Pharmacokinetic analysis of levodopa and carbidopa following subcutaneous infusion: A population pharmacokinetics model

Introduction & Objectives
- ND0612 is an investigational subcutaneous delivery system providing minimally invasive, continuous infusion of liquid levodopa/carbidopa. By avoiding gastric involvement, ND0612 provides increased bioavailability and reduced variability of levodopa/carbidopa plasma levels, potentially offering more reliable, sustained relief of motor fluctuations in people with Parkinson's disease.
- Several pharmacokinetic (PK) studies have been performed and have confirmed stable, clinically relevant levodopa and carbidopa plasma levels following ND0612 administration.1,2
- Here we describe the development of a model to describe the PK characteristics of levodopa and carbidopa following subcutaneous infusion with ND0612, with and without oral therapy, including associated interindividual variability and residual unexplained variability.

Methods
- Two integrated population PK models (for levodopa and for carbidopa) were developed using data from two Phase I studies of ND0612 in healthy volunteers and PD patients.
  1. Study 004, a randomized, multicenter, dose finding study including 16 PD patients on active treatment (n=1438 PK observations).2
  2. Study 005, including 36 healthy volunteers on active treatment (n=5417 PK observations).3
- The predictivity performance of each model was then tested using data from Study 114, which included 24 healthy volunteers on active treatment (n=2959 PK observations).4
- Model refinement was performed using aggregated data from the 3 studies, and will be continually updated as more PK data from ND0612 studies becomes available.
- Population PK models were developed by using non-linear mixed-effects modeling techniques as implemented in the NONMEM 7.3 software.

Conclusions
- Both levodopa and carbidopa follow a one-compartment PK with first-order oral and SC absorption.
- The levodopa population PK model also takes into account DDC and COMT elimination from the central compartment.
- Structural covariates include body weight and entacapone coadministration.
- Apparent clearance and volume of distribution decrease with increasing age for both compounds.

Results
Levodopa and carbidopa population PK were both adequately described by a one-compartment disposition model with first-order oral and SC absorption.

Apparent clearance and volume of distribution decreases with increasing age for both compounds.

References
2. Smania et al. Mov Disord. 2017; 32 (S2).
3. Oren et al. Mov Disord. 2017; 32 (S2).