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Taldefgrobep Alfa: Preclinical and Clinical Data Supporting the Phase 3 RESILIENT Study in Spinal Muscular Atrophy

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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.[1,2] Although SMN upregulators have been approved to treat SMA, many patients continue to experience weakness, impairing function and quality of life.[1]
- In murine models of SMA, pharmacologic myostatin inhibitors have shown promise for increasing muscle mass and function when used with SMN upregulators.
  - A study of a mouse model of SMA demonstrated that in the presence of both SMN restoration and a myostatin inhibitor, compared with the use of SMN restoration alone, gastrocnemius muscle mass increased by 50%, tibialis anterior muscle mass increased by 38%, muscle fiber size increased by 35%, and survival increased by 40%; other muscular and neuronal improvements, such as seen in hanging wire grip test performance and neuromuscular junction maturation and innervation, were also observed.[2]
  - Another study of an SMA mouse model showed that treatment with the SMN upregulator SMN-C1 and an antibody that inhibits myostatin activation resulted in improvements in muscle mass and function, including significant improvements in plantarflexor maximal torque.[1,3]
- Taldefgrobep alfa (BHV-2000) is differentiated by both targeting the myostatin pathway to directly inhibit myostatin and blocking key downstream receptor signaling by myostatin.[4]
- Extensive nonclinical studies and a well-established safety profile in patients with neuromuscular disease support continued development of taldefgrobep.[5]

OBJECTIVE

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

METHODS

Preclinical studies

- The combination of taldefgrobep and the SMN upregulator SMN-C1 was evaluated in 2 different preclinical studies of murine SMA models using SMNΔ7 mice, with SMN-C1 delivered at varied dosages, in addition to vehicle; wild-type mice were also included as controls.
- In the first preclinical study (RK050216), in the experimental group of 9 mice, taldefgrobep was given from postnatal day (PND) 24 (PND24) through PND52, while high-dose SMN-C1 was given from PND24 to PND52, after low-dose SMN-C1 from PND1 to PND24; 10 SMA control mice received SMN; 10 SMA control mice received SMN-C1 with the same dosage schedule.
- In the second preclinical study (RK100115), in the experimental group of 20 mice, taldefgrobep was given from PND21 to PND42, while low-dose SMN-C1 was given from PND2 to PND62; 15 SMA control mice received SMN-C1 with the same dosage schedule.
- Multiple outcomes related to body weight, muscle weight, and/or muscle structure and function were evaluated in these preclinical studies.

Clinical studies

- Two randomized phase 1 studies have been conducted in healthy adults to evaluate safety, pharmacokinetics, and/or pharmacodynamics or other parameters for taldefgrobep.
  - One study evaluated taldefgrobep dosing, while the other evaluated subcutaneous injection of taldefgrobep in the abdomen, arm, or thigh.
- A phase 1b/2 randomized, double-blind, placebo-controlled study evaluated the safety, tolerability, and pharmacokinetics of taldefgrobep in pediatric patients with neuromuscular disease who were receiving corticosteroids.
  - A 24-week double-blind phase was followed by a 48-week open-label phase (with all patients receiving taldefgrobep) and a 228-week open-label extension.
- A phase 2/3 randomized, double-blind, placebo-controlled study evaluated efficacy, safety, and tolerability of taldefgrobep in pediatric patients with neuromuscular disease who were receiving corticosteroids.
  - Taldefgrobep was administered weekly in low-dose (7.5 mg or 15 mg) and high-dose groups (35 mg or 50 mg), with specific dose based on body weight.
  - A 48-week double-blind phase was followed by a 48-week open-label phase in which participants received either high- or low-dose taldefgrobep.

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 taldefgrobep for up to 228 weeks) support conducting the global, prospective, randomized, double-blind, placebo-controlled phase 3 RESILIENT study (NCT05337553).[5]
- 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 data from clinical neuromuscular studies and nonclinical SMA models.[5]

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Table 1.
Adverse events reported in studies of pediatric patients with neuromuscular disease, across the phase 2/3 study (randomization period and whole study) and among those receiving taldefgrobep across the whole phase 1b/2 study.

	AEs reported in the randomized period of the phase 2/3 study			AEs in patients who received ≥1 dose of taldefgrobep in the phase 2/3 study		AEs in patients who received ≥1 dose of taldefgrobep in the phase 1b/2 study
n (%)	Low-dose taldefgrobep (n = 55)	High-dose taldefgrobep (n = 55)	Placebo (n = 56)	Low-dose taldefgrobep (n = 69)	High-dose taldefgrobep (n = 68)	Whole study analysis N = 43
Serious AEs	2 (3.6)	4 (7.3)	3 (5.4)	2 (2.9)	4 (5.9)	6 (14.0)
Related serious AEs	0	1 (1.8)	0	0	1 (1.5)	0
AEs leading to discontinuation of study drug	0	1 (1.8)	0	0	1 (1.5)	0
Deaths	0	1 (1.8)*	0	0	1 (1.5)*	0
Related AEs	22 (40.0)	24 (43.6)	18 (32.1)	23 (33.3)	28 (41.2)	27 (62.8)
Severe AEs	1 (1.8)	3 (5.5)	2 (3.6)	1 (1.5)	4 (5.9)	5 (11.6)
AEs in ≥15% of patients in any group of the phase 2/3 study						
Nasopharyngitis	13 (23.6)	13 (23.6)	13 (23.2)	15 (21.7)	13 (19.1)	16 (37.2)
Injection site erythema	11 (20.0)	12 (21.8)	8 (14.3)	11 (15.9)	16 (23.5)	12 (27.9)
Pyrexia	9 (16.4)	8 (14.5)	8 (14.3)	12 (17.4)	10 (14.7)	13 (30.2)
Diarrhea	10 (18.2)	4 (7.3)	3 (5.4)	10 (14.5)	6 (8.8)	13 (30.2)
Cough	8 (14.5)	7 (12.7)	10 (17.9)	9 (13.0)	8 (11.8)	13 (30.2)
Headache	14 (25.5)	10 (18.2)	9 (16.1)	15 (21.7)	11 (16.2)	16 (37.2)
Injection site reactions	19 (34.5)	20 (36.4)	14 (25.0)	20 (29.0)	24 (35.3)	25 (58.1)
Hypersensitivity/ allergic reactions	19 (34.5)	20 (36.4)	19 (33.9)	22 (31.9)	21 (30.9)	21 (48.8)
Immunogenicity (antidrug antibody)	6 (10.9)	5 (9.1)	1 (3.7)	Not applicable	Not applicable	1 (2.3)

*Considered by investigator as unrelated to study treatment as the patient experienced a cardiac arrest following cardiac ablation.

RESULTS

PRECLINICAL STUDIES

- In the first preclinical study (RK050216), in SMA mice at PND52, masseter muscle function appeared similar between treatment groups, but the combination of taldefgrobep and high-dose SMN-C1 was associated with improved plantarflexor muscle function (*P*<.05; **Figure 1**) and a nonsignificant trend toward higher gastrocnemius muscle weight (*P*=.08), compared with SMN-C1 alone.
  - Additionally, muscle fiber type composition and cross-sectional area overall were similar between groups, but there was a nonsignificant trend toward an increase in plantarflexor muscle fiber mean cross-sectional area for SMA mice with the combination treatment, compared with SMN-C1 treatment alone (*P*=.14).
- In the second preclinical study (RK100115) in SMA mice, the addition of taldefgrobep to low-dose SMN-C1 was associated with the following results, compared with SMN-C1 alone:
  - Increased body weight at PND48 (*P*<.05) and increased gastrocnemius muscle weight at PND62 (*P*<.05).
  - Improvements across several metrics of gastrocnemius muscle performance and contraction and/or relaxation kinetics at PND48 and/or at PND62 (*P*<.05; **Figure 2**).
  - Improved maximal torque in the masseter muscle at 150 Hz at PND62 (*P*<.05), with nonsignificant trends toward improved maximal force normalized to body weight (*P*=.11) and the maximum rate of relaxation at 150 Hz (*P*=.05).
  - Increased mean muscle fiber cross-sectional area at PND48 (*P*<.05) and type IIb muscle fiber cross-sectional area at PND48 (*P*<.05), in addition to restoration of type IIa atrophic muscle fibers at both PND48 and PND62 (*P*<.05; **Figure 3**).

Figure 1.
Plantarflexor muscle function in the RK050216 study at PND52, based on maximum torque.

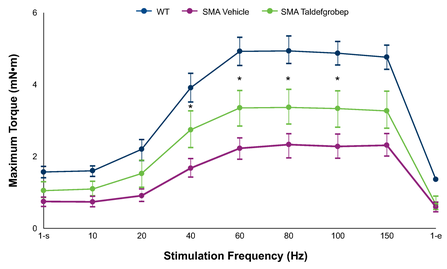


Figure 2.
Gastrocnemius muscle function in the RK100115 preclinical study: muscle performance at PND48, based on maximal torque normalized to gastrocnemius weight.

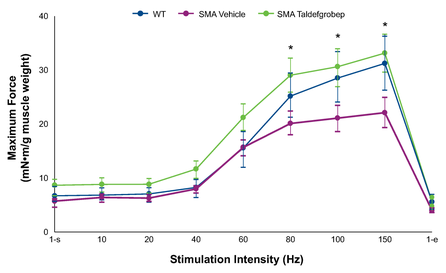
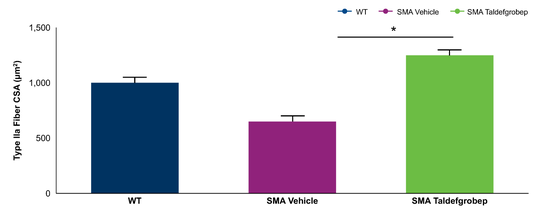


Figure 3.
Type IIa muscle fiber cross-sectional areas in the RK100115 preclinical study at PND48.



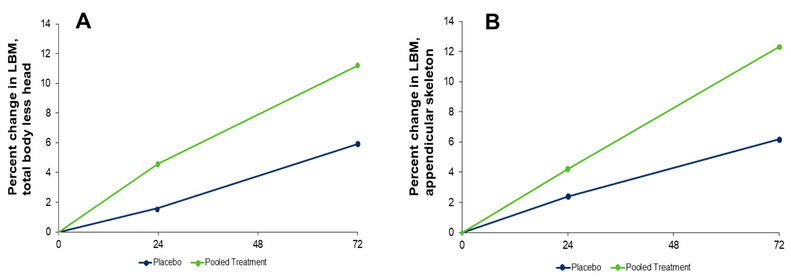
*P<0.05 for taldefgrobep-treated SMA mice vs vehicle-treated SMA mice.

CLINICAL STUDIES

Phase 1b/2 and phase 2/3 clinical studies

- A total of 359 individuals have received taldefgrobep in studies to date, including 179 healthy adults and 180 pediatric patients with neuromuscular disease.
- In healthy adults, phase 1 analyses revealed serum free myostatin suppression that increased in a dose-dependent manner with taldefgrobep as well as comparable taldefgrobep exposure regardless of site of subcutaneous injection.
- Additionally, in healthy adults, analysis of magnetic resonance imaging showed that the right thigh muscle volume percent change compared with baseline was increased with taldefgrobep**.**
- In the phase 1b/2 study of pediatric patients with neuromuscular disease, dual x-ray absorptiometry imaging indicated percent increases in lean body mass over the course of the study that were numerically larger for patients in the pooled taldefgrobep treatment group compared with the placebo group.
  - Changes in lean body mass and lean body mass index through week 72 are shown in **Figure 4** for the placebo and pooled taldefgrobep treatment groups; patients on placebo had switched to taldefgrobep treatment at week 24.

Figure 4.
Percent change from baseline in lean body mass (LBM): (A) total body less head and (B) appendicular skeleton.



Taldefgrobep was associated with a lean body mass increase of 11.2% and 12.3% in the total body less head, and appendicular skeleton, respectively, by week 72.

Safety with taldefgrobep

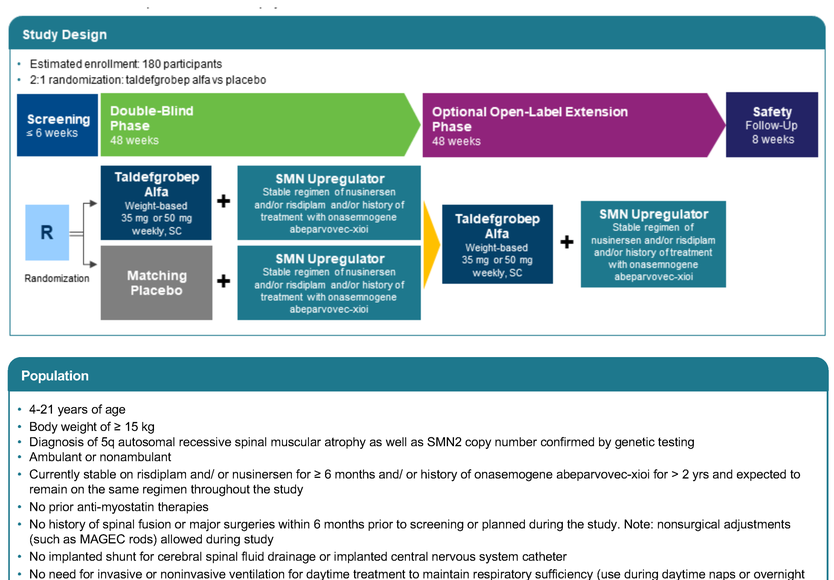
- In the randomized portion of the phase 2/3 study of pediatric patients with neuromuscular disease, which included 55 patients in the taldefgrobep low-dose group, 55 patients in the taldefgrobep high-dose group, and 56 patients in the placebo group (**Table 1**, which also includes safety data across the whole phase 2/3 and phase 1b/2 studies in pediatric patients with neuromuscular disease):
  - Adverse events (AEs) were reported in 48 (87.3%), 49 (89.1%), and 46 (82.1%) patients, respectively.
  - One fatality was reported in a patient in the high-dose taldefgrobep group (1.8%), which involved cardiac arrest following cardiac ablation and was deemed unrelated to the study drug by the investigator; this AE was also associated with discontinuation of the study drug in this patient.
  - One serious AE of hyperbilirubinemia in the high-dose taldefgrobep group was considered related to taldefgrobep.
  - The most frequently reported AEs that were deemed to be related to the study drug involved injection site reactions, which were mostly mild.
- In the randomized portion of 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:
  - AEs were reported in 29 (90.6%) and 9 (81.8%) patients, respectively, with serious AEs in 1 (3.1%; spinal compression fracture) and 1 (9.1%; skull fracture) patient of each treatment group, respectively, while severe AEs, AEs leading to discontinuation of the study drug, and related serious AEs were each reported in 0 patients in either group during this period.
  - AEs reported in ≥15% of patients in the taldefgrobep group during this period included headache, pyrexia, nasopharyngitis, upper respiratory tract infection, injection site bruising, and vomiting.
- In the studies of pediatric patients with neuromuscular disease:
  - Participants receiving taldefgrobep showed numerically greater percent increases in lean body mass than did those given placebo.
  - Taldefgrobep was considered well tolerated, with an acceptable safety profile.

PHASE 3 RESILIENT

The phase 3 RESILIENT study

- Preclinical and clinical data on taldefgrobep support the development of this agent as a possible treatment for SMA, and a phase 3 study is now underway to evaluate the efficacy and safety of taldefgrobep in ambulatory and nonambulatory patients with SMA (regardless of SMA type) receiving SMN-upregulating therapies.[5]
- In the RESILIENT study, patients are being randomized 2:1 into study arms receiving either taldefgrobep according to weight-based dosing plus standard of care or placebo with standard of care (**Figure 6**).
- The RESILIENT study is recruiting patients with SMA, with a goal of enrolling patients from the US, Czech Republic, France, UK, Germany, Poland, Spain, Italy, Netherlands, and Belgium. Patients are being recruited from approximately 30 sites in the US.

Figure 6.
Phase 3 RESILIENT study design, patient population, and primary outcome.[6,7]



AE, adverse event; LBM, lean body mass; MAGEC, magnetic expansion control; PND, postnatal day; SC, subcutaneous; SMA, spinal muscular atrophy; SMN, survival of motor neuron; WT, wild type.

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