Background

Skeletal muscle atrophy (SMa) is a devastating, progressive, genetic condition that results from a hereditary or unknown etiology of the survival motor neuron gene SMN1, leading to diminished levels of survival motor neuron protein (SMN1) and associated function and quality of life.5 When administered in combination with SMN upregulators in mouse models of SMA, pharmacologic myostatin inhibition has shown promise for increasing muscle mass and function.6

In a SMA1 mouse model, the presence of both SMN1 activation and a myostatin inhibitor increased gastrocnemius muscle mass by 8%, while muscle area increased by 26%, and muscle tone was improved by 22%.7 Myostatin protein is decreased by 30% and myostatin protector protein is increased by 30% in the same model.8 Myostatin receptor expression increases in skeletal muscle of patients with SMA.9

Taldefgrobep (BHV-2001, bio-gropep) is a recombinant human myostatin inhibitor, which directly inhibits free myostatin and blocking key downstream receptor signaling.10-12 Pharmacologic myostatin inhibition has shown promise for increasing muscle mass and function and quality of life.13

Methods

Preclinical studies

- Two different studies of SMA mouse models using SMH18 mice evaluated taldefgrobep in combination with the SMN upregulator SMN-C1. STaMK-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 PND92. After subjects received low-dose SMN-C1 from PND1 to PND21, high-dose SMN-C1 was provided from PND42 to PND92. STaMK-C1 control mice received SMN-C1 with the same dosing schedule.14

- In the second preclinical study (RK100115), taldefgrobep was given from PND12 to PND21 in an experimental group of 20 mice (with 10 mice per group). PND22 to PND100, SMN1 control mice received SMN-C1 with the same dosing 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 for taldefgrobep.

Clinical studies

One study evaluated taldefgrobep dosing, and the other study evaluated subcutaneous delivery of taldefgrobep in the abdomen, with both studies blinded, placebo-controlled, and randomized. Results from these studies demonstrated safety and tolerability of taldefgrobep in pediatric participants with neuromuscular disease who were receiving concomitant therapies.

A 24-week, double-blind, placebo-controlled study evaluated the efficacy, tolerability, and pharmacokinetics of taldefgrobep in pediatric participants with neuromuscular disease who were receiving concomitant treatments.

A phase 2b/3 randomized, double-blind, placebo-controlled study evaluated the efficacy, tolerability, and pharmacokinetics of taldefgrobep in pediatric participants with neuromuscular disease who were receiving concomitant therapies.

A phase 2b randomized, double-blind, placebo-controlled study evaluated the efficacy, safety, and tolerability of taldefgrobep in pediatric participants with neuromuscular disease who were receiving concomitant therapies.

Results

Preclinical studies

- At PND21 in the first preclinical study (RK050216), muscle mass 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<0.05; Figure 1) and a non-significant trend toward higher gastrocnemius muscle weight (P=0.14) compared to SMN-C1 alone.

- Additional muscle fiber shape comparisons were made across treatment groups, but there was a non-significant trend toward increased muscle fiber type IIa muscle fiber area overall were similar across groups, but there was a non-significant trend toward increased muscle fiber type IIa muscle fiber area.

- 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<0.05).
  - Increased mean muscle fiber cross-sectional area at PND48 (P<0.05), in addition to restoration of plantarflexor muscle fiber cross-sectional area overall were similar across groups, but there was a non-significant trend toward increased muscle fiber type IIa muscle fiber area.

  - Improved maximal torque in the masseter muscle at 150 Hz at PND62 (P<0.05).

  - Increased mean muscle fiber cross-sectional area in SMA mice that received the combination treatment vs SMN-C1 alone.

  - Reduction in growth retardation and/or muscle atrophy.

  - Improved mean muscle fiber cross-sectional area at PND62 (P<0.05), in addition to restoration of plantarflexor muscle fiber cross-sectional area at PND62 (P<0.05).

  - One study evaluated taldefgrobep dosing, and the other study evaluated subcutaneous delivery of taldefgrobep in the abdomen, with both studies blinded, placebo-controlled, and randomized. Results from these studies demonstrated safety and tolerability of taldefgrobep in pediatric participants with neuromuscular disease who were receiving concomitant therapies.

  - A phase 2b randomized, double-blind, placebo-controlled study evaluated the efficacy, safety, and tolerability of taldefgrobep in pediatric participants with neuromuscular disease who were receiving concomitant therapies.

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