Semi-Mechanistic Pharmacokinetic Model for MaNAc and Sialic Acid in GNE Myopathy Subjects

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Objectives: N-acetylmannosamine (ManNAc) is being explored as a potential therapy for Neu5Ac replacement in GNE myopathy (GNEM), a muscle disease caused by deficiency of an enzyme required for sialic acid (Neu5Ac) biosynthesis. A population pharmacokinetic (PK) model was developed for ManNAc and its metabolite Neu5Ac.

Methods: Data were obtained from a single-dose Phase 1 study in 22 subjects administered placebo or ManNAc (3 -10 g) and a Phase 2 study in 12 subjects receiving 3 or 6 g ManNAc Q12H for 7 days and then 6 g for 1 year. Serial-sampled plasma ManNAc and Neu5Ac concentrations were measured using LC/MS-MS. A structural model (Figure) was developed to simultaneously characterize ManNAc and Neu5Ac PK. ManNAc PK was described using a first-order absorption following ManNAc dosing (k_a), apparent clearance (CL_M/F) and central volume of distribution (V_M/F).

A precursor indirect response model with first-order production of Neu5Ac (k_pro) and first-order elimination (k_out) and a Hill function to characterize changes in Neu5Ac due to ManNAc was included. Initial starting concentrations (ManNAc_0 and Neu5Ac_0) were estimated while k_syn and k_pro were calculated.

Results: The structural model provided an excellent fit to the data. ManNAc_0 was 60.8 ng/mL, Neu5Ac_0 was 147 ng/mL, CL_M/F was 645 L/hr and V_M/F was 526 L. ManNAc oral bioavailability decreased with dose using a power function. Enzymatic conversion of ManNAc to Neu5Ac was reduced to a linear slope (SLP). A time-dependent increase in SLP was required, where the initial starting slope (SLP_0 = 0.000791 hr^-1) increased to a steady-state value (SLP_SS = 0.00346 hr^-1). Simulations demonstrated that steady-state Neu5Ac concentrations are achieved by Days 3-5 and that administering the same daily dose Q8H rather than Q12H can improve tolerability, bioavailability, and further boost Neu5Ac exposures.

Conclusions: A structural model simultaneously characterizing ManNAc and Neu5Ac was developed and simulations performed to identify ManNAc dosing regimens which can safely produce sustained increases in Neu5Ac in GNEM subjects.