Pharmacokinetic analysis of levodopa and carbidopa following subcutaneous infusion

A population pharmacokinetics model

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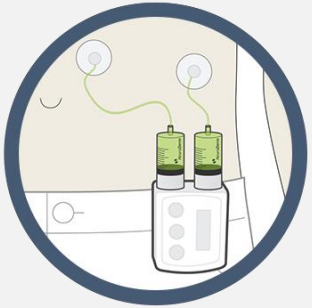
Background & Methods

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.[1-3]



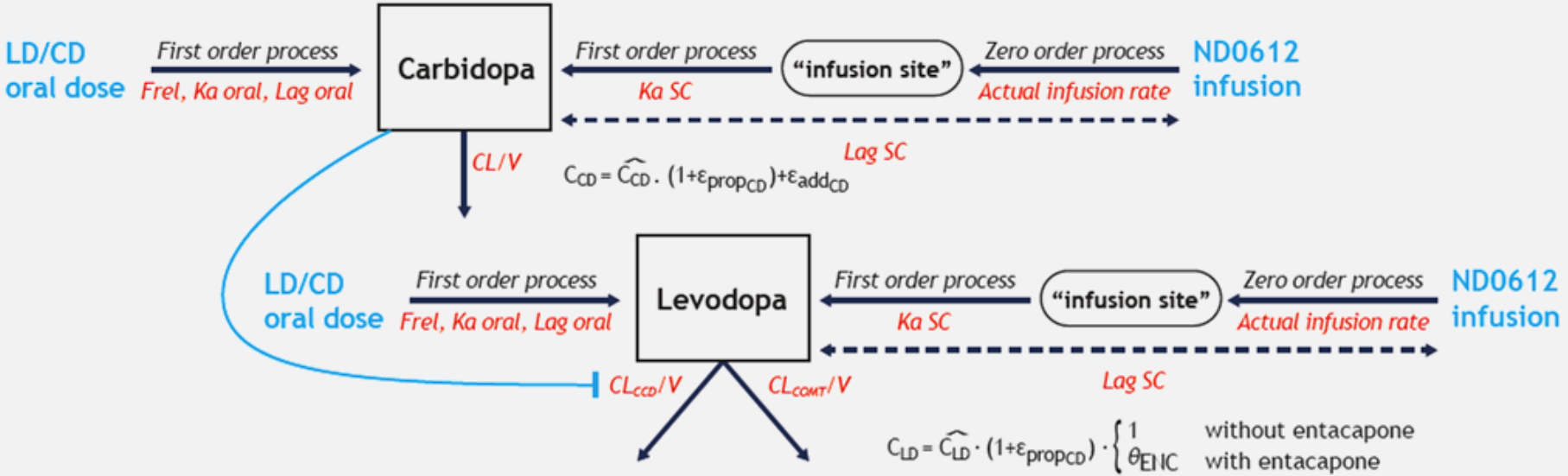
Objective: Describe population PK characteristics of levodopa and carbidopa following subcutaneous infusion with ND0612, with and without oral therapy, including associated interindividual variability and residual unexplained variability.

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.

1. Giladi et al. Mov Disord. 2017; 32 (S2). 2. Adar et al. Neurology 2017; 88 (S16): P1.019. 3. Adar et al. Mov Disord. 2017; 32 (S2).

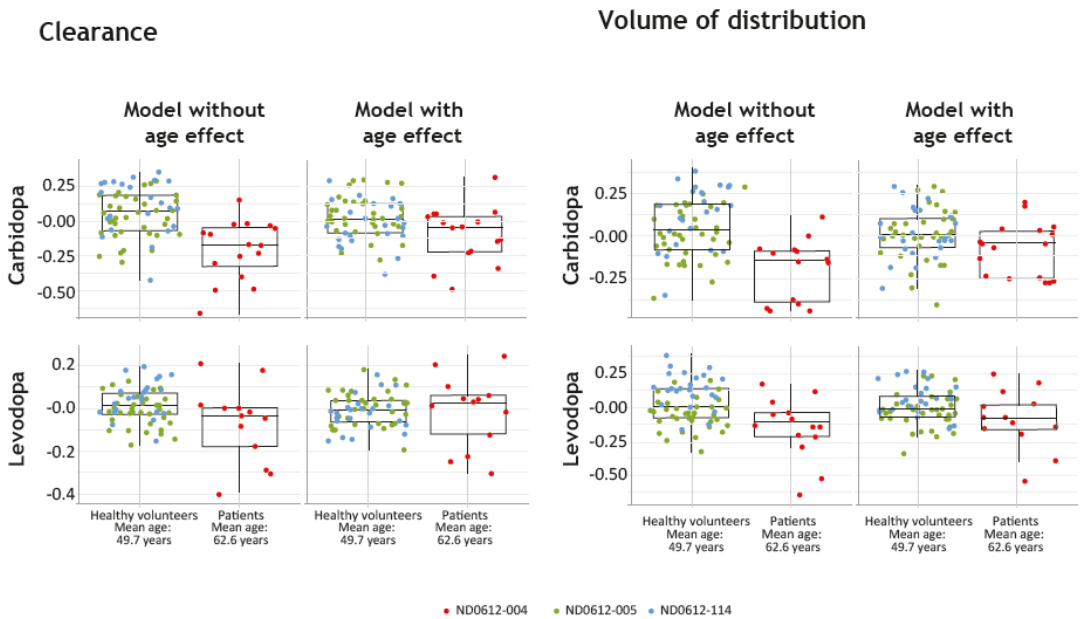
Levodopa and carbidopa population PK were both adequately described by a one-compartment disposition model with first-order oral and SC absorption



- 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: fi rst-order absorption rate constant, θENC: relative LD bioavailability with entacapone, Lag: lag time, SC: subcutaneous, V: volume of distribution.

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



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