**BACKGROUND**

- Spinal muscular atrophy (SMA) is a debilitating, progressive, genetic condition characterized by weakness and motor neuron loss due to deficient survival of motor neuron (SMN) protein. Although SMN upregulations have been approved to treat SMA, many patients continue to experience serious side effects and limited improvements.

- In randomised trials, SMN therapeutic agents have shown promise for increasing disease-modifying effects and functional outcomes compared with placebo. However, some patients have experienced serious AEs, and long term efficacy and safety of SMN agents are not well characterized.

- Taldefgrobep alfa (BHV-19) is a SMN upregulator and myostatin inhibitor, which is associated with improvements in muscle mass and function, including significant improvements in plantarflexor performance.

**OBJECTIVE**

- To review the preclinical and clinical data on taldefgrobep and to advance the conduct of a phase 3 clinical trial of treatment with approved SMN upregulators and taldefgrobep.

**RESULTS**

**PRECLINICAL STUDIES**

- In the first preclinical study (RK032706), in SMA mice, taldefgrobep was compared with placebo over a 3-week period. Taldefgrobep was associated with increased plantarflexor muscle mass and function (Figure 1A) and a nonsignificant trend toward higher gastrocnemius muscle weight (P = 0.11) compared with placebo (P = 0.06).

- In a second study (RK100115), taldefgrobep was given to two groups of SMA mice, the combination of taldefgrobep and high dose SMN was associated with improved plantarflexor function mass (Figure 1B) and muscle cross-sectional area (Figure 1C) compared with the treatment group mean (P = 0.06).

**CLINICAL STUDIES**

- In the Phase 1b/2 studies, taldefgrobep was administered to pediatric patients with severe SMA who were receiving SMN therapies and was well tolerated with improvements in muscle mass and function.

- In the Phase 2/3 study, taldefgrobep demonstrated improvements in muscle mass and function, compared with the use of SMN-C1 alone.

**CONCLUSIONS**

- In preclinical studies using an SMA mouse model, the combination of taldefgrobep and SMN-C1 demonstrated improvements in muscle size and function, compared with the use of SMN-C1 alone.

- Preclinical results along with the data from safety analyses across 2 clinical studies involving a total of 180 pediatric patients with neuromuscular disease (including a phase 1b/2 open-label extension, in which 41 patients received ≥1 dose of taldefgrobep) support conducting the global, prospective, randomized, double-blind, placebo-controlled phase 3 RESILIENT study (NCT03735753).

- The RESILIENT study, aimed at evaluating the efficacy and safety of taldefgrobep, is enrolling ambulatory and nonambulatory patients with SMA (regardless of SMA type) who are receiving SMN-upregulating therapies and is well supported by the demonstrated safety from clinical neuromuscular studies and nonclinical SMA models.

**METHODS**

- This study included 203 patients with SMA with disease symptoms and confirmed genetic defects consistent with the clinical diagnosis of SMA. Patients were randomized to receive taldefgrobep or placebo in a 2:1 ratio.

- In the phase 3 RESILIENT study, the safety and tolerability were evaluated using adverse events (AEs) and serious AEs (SAEs) as key primary endpoints.

- The primary safety endpoint was the incidence of related AEs and serious AEs in the taldefgrobep group compared with the placebo group.

- The secondary safety endpoint was the incidence of AEs that were considered related to taldefgrobep treatment compared with placebo.

- The RESILIENT study was conducted in pediatric patients with SMA, with 28 patients in the US, 11 patients in the Czech Republic, and 4 patients in the Netherlands. Patients were randomized to receive placebo or taldefgrobep at a 2:1 ratio for 2 years, followed by a 2-year open-label extension.

**Safety with taldefgrobep**

- In the randomized portion of the phase 2/3 study of pediatric patients with neuromuscular disease, which included 55 patients in the taldefgrobep low-dose group, 50 patients in the taldefgrobep high-dose group, and 50 patients in the placebo group (Table 1), which also includes safety data across the 32 patients who participated in the phase 1b/2 study (n = 27), we evaluated the safety and tolerability of taldefgrobep.

- In the phase 1b/2 study of pediatric patients with neuromuscular disease, which included 32 patients in the taldefgrobep group and 11 patients in the placebo group, taldefgrobep was well tolerated, with AEs reported in 38 (93%) and 6 (55%) respectively.

**CLINICAL STUDIES**

- In the Phase 1b/2 and Phase 2/3 clinical studies conducted in pediatric patients with severe SMA who were receiving SMN therapies, taldefgrobep was associated with improvements in muscle mass and function.

- In the Phase 3 RESILIENT study, taldefgrobep was associated with improvements in muscle mass and function compared with placebo.

- Changes in lean body mass and lean body mass index through week 72 are shown in Figure 2A and B. Changes in lean body mass through week 72 in taldefgrobep treatment group patients on placebo had no values for taldefgrobep at week 24.

- Taldefgrobep was associated with a lean body mass increase of 11.2% and 12.3% in the total body less head, and appendicular s.