ND0701: A New Concentrated Formulation of Apomorphine for Continuous Subcutaneous Administration - Human Pharmacokinetic Data

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Introduction

ND0701 (apomorphine base) is a new, concentrated formulation of apomorphine for continuous subcutaneous (SC) infusion. It is developed for the treatment of motor fluctuations in patients with Parkinson’s disease (PD) who are not sufficiently controlled with oral antiparkinson mediations and are intolerant to other therapies.

Commercial apomorphine formulations, such as APO-go® (Brittania Pharmaceuticals Ltd., Bethesda, USA), are based on apomorphine HCl formulations. ND0701 is supplied as 1 mg/mL and 2 mg/mL solutions. Because of the higher volume of the solution and recommended hourly infusion rates ranging between 1 mg and 6 mg, delivery is limited to syringe pumps, which may affect management, comfort, and tolerability challenges to patients with advanced PD.

The concentrated formulation of ND0701 comprises apomorphine base instead of the commercially available HCl formulation, allowing for a reduction in the infusion volume, and is thus suitable for use in combination with a pump infusion device. Based on preclinical studies, ND0701 is safe for a duration of up to 20 hours via SC infusion.

The study reported here evaluated ND0701 and APO-go® pharmacokinetics in healthy volunteers, to assess safety/tolerability.

Study Objectives

Primary objectives

- To determine the plasma PK of ND0701 over 12 hours of SC infusion of ND0701 and APO-go®
- To assess the relative bioavailability of ND0701 and APO-go® after 12 hours following a single SC infusion

Secondary objectives

- To assess the safety and tolerability of ND0701 and APO-go® administered by SC infusion over 12 hours

Study Design

Study Design

- Phase 1, randomized, open-label, parallel cross-over pilot study comparing the PK of ND0701 with that of APO-go® in healthy subjects
- Subjects provided written informed consent prior to study enrollment
- Eight healthy male subjects were recruited
- All subjects received an initial dose of ND0701 1 mg/h on Day 1, followed by ND0701 2 mg/h and APO-go® 3 mg/h on subsequent dosing days in a randomized, parallel cross-over design
- In the recommend stretching of ND0701 from an initial dose of 1 mg/h apomorphine HCl (0.1 mg/h) for better tolerability

Study Population

- 18 subjects included in the safety and PK populations
- Mean age of all subjects was 43 years (range, 20-60 years)
- 17 subjects were white, and none were female
- All subjects were male
- Median BMI was 26.6 kg/m² (range, 18.0-32.0 kg/m²)
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Safety

- Safety and tolerability assessments were completed at specified time points until completion of the follow-up visit
- Evaluation of safety parameters associated with a predose AE was performed

Pharmacokinetics

- Following 12 hours of SC infusion with the 3 regimens, plasma concentrations of apomorphine generally rose steadily up to a plateau at approximately 4.5 hours
- Plasma levels fluctuated for the remainder of the duration and then rapidly declined in a mono- or biphasic manner upon infusion completion (Table 1)
- Bioavailability of apomorphine from ND0701 (24.00 mg [2 mg/h]) was comparable to that of APO-go® (24.28 mg [2 mg/h])

Results

Population

18 subjects included in the safety and PK populations. Mean age of all subjects was 43 years (range, 20-60 years). 17 subjects were white, and none were female. All subjects were male. Median BMI was 26.6 kg/m² (range, 18.0-32.0 kg/m²). All 18 subjects were included in the safety and PK populations.

Pharmacokinetics

Following 12 hours of SC infusion with the 3 regimens, plasma concentrations of apomorphine generally rose steadily up to a plateau at approximately 4.5 hours. Plasma levels fluctuated for the remainder of the duration and then rapidly declined in a mono- or biphasic manner upon infusion completion (Table 1). Bioavailability of apomorphine from ND0701 (24.00 mg [2 mg/h]) was comparable to that of APO-go® (24.28 mg [2 mg/h]).

Table 1: Arithmetic Mean (Arithmetic SD) Plasma PK Parameters of ND0701 or APO-go®

| Parameter | ND0701 (25 mg/mL) | APO-go® (10 mg/mL) | Ratio (ND0701/APO-go®)
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<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>236.0 (16.4)</td>
<td>200.0 (13.2)</td>
<td>1.18</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>AUC0-12h (ng•h/mL)</td>
<td>2737.0 (247.3)</td>
<td>2232.0 (176.8)</td>
<td>1.23</td>
</tr>
<tr>
<td>AUC0-inf (ng•h/mL)</td>
<td>3414.0 (285.2)</td>
<td>2732.0 (213.0)</td>
<td>1.25</td>
</tr>
</tbody>
</table>

Safety

Both ND0701 and APO-go® appeared to be safe and well tolerated under the conditions of the study and no serious or treatment-emergent AEs (TEAEs) were reported for any subject (Table 3).

Table 2: Subjects Reporting TEAEs by Treatment

<table>
<thead>
<tr>
<th>TEAEs</th>
<th>ND0701 (2 mg/h)</th>
<th>APO-go® (2 mg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyskinesias</td>
<td>16 (83.3%)</td>
<td>16 (83.3%)</td>
</tr>
<tr>
<td>Allergies</td>
<td>5 (29.4%)</td>
<td>3 (16.7%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (5.6%)</td>
<td>1 (5.6%)</td>
</tr>
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Conclusions

The findings of this pilot study suggest that ND0701 may offer a convenient, safe, and more tolerable alternative to available apomorphine HCl drug products.

Disclosures

Liat Adar, Cécile Durlich, Oron Yacoby-Zeevi, Dan Fishelovitch, and Sheila Oren are employees of NeuroDerm, Ltd.
Please contact Sheila Oren (sheila@neuroderm.com) for more information.
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References