**INTRODUCTION**

- Spinal muscular atrophy (SMA) is a progressive, debilitating genetic condition that results from a homologous deletion or mutation in the survival motor neuron (SMN) 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 divided 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).4 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.5
- 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 target motor neuron loss and muscular atrophy.4
- 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

**STUDY DESIGN**

**Rationale:** RESILIENT’s design includes a screening period of up to 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.

**Phase 3 RESILIENT Study Design**

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

  **Study Design:**
  - Randomization: 1:2 (taldefgrobep:placebo)
  - Allocation: Single-blind
  - Masking: Double-blind
  - Placebo-Controlled
  - Endpoint: Primary outcome

  **Study Population:**
  - Pediatric and adult patients with SMA types 1 through 3 who are 2 to 21 years of age and currently stable on SMN upregulators.
  - Ambulatory status, background therapy, or SMA type.

  **Eligibility & Primary Outcome**
  - According to RESILIENT, the index ambulant and nonambulant patients with any SMA type who are 4 to 21 years of age and currently stable on SMN upregulators.
  - Participant inclusion and exclusion criteria are highlighted in Table 3.

  **Conclusions:**
  - SMA is a debilitating, progressive, rare genetic disease characterized by deficient SMN protein, resulting in muscle 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 limited 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.
  - RESILIENT is a global, prospective, randomized, double-blind, placebo-controlled, phase 3 study (NCT03573553) that is investigating the efficacy and safety of taldefgrobep as an adjunctive therapy along with SMN upregulators in patients with SMA.

**DISCUSSION**

- **Table 3: Key Regulatory Agency Approvals in the US**

**References:**


**Acknowledgments:**

- Research support provided by Biohaven, Ltd.

**Supporting Information:**

- 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.

**CONCLUSIONS**

- SMA is a debilitating, progressive, rare genetic disease characterized by deficient SMN protein, resulting in muscle 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 diseases to date, taldefgrobep has a well-established safety profile.
- RESILIENT is a global, prospective, randomized, double-blind, placebo-controlled, phase 3 study (NCT03573553) 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.