

Target-mediated drug disposition model of RG6206 (RO7239361), an anti-myostatin adnectin-IgG1-Fc-fusion protein, with positive feedback on myostatin endogenous production in healthy adults but not in boys with Duchenne Muscular Dystrophy



Valérie Cosson¹, Vincent Buchheit¹ and Heidemarie Kletzl¹

¹ Clinical Pharmacology, Pharmaceutical Sciences, Roche Pharma Research & Early Development (pRED), Roche Innovation Center Basel, Switzerland

Background and Objective

- Duchenne Muscular Dystrophy (DMD), an X-linked human orphan disease, is the most common genetic muscle disorder affecting boys. Mutations/deletions in dystrophin gene result in progressive and profound muscle weakness.
- DMD causes progressive weakness of skeletal, respiratory, and cardiac muscles due to the absence of dystrophin in the subsarcolemmal cytoskeleton. Progressive weakness and contractures lead to loss of ambulation by age 13 and death from cardiorespiratory failure by the late 20s to early 30s.
- RG6206 (RO7239361) is a fully human anti-myostatin adnectin-IgG1-Fc-fusion protein that binds to and neutralizes the biological activity of myostatin, a protein that prevents muscle cell growth and differentiation. This blockade is expected to lead to larger and stronger muscles in human. The compound is currently in development for the treatment of patients with DMD.
- The objectives of the analysis are to describe the PK of RG6206 and the PKPD relationship between total RG6206 and free myostatin serum concentrations in healthy adults (HVs) and DMD patients using the population approach.

PKPD Results in Healthy Subjects

- The disposition of RG6206 is described by a one-compartmental model with linear absorption and elimination. CL/F and V/F increase with BW with exponents equal to 0.75 for CL/F and 1 for V/F. To account for the more than dose-proportional increase of exposure, a dose effect, centered on 45 mg, on relative bioavailability (relF) was included.
- A positive feedback control was added on the myostatin endogenous production to describe the rebound of the free myostatin concentrations after the end of the treatment. It is known that increasing levels of active myostatin protein down-regulate its own expression [5,6] and an up-regulation can therefore be expected in case of inhibition of myostatin activity.

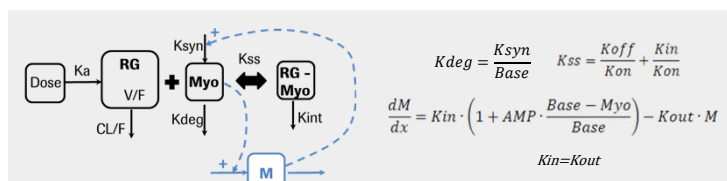


Figure 1. Schematic representation of the PK model, the corresponding parameters are included in Table 1

- When the free myostatin is saturated, the half-life of RG6206 is estimated at ~14 days.

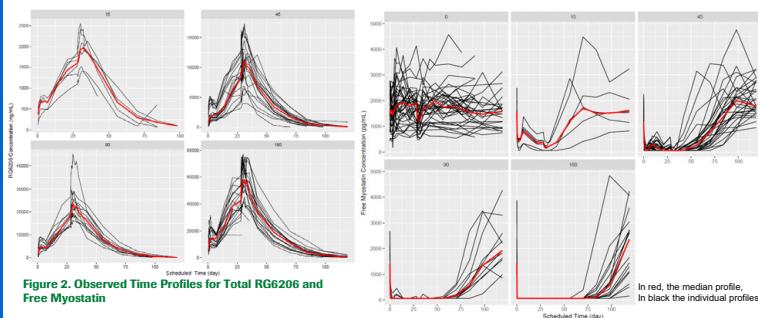


Figure 2. Observed Time Profiles for Total RG6206 and Free Myostatin

Parameters	Typical Value (RSE%)	BSV %CV (RSE%) [Shrinkage %]
Structural Parameters		
CL/F (L/day)	0.241 (4.9)	19.6 (44) [26]
V/F (L)	4.90 (4.1)	29.0 (21) [21]
Ka (1/day)	0.852 (10)	82.5 (21) [20]
Ksyn (nM/day)	0.178 (27)	37.1 (72) [44]
Kss (nM)	2.71 (38)	-
Kint (1/day)	4.14 (34)	35.8 (59) [41]
Kin (1/day)	0.00585 (20)	53.0 (74) [48]
Amp	7.37 (24)	-
Dose effect Parameter		
Dose on relF	0.206 (22)	-
Residual Variability		
Prop. Err for RG	13.8 (5.1)	-
Add. Err for RG	97 (21)	-
Prop. Err for Myo	18.7 (4.8)	-
Add. Err for Myo	95 (11)	-

Table 1. Final population PKPD parameters

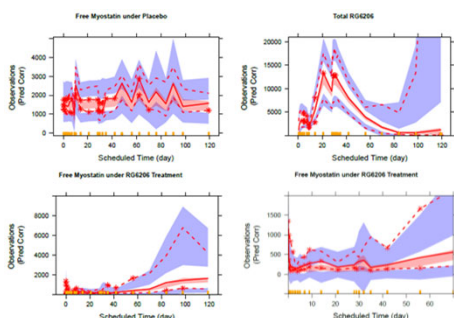


Figure 3. Prediction-corrected Visual Predictive Check of the pop PKPD model

Material and Method

Study design and Treatment

- Blood samples for RG6206 and myostatin were collected in two trials after SC administration: a single and multiple ascending dose (MAD) study in HVs and a MAD study in DMD boys [5-11 yr]. In total data from 109 HVs and 43 DMD boys were included in this analysis. The MAD doses investigated in HVs were: 15, 45, 90, 180 mg Q1W and 45 mg Q2W or placebo for 4 weeks. The MAD doses investigated in DMD boys with weight (BW) between 15-45 kg and BW ≥ 45 kg were: 4 mg (BW ≥ 15 kg), 12.5/20 mg, 35/50 mg Q1W or placebo for 24 weeks.

Population Modelling

- Both total RG6206 and free myostatin serum concentrations were fitted together using the quasi-steady-state approximation of the full target-mediated drug disposition (TMDD) model [1-3]. HVs and DMD patient data were modelled separately since the bioanalytical methods for measurement of free myostatin were different.
- PK/PD analysis was performed using nonlinear mixed-effect approach (NONMEM) software (Version 7.2.0) [4]. The Monte Carlo expectation-maximization Importance sampling (IMP) method with INTERACTION and LAPLACIAN was used.

PKPD Results in DMD Boys

- The PK of RG6206 is described by the same model as in HVs but without dose effect on relF and with an additional BW effect on Ka to capture the slower absorption observed with increasing BW. To ensure PK continuity between the two populations, the parameters of CL/F and V/F and their associated BW effect in DMD boys are fixed to those in HVs.
- The limitation of the PD sampling scheme and the absence of sampling after the end of treatment prevent the estimation of all TMDD parameters so Kss is fixed to that in HVs.
- Contrary to HVs, the positive feedback control on the myostatin synthesis was not supported by the data from DMD boys. Although a feedback as estimated in HVs should lead to a slow increase of the free myostatin trough levels under treatment, which is not observed in DMD boys, additional data after end of treatment might be needed to draw a final conclusion on the presence of a feedback mechanism in DMD patients.

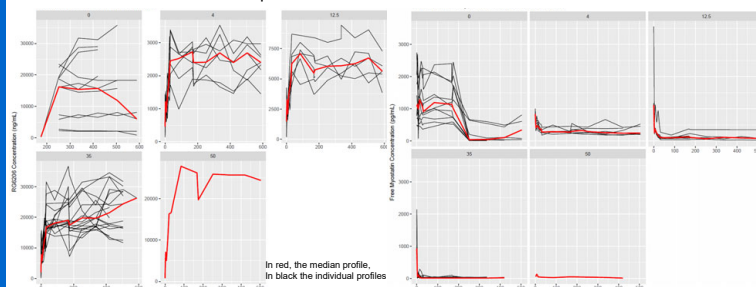


Figure 4. Observed Time Profiles for Total RG6206 and Free Myostatin

Parameters	Typical Value (RSE%)	BSV %CV (RSE%) [Shrinkage %]
Structural Parameters		
CL/F (L/day)	0.241 (fix)	21.1 (46) [15]
V/F (L)	4.90 (fix)	25.7 (29) [29]
Ka (1/day)	2.24 (14)	59.5 (42) [34]
Ksyn (nM/day)	0.0834 (20)	79.7 (36) [12]
Kss (nM)	2.71 (fix)	-
Kint (1/day)	0.715 (14)	-
Weight effect Parameter		
Weight on Ka	-1.91 (20)	-
Residual Variability		
Prop. Err for RG	13.8 (8.0)	-
Add. Err for RG	499 (19)	-
Prop. Err for Myo	16.9 (11)	-
Add. Err for Myo	35 (16)	-

Table 2. Final population PKPD parameters

- The simulations show that the PK and PD steady states were reached after ~12 and 6 weeks, respectively, of QW administration of RG6206 to DMD boys weighing 16 to 46 kg
- At steady-state, RG6206 maintains a reduction in free myostatin from baseline of ~77, 92 and 97% over the dosing interval with the weekly 4, 12.5 and 35 mg dose, respectively.

Figure 6. Simulation of Free Myostatin Change from Baseline Profiles in DMD Boys

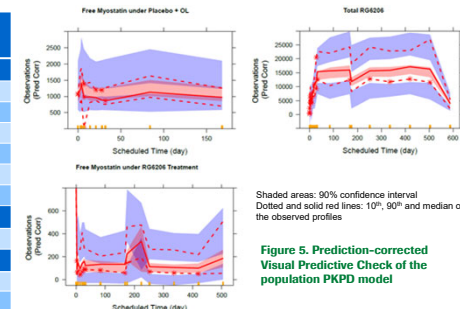
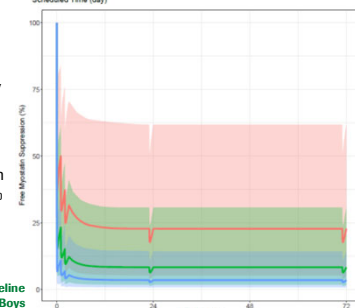


Figure 5. Prediction-corrected Visual Predictive Check of the population PKPD model



Conclusion

- The PK of RG6206 and its effect on the free myostatin in HVs were accurately described by a model based on the TMDD concept with a positive feedback on the synthesis of myostatin. In DMD boys, a similar PKPD model structure as in adult HVs could accurately describe the data however no positive feedback was needed to describe the currently available data.

References [1] G. Levy. Pharmacologic target-mediated drug disposition. *Clin Pharmacol Ther.* 56:248-252 (1994). [2] D. E. Mager and W. J. Jusko. General Pharmacokinetic Model for Drugs Exhibiting Target-Mediated Drug Disposition. *J Pharmacokin Pharmacodyn.* 28:507-532 (2001). [3] L. Gibiansky, E. Gibiansky, T. Kakkar, P. Ma. Approximations of the target-mediated drug disposition model and identifiability of model parameters. *J Pharmacokin Pharmacodyn.* 35(5): 573-59 (2008) [4] S. L. Beal, L. B. Sheiner, A. J. Boeckmann, and R. J. Bauer (Eds.). *NONMEM Users Guides*. 1989-2011. Icon Development Solutions, Ellicott City, Maryland, USA. [5] C. McFarlane, et al. Proteolytic processing of myostatin is auto-regulated during myogenesis. *Developmental Biology.* 283:58-69 (2005). [6] D. Forbes, et al. Myostatin auto-regulates its expression by feedback loop through Smad7 dependent mechanism. *J Cell Physiol.* 206: 264-272 (2006).