. The mechanism of action of these agents directly relates to SMN protein expression and involves rescuing neuronal cell death; these agents do not target muscle.[5-7]
- As such, SMN upregulators improve survival and help patients achieve milestones. Nonetheless, functional deficits and significant quality-of-life impairment remain.[3,6,8]

Figure 1.
Taldefgrobep Mechanism of Action



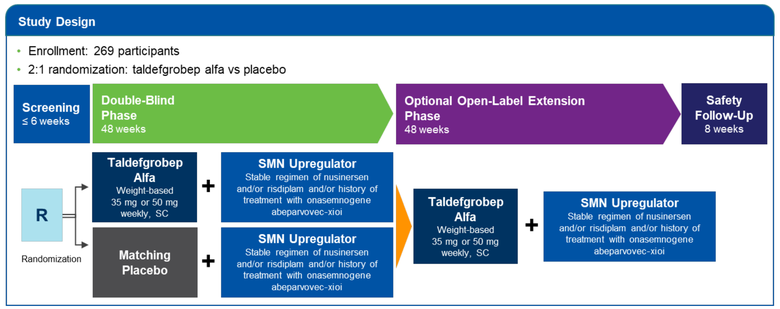
- When administered along with SMN upregulators in murine SMA models, pharmacologic inhibitors of myostatin have shown promise for increasing muscle mass and function, beyond the use of SMN upregulators alone. Myostatin inhibition acts through a 2-pronged approach that targets the whole motor unit. The effect results in both: 1) optimizing SMN protein and directly restoring function in the motor neuron, and 2) directly fortifying muscle through the myostatin pathway by preventing muscle wasting.[1,2,3,10]
- 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. As such, taldefgrobep effectively suppresses free myostatin, with activity that continues for weeks after dosing stops (**Figure 1**).[7,11]
- Taldefgrobep is unique among anti-myostatins because it both blocks active myostatin and inhibits activin receptor type IIB signaling in skeletal muscle as it increases muscle mass. 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 participants with neuromuscular disease (n = 180) support taldefgrobep's well-established safety profile.[7]
- Here we report the design of RESILIENT, a global, prospective, randomized, double-blind, phase 3, placebo-controlled study (NCT05337553) that is currently investigating the efficacy and safety of taldefgrobep as an adjunctive therapy to SMN upregulators in participants with SMA.[7,12]

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.
- 269 participants have been enrolled.

Figure 2.
Phase 3 RESILIENT Study Design
48-Week, Double-Blind, Placebo-Controlled Study in Pediatric and Adult Participants With Spinal Muscular Atrophy



- Participants receive 35.0 mg or 50.0 mg of taldefgrobep subcutaneously, 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 the SMN upregulator (including nusinersen and/or risdiplam and/or onasemnogene abeparvovec-xioi) that they were receiving prior to study enrollment.

ELIGIBILITY & PRIMARY OUTCOME

- Given the high unmet need and changing treatment paradigms, RESILIENT utilizes 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 participants 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.
RESILIENT Population and Primary Outcome

Population

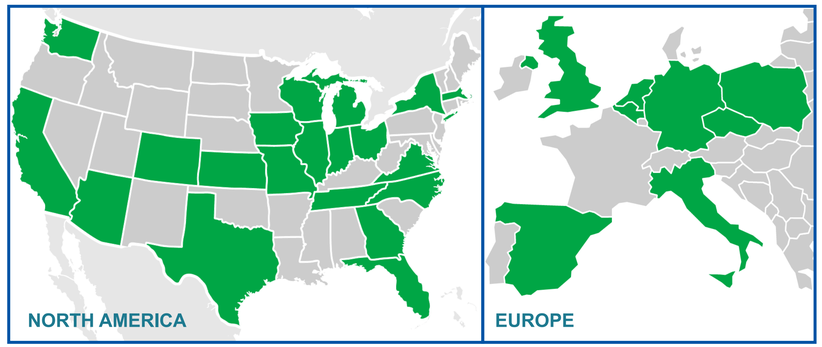
- 4-21 years of age
- Body weight of ≥ 15 kg
- Diagnosis of 5q autosomal recessive SMA as well as SMN2 copy number confirmed by genetic testing
- Ambulant or nonambulant
- Currently stable on risdiplam and/or nusinersen for ≥ 6 months and/or history of onasemnogene abeparvovec-xioi for > 2 years and 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 respiratory insufficiency, defined by the medical necessity for invasive or non-invasive ventilation for daytime treatment while awake (use overnight or during daytime naps is acceptable)

Primary Outcome

- Change in 32-item Motor Function Measure total score from baseline to week 48

- Enrollment has occurred at 53 hospitals and research or academic centers in 9 countries around the world, including Belgium, the Czech Republic, Germany, Italy, the Netherlands, Poland, Spain, the UK, and the US (full list of sites available at clinicaltrials.gov) (**Figure 4**).[7,12]
- The double-blind phase of RESILIENT will conclude in the second half of 2024.

Figure 4.
RESILIENT Participant Enrollment Across the World



Abbreviations: ActRIIB, activin receptor type IIB; MAGEC, magnetic expansion control; SC, subcutaneously; SMA, spinal muscular atrophy; SMN, survival motor neuron.