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Pharmacokinetics of ND0612 administered at different infusion sites and with different cannula lengths: An open-label, randomized, cross-over study in healthy volunteers

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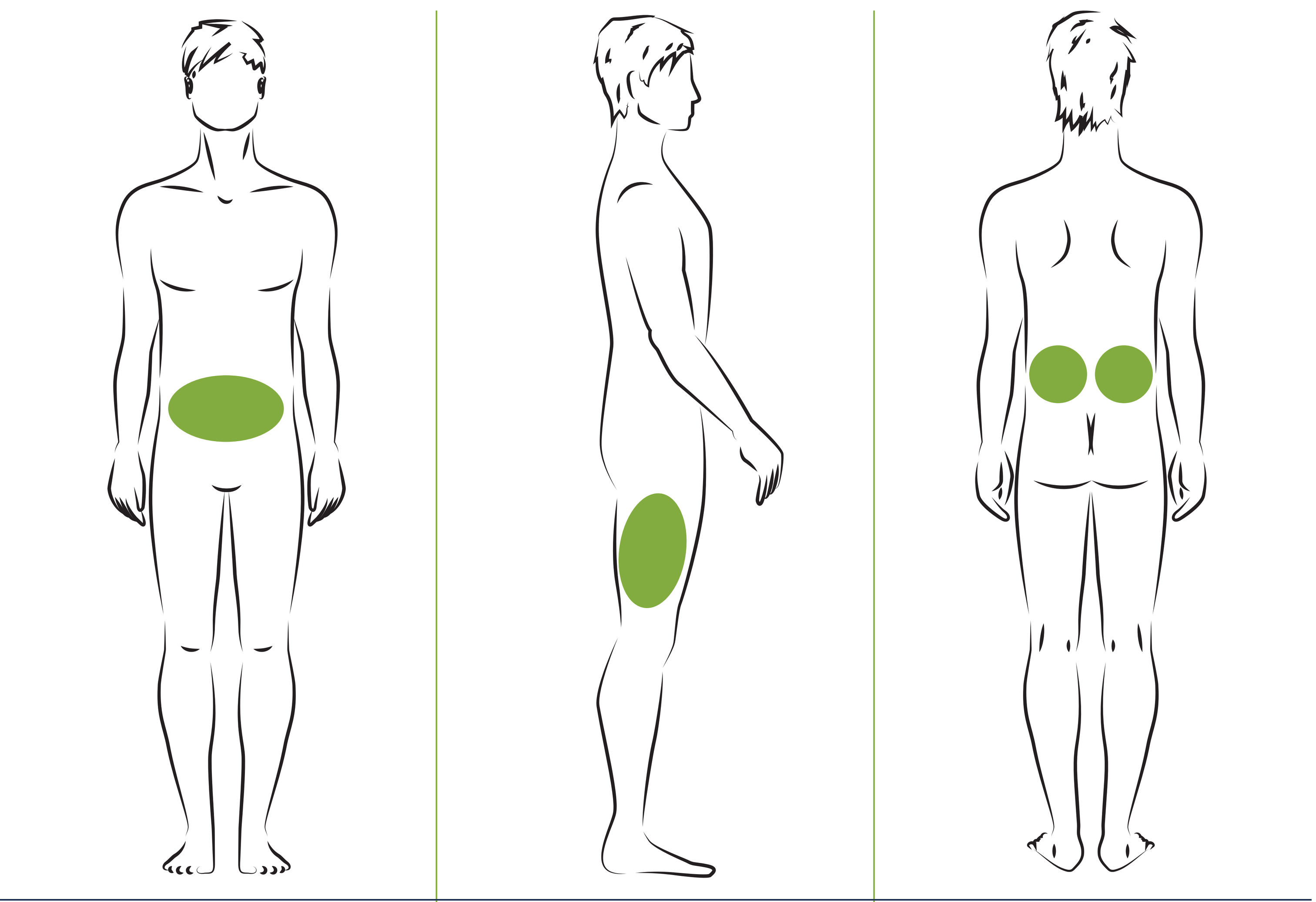
Background

- Continuous levodopa/carbidopa (LD/CD) infusion is considered an appropriate delivery route for treating patients with Parkinson's disease (PD) and advanced motor fluctuations because it has been shown to avoid the peaks and troughs associated with oral dosing.[1]
- Due to poor levodopa solubility, current infusion systems must be surgically routed to the duodenum and are associated with potentially serious complications.[2]
- ND0612 is an investigational non-surgical drug-device combination designed to provide continuous delivery of LD/CD subcutaneous (sc) solution for patients with PD experiencing motor fluctuations.
- Two previous phase 2 trials have demonstrated that ND0612 maintained steady, therapeutic levodopa plasma concentrations that were associated with reduced OFF time.[3,4]
- Prior studies have primarily used the abdomen as the main infusion site. The aim of this study was to evaluate the impact of sc infusion site location (outer thigh and back vs. the abdomen) and cannula length (short [6 mm] vs. long length [10 mm]) on levodopa pharmacokinetics administered as a single 16-hour sc infusion of ND0612 in healthy volunteers.

Methods

- This study was a single center, open-label, randomized, single-dose, 4-period, crossover study in 24 healthy volunteers (16 male and 8 female).
- Volunteers were randomized 1:1:1:1 into one of four sequences. Each volunteer sequentially received ND0612 (LD/CD 60/7.5 mg/mL) at three different infusion sites (**Figure 1**), with the abdomen infused twice, once with a long cannula (the reference route of administration) and once with a short cannula. The outer thigh and back sites were assessed with long cannula. Each of the 4 individual 16-hour dosing periods were separated by a 32-hour washout period.

Figure 1. Study design



Pharmacokinetic analysis

- Blood samples for PK analysis were collected before, during, and up to 12 hours after the end of ND0612 infusion.
- Relative bioavailability of levodopa and carbidopa was determined for the alternative treatment groups (short cannula abdomen, outer thigh and back) compared to the abdominal with long cannula based on key pharmacokinetic parameters.
- Bioequivalence criteria were confirmed if the 90% confidence intervals for pharmacokinetic parameters were within 80–125%.

Results

Pharmacokinetic analysis of bioequivalence between different treatment groups

- Mean levodopa and carbidopa plasma concentration versus time curves were similar between the reference treatment group (abdomen with long cannula) and each of the alternative administrations (**Figures 2 and 3**).
- 90% confidence intervals for all PK parameters were within the pre-defined limits of 80-125% between all tests and the reference, indicating bioequivalence (**Table 1**).

Figure 2 Levodopa plasma profiles were similar in the different treatment groups

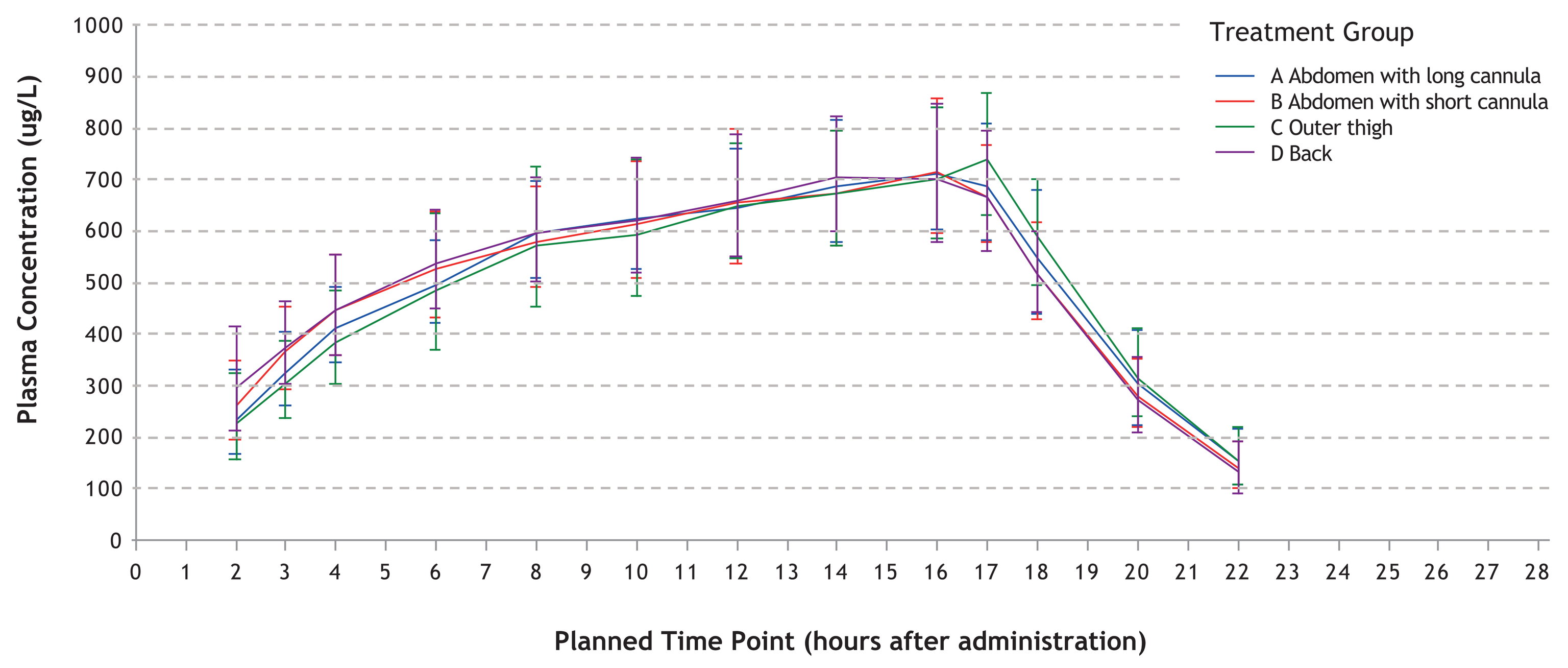


Figure 3 Carbidopa plasma profiles were similar with treatment groups

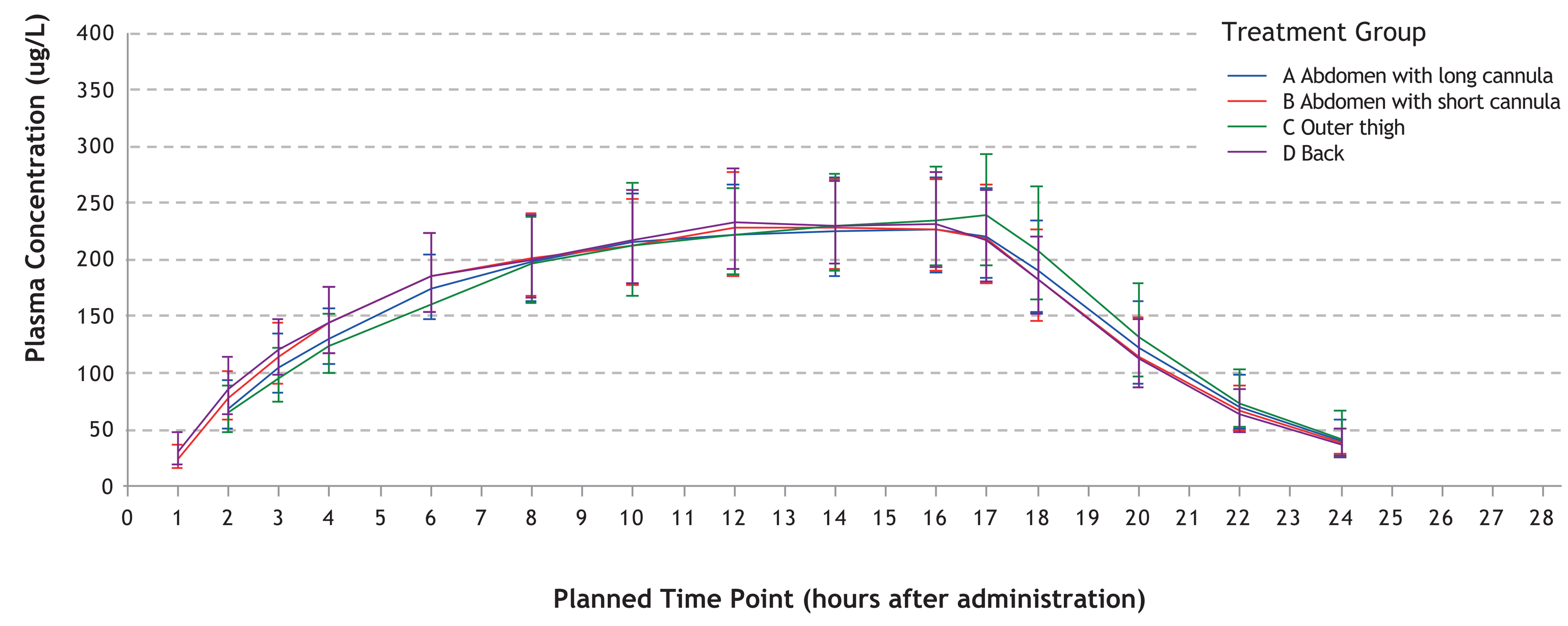


Table 1. PK parameters confirmed bioequivalence of test groups vs reference

Parameter	Statistics	Abdomen with long cannula (reference) (N=24)	Abdomen with short cannula (N=24)	Outer thigh with long cannula (N=23)*	Back with long cannula (N=24)
C_{max}	Geometric mean (ng/mL)	744.9	741.2	787.2	768.7
	Means ratio		99.51	106.92	103.20
	CI (90%)		95.72, 103.45	102.84, 111.17	99.59, 106.94
$AUC_{(0-24)}$	Geometric mean (ng/mL)	10940	10920	10770	11090
	Means ratio		99.77	99.45	101.31
	CI (90%)		97.39, 102.20	97.50, 101.45	99.30, 103.36
$AUC_{(0-t)}$	Geometric mean (ng/mL)	10980	10890	10760	11050
	Means ratio		99.17	98.90	100.61
	CI (90%)		96.89, 101.50	96.87, 100.97	98.65, 102.61
$AUC_{(0-inf)}$	Geometric mean (ng/mL)	11240	11130	10930	11w320
	Means ratio		99.07	98.70	100.71
	CI (90%)		96.71, 101.49	96.50, 100.96	98.65, 102.81

One volunteer had an unscheduled pump interruption

Safety and tolerability

- The most common treatment emergent AE was infusion site nodules which affected 37.5% to 54.2% of volunteers (**Table 2**). There were no major differences in local safety between the treatment groups.
- No TEAEs were classified as serious or severe and none led to study discontinuation.

Table 2 Treatment emergent adverse events

TEAEs; n (%)	Abdomen with long cannula (N=24)	Abdomen with short cannula (N=24)	Outer thigh with long cannula (N=24)	Back with long cannula (N=24)
Any TEAEs	13 (54.2)	16 (66.7)	15 (62.5)	12 (50.0)
Infusion site reactions group	10 (41.7)	13 (54.2)	12 (50.0)	9 (37.5)
Severe AEs	0	0	0	0
Serious AEs	0	0	0	0
Any TEAEs	13 (54.2)	16 (66.7)	15 (62.5)	12 (50.0)
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Severe AEs	0	0	0	0
Serious AEs	0	0	0	0

Conclusions

- This Phase 1 study shows that in healthy volunteers both the rate and extent of absorption of ND0612 were similar when administered using different injection site locations and cannula lengths.
- Infusion to back and outer thigh is not expected to affect levodopa efficacy, potentially offering alternative infusion locations for long-term ND0612 use.
- Rotation of infusion sites on a daily basis may help patients tolerate local infusion site reactions.

References

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Disclosures

Tal Birnberg, Tami Yardeni, Sheila Oren, Olivia Rosenfeld and Liat Adar are employed by NeuroDerm.

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