1801-P

PK/PD Modeling Demonstrates Potential for Taldefgrobep Alfa, a Novel Myostatin/Activin Pathway Inhibitor, To Achieve High-Quality Weight Loss in Obesity

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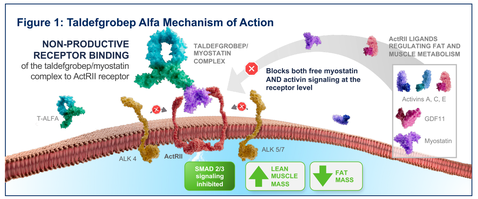
INTRODUCTION

- Obesity is a disease of excess and abnormal adipose tissue.[1-3]
- GLP-1 receptor agonists achieve significant reductions in total body weight, in part because of excessive loss of lean muscle mass.[4-7]
- Taldefgrobep is a myostatin/activin pathway inhibitor designed to achieve high-quality weight loss by directly targeting fat while increasing lean muscle mass and bone density.
- Taldefgrobep works by forming stable, pharmacologically active complexes with myostatin which then bind to activin type II receptors (ActRII) in a manner that favorably affects muscle and fat metabolism (**Figure 1**).[8]
- In an obese mouse model, taldefgrobep, as monotherapy and in combination with a GLP-1 agonist, achieved significant reductions in total body weight and total body fat while increasing lean muscle mass.[9]
- In the clinic, taldefgrobep has demonstrated a favorable safety profile across >700 trial participants and has produced meaningful reductions in fat mass and increases in lean mass in non-obese populations.
- A Phase 2 study is ongoing to evaluate the PK/PD, efficacy, and safety of taldefgrobep in adults living with overweight and obesity; results are expected in the second half of 2026.

Figure 1: Taldefgrobep Alfa Mechanism of Action



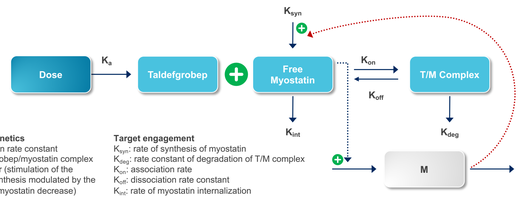
OBJECTIVE

- Pharmacokinetic/pharmacodynamic (PK/PD) modeling was conducted to inform taldefgrobep dosing in the ongoing Phase 2 proof-of-concept study in people living with overweight and obesity.

METHODS

- A population PK/PD model using target-mediated drug disposition (TMDD) with feedback regulation was previously developed using data from healthy adults.[10] This model was used to simulate taldefgrobep doses and associated taldefgrobep pharmacokinetics, free myostatin suppression, and taldefgropeb/myostatin (T/M) complex concentrations in an overweight/obese population.
- The model incorporated body weight effects on clearance and volume of distribution, and dose-dependent effects on relative bioavailability.
- Using demographics from National Health and Nutrition Examination Survey (NHANES), simulations were conducted in 500 virtual adults with body weight 60-160 kg and BMI 30-40 kg/m^2.[11]
- Taldefgrobep was best described by a 1-compartment model with linear absorption and elimination (**Figure 2**). The model assumes the binding rate of taldefgrobep to free myostatin is balanced by the sum of the dissociation rate (K_{off}) and degredation rate of the T/M complex (K_{deg}).
- Demographics of the virtual population are described in **Table 1**.

Figure 2. TMDD Taldefgrobep/Myostatin Complex Formation and Disposition



Pharmacokinetics
K_a: absorption rate constant
T/M: taldefgrobep/myostatin complex
M: moderator (stimulation of the myostatin synthesis modulated by the level of free myostatin decrease)

Target engagement
K_{syn}: rate of synthesis of myostatin
K_{deg}: rate constant of degradation of T/M complex
K_{on}: association rate
K_{off}: dissociation rate constant
K_{int}: rate of myostatin internalization

Table 1. Demographics of Virtual Obese Population

	Mean (SD)	Median (CV %)	[Min, Max]	n (%)
Age, years	52.8 (16.4)	54.4 (31.1)	[18.2, 79.8]	
Sex, female				245 (49)
Body weight, kg	94.8 (13.5)	94.2 (14.2)	[65.9, 143]	
BMI, kg/m^2	33.4 (2.64)	32.8 (7.9)	[30.0, 40.0]	

RESULTS

- The model estimates a modest apparent central clearance of 0.1661 L/day and a volume of distribution of 3.565 L, suggesting relatively slow elimination and limited distribution for taldefgrobep. The absorption rate constant was estimated at 0.7759 day^{-1}, with moderate uncertainty (RSE 12.7%), indicating reasonably supported first-order absorption (**Table 2**).
- Goodness-of-fit plots demonstrate the model adequately predicts the data from which the model is based (**Figures 3A–C**).
- Taldefgrobep 100 mg once weekly (Q1W) and 150 mg once every four weeks (Q4W) are predicted to suppress free myostatin >80% (**Figure 4A**) — a level associated with favorable body composition changes in pre-clinical models — and yield T/M complex concentrations predicted to competitively inhibit ActRII signaling (**Figure 4B**). These doses were selected for the ongoing Phase 2 proof-of-concept study.
- Predicted serum concentrations of taldefgrobep and T/M complex and % myostatin suppression through 12 weeks of dosing with taldefgrobep 100 mg Q1W and 150 mg Q4W dosing are shown in **Table 3**.

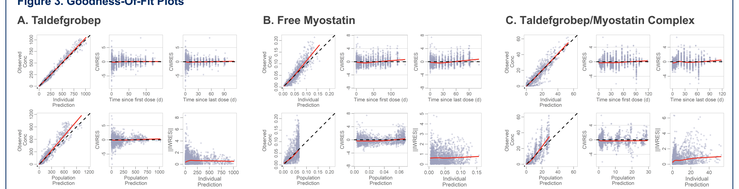
Table 2. Model Parameter Estimates

Parameters	Estimates	%RSE
CL/F (L/day)	0.1661	4.3
V/F (L)	3.565	4.4
K_a (day^{-1})	0.7759	12.7
K_{deg} (day^{-1})	3.85	7.0
K_{int} (day^{-1})	0.1227	3.6
K_{e0} (day^{-1})	0.1135	4.2
AMP	2.175	4.1
K_{on} (nM*day^{-1})	2.72	n/a
K_{off} (day^{-1})	0.04516	5.2
Baseline myostatin (nM)	0.05116	3.5

Parameters (cont.)	Estimates	%RSE
Dose effect on bioavailability	0.1434	19.8
Dose effect on AMP	18.91	38.5
Dose effect on K_{off}	0.8798	7.0
IIV on CL/F	0.0592	15.5
IIV on V/F	0.0795	13.3
Cor (CL/F, V/F)	0.0271	n/a
IIV on K_a	0.511	12.4
IIV on K_{deg}	0.176	16.4
IIV on K_{int}	0.079	17.0
IIV on Baseline myostatin	0.109	14.7

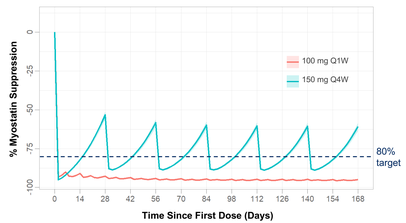
AMP, the extent of the stimulation of the moderator production; **CL/F**, apparent central clearance; **Cor**, correlation; **IIV**,interindividual variability; **K_{e0}**, first-order effect compartment equilibration rate constant; **RSE**, relative standard error; **V/F**, apparent central volume of distribution

Figure 3. Goodness-Of-Fit Plots



CWRES, conditional weighted residuals; **IWRES**, individual weighted residuals

Figure 4. Model-Predicted Myostatin Suppression and T/M Complex Formation



Dotted line represents the estimated IC_{50} level of T/M complex competitive inhibition of the ActRII receptor for it's native TGF-ß ligands

Table 3. Predicted Serum Concentrations of Taldefgrobep and T/M Complex and % Myostatin Suppression at the End of the Dosing Interval

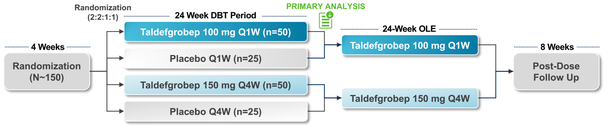
Dose	Duration	Taldefgrobep ng/mL (mean ± SD)	% myostatin suppression (mean ± SD)	T/M complex nM (mean ± SD)
100 mg Q1W	Predose	n/a	n/a	n/a
	Week 1	12600 ± 1.87	92.7 + 0.22	4.53 ± 0.15
	Week 4	21500 ± 2.18	92.7 + 0.26	12.0 ± 0.40
	Week 8	29200 ± 3.54	94.1 + 0.23	14.1 ± 0.47
	Week 12	32200 ± 4.43	94.6 + 0.21	14.4 ± 0.49
150 mg Q4W	Predose	n/a	n/a	n/a
	Week 1	11800 ± 1.32	90 + 0.30	5.34 ± 0.18
	Week 4	4990 ± 0.928	53.1 + 2.34	12.0 ± 0.32
	Week 8	6410 ± 1.49	58.3 + 2.29	13.7 ± 0.36
	Week 12	6930 ± 1.77	59.9 + 2.29	13.9 ± 0.37

With 100 mg Q1W and 150 mg Q4W, maximum % myostatin suppression (at nadir) is predicted to be 95.3 + 0.18 and 88.6 + 0.28, respectively.

ONGOING PHASE 2 STUDY

- The Phase 2 proof-of-concept study (NCT07281495) is a placebo-controlled trial evaluating once-weekly and once-monthly taldefgrobep as monotherapy, via self-administered autoinjector, in overweight and obese adults (**Figure 5**).
- Preliminary myostatin suppression and T/M complex concentration data from 30% of study participants at Week 12 of the ongoing Phase 2 study are shown in **Figure 6**.

Figure 5. Phase 2 Proof-of-Concept Study Design

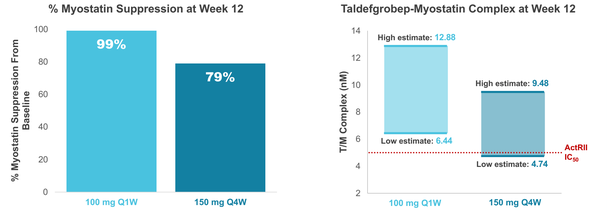


KEY STUDY DETAILS

Study design: Phase 2, randomized, double-blind, placebo-controlled dose-ranging study
Population: Male and female adults (18 to 65 years old) with overweight or obesity
Blinded interim analysis (when 30% complete Week 12): Taldefgrobep PK/PD (free myostatin and T/M complex concentrations) by treatment assignment
Endpoints: % change in total body weight, fat mass and lean mass at Week 24

Sparse PK and PD samples are collected for deriving PK and PD parameters using population PK/PD modeling
DBT, double-blind treatment; **OLE**, open-label extension

Figure 6. Observed Myostatin Suppression and T/M Complex Concentrations in Overweight/Obese Adults



CONCLUSIONS

- Taldefgrobep is a novel myostatin-activin pathway inhibitor (MAPI) that directly targets both fat and muscle with a favorable, well-established safety profile.
- Simulations in a virtual obese population were used to select two taldefgrobep dose levels (100 mg Q1W and 150 mg Q4W) for a Phase 2 proof-of-concept study in adults with overweight and obesity.
- Serum concentrations of taldefgrobep/myostatin complex are predicted to reach levels higher than *in vitro* IC_{50} values with both doses, potentially allowing for monthly dosing of taldefgrobep.
- The Phase 2 study is now fully enrolled with topline results expected in the second half of 2026.
- Preliminary results from 30% of Phase 2 study participants at Week 12 demonstrated robust suppression of free myostatin with Q1W and Q4W dosing.
- Taldefgrobep/myostatin complex concentrations are comparable between dosing regimens and ≥ ActRII IC50.
- Taldefgrobep may represent an important addition to the anti-obesity treatment paradigm, achieving high-quality weight loss with a favorable side effect profile in people living with obesity.

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