Pharmacokinetic analysis of levodopa and carbidopa following subcutaneous infusion

A population pharmacokinetics model

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Background

- 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 PD.
- Several pharmacokinetic (PK) studies have been performed and have confirmed stable, clinically relevant levodopa and carbidopa plasma levels following ND0612 administration.\textsuperscript{1-3}

Objective: Describe population 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 Phase I studies of ND0612.
- Predictive performance of the models was tested based on external Phase I data in healthy volunteers.
- Model refinement was performed using aggregated data and will be continually updated as PK data from late-phase trials becomes available.
Levodopa and carbidopa population PK were both adequately described by a one-compartment disposition model with first-order oral and SC absorption

- Levodopa had parallel DDC and COMT elimination from the central compartment, in which the inhibition of apparent DDC-mediated clearance was driven by carbidopa plasma concentrations
- Carbidopa had linear elimination

**CL:** clearance, **CCD:** measured CD concentration, ^CCD:** predicted CD concentration, **CLD:** measured LD concentration, ^CLD:** predicted LD concentration, **CLDDC:** DDC-mediated CL, **CLCOMT:** COMT-mediated CL, εaddCD ~N (0,σ2 addCD), εpropCD ~N(0,σ2 propCD), εpropLD (0,σ2 LD), **Frel:** relative bioavailability between oral and SC administration, **Ka:** first-order absorption rate constant, θENC: relative LD bioavailability with entacapone, **Lag:** lag time, **SC:** subcutaneous, **V:** volume of distribution.
Take home points

- Model diagnostics for the carbidopa and levodopa population PK models indicated a satisfactory predictive performance
  - supporting their usability to derive individual predictions of exposure to be used in future pharmacokinetic-pharmacodynamic analyses

- Both levodopa and carbidopa follow a one-compartment PK with first-order oral and SC absorption

- Apparent clearance and volume of distribution decrease with increasing age for both levodopa & carbidopa