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

Liat Adar, PhD; Cécile Durlach, MD, MSc; Oron Yacoby-Zeevi, PhD; Dan Fishelovitch, PhD; Sheila Oren, MD, MBA

NeuroDerm Ltd., Rehovot, Israel

Introduction

- ND0701 (apomorphine base) is a new, concentrated formulation of apomorphine for continuous subcutaneous (SC) infusion, in development for the treatment of motor fluctuations in patients with Parkinson's disease (PD) who are not sufficiently controlled with oral antiparkinson medication (NeuroDerm Ltd., Rehovot, Israel)
- Commercial apomorphine formulations, such as APO-go® (Brittania Pharmaceuticals Ltd., Berkshire, UK), are based on apomorphine-HCl formulations. APO-go® is supplied as 5 mg/mL and 10 mg/mL solutions.[1] Because of the "high volume" of the solution and recommended hourly infusion rates ranging between 1 mg and 4 mg, delivery is limited to syringe pumps, which may pose 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 patch pump device. Based on preclinical studies, ND0701 is safe for a duration of up to 20 hours per infusion site (data on file)
- The study reported here evaluated ND0701 and APO-go® pharmacokinetics (PK), relative bioavailability, and safety/tolerability

Study Objectives

Primary objectives

- To evaluate the PK of 12-hour SC infusions of ND0701 and APO-go®
- To assess the relative bioavailability of ND0701 and APO-go® after 12 hours following a single SC infusion dose

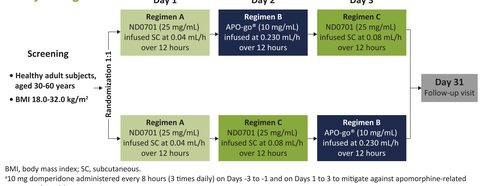
Secondary objective

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

Methods

Study Design

Study Design[a,b]



BMI, body mass index; SC, subcutaneous.
[1]10 mg domperidone administered every 8 hours (3 times daily) on Days -3 to -1 and on Days 1 to 3 to mitigate against apomorphine-related nausea and vomiting.
[b]Dosing was separated by a minimum washout of 12 hours between the end of one infusion and commencement of the next.

- Phase 1, randomized, open-label, partial cross-over, pilot study comparing the PK of ND0701 with that of APO-go® in 18 healthy subjects
- Subjects provided written informed consent prior to study enrollment
- All subjects received an initial dose of ND0701 1 mg/h on Day 1, followed by ND0701 2 mg/h and APO-go® 2 mg/h on subsequent dosing days in a randomized, partial cross-over manner, based on the recommendation of titrating APO-go® from an initial rate of 1 mg/h apomorphine HCl (0.1 mL) for better tolerability
- Subjects were randomized into 2 sequences to receive 3 consecutive doses of the following treatments (ie, ABC or ACB)
  - **Regimen A:** ND0701 (25 mg/mL) infused SC at 0.04 mL/h (1 mg/h) over 12 hours; total dose of 12.00 mg apomorphine free base and total volume of 0.48 mL
  - **Regimen B:** APO-go® (10 mg/mL) infused at 0.230 mL/h (2 mg/h) over 12 hours; total dose of 27.60 mg APO-go® (equivalent to 24.28 mg apomorphine free base) and total volume of 2.76 mL
  - **Regimen C:** ND0701 infused SC at 0.08 mL/h (2 mg/h) over 12 hours; total dose of 24.00 mg apomorphine free base and total volume of 0.96 mL
- PK blood samples were collected predose and at predetermined time points up to 24 hours after start of final infusion for determination of apomorphine plasma concentrations
- Safety and tolerability assessments were completed at specified time points until completion of the follow-up visit. Evaluation of safety parameters included analysis of adverse events (AEs), laboratory variables, vital signs, electrocardiograms (ECGs), infusion site reactions, and physical examination findings

Subjects

- Subjects were screened for eligibility to participate in the study up to 28 days before dosing
- Key inclusion criteria included
  - Healthy men and nonpregnant, nonlactating healthy women, aged 30 to 60 years
  - Body mass index of 18.0 to 32.0 kg/m^2; if outside that range, considered not clinically significant by the investigator
- Subjects were considered evaluable if they had
  - Received the reference APO-go® regimen (Regimen B) and both test ND0701 regimens (Regimens A and C)
  - Completed the PK sampling schedule up to 20 hours after start of infusion for each dose

Results

Population

- All 18 subjects were included in the safety and PK populations. Mean age of all subjects was 49.1 years (range, 34-60 years), 17 subjects were white, 2/3 of all subjects were male, and mean BMI was 26.6 m/kg^2 (range, 20.7-30.9)
- PK analysis datasets were defined for formal statistical analysis and comprised 16 subjects as 2 subjects withdrew from the study

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 infusion 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 2)

Table 1: Arithmetic Mean (Arithmetic SD) Plasma PK Parameters of Apomorphine Following a Single 12-Hour Subcutaneous Infusion of ND0701 or APO-go® to Healthy Subjects

	Regimen A ND0701 (1 mg/h) 12.00 mg n=18	Regimen B APO-go® (2 mg/h) 24.28 mg n=17	Regimen C ND0701 (2 mg/h) 24.00 mg n=16
C_{max}, ng/mL	5.12 (2.94)	9.22 (2.52)	10.1 (5.44)
C_{max}/D, mean (SD)	0.427 (0.245)	0.380 (0.104)	0.421 (0.226)
$AUC_{0\text{-last}}$, ng•h/mL	33.4 (12.6)[a]	86.1 (25.8)	79.7 (38.7)
$AUC_{0\text{-last}}$/D, mean (SD)	2.79 (1.05)[a]	3.55 (1.06)	3.32 (1.61)
$AUC_{0\text{-inf}}$, ng•h/mL	33.6 (12.6)[a]	87.9 (27.0)	92.0 (41.0)[b]
$AUC_{0\text{-inf}}$/D, mean (SD)	2.80 (1.05)[a]	3.62 (1.11)	3.83 (1.71)[b]

C_{max}, maximum observed concentration; C_{max}/D, maximum observed concentration dose corrected; AUC, area under the concentration-time curve; $AUC_{0\text{-last}}$, AUC from 0 time to last measurable concentration; $AUC_{0\text{-last}}$/D, AUC from 0 time to last measurable concentration dose corrected; $AUC_{0\text{-inf}}$, AUC from 0 time extrapolated to infinity; $AUC_{0\text{-inf}}$/D, AUC from 0 time extrapolated to infinity dose corrected.
[a]One subject was excluded due to incomplete PK profile for one or both relevant regimens.
[b]Five subjects were either excluded due to incomplete PK profile for one or both relevant regimens or Rsq of regression was <0.9 for one or both relevant regimens.

Table 2: Statistical Analysis of Relative Bioavailability Comparison Between ND0701 24.00 mg (Regimen C) and APO-go® 24.28 mg (Regimen B) (for dose corrected C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$)

	Regimen C		Regimen B			
Parameter	n	Adjusted Geometric Mean[a]	n	Adjusted Geometric Mean	Ratio[b] (%)	90% CI[c] (%)
C_{max}/D, ng/mL/mg	16	0.379	16	0.365	103.76	92.04, 116.99
$AUC_{0\text{-last}}$/D, ng•h/mL/mg	16	2.99	16	3.36	88.94	74.15, 106.68
$AUC_{0\text{-inf}}$/D, ng•h/mL/mg	11	3.75	11	3.74	100.17	77.49, 129.50

C_{max}/D, maximum observed concentration dose corrected; $AUC_{0\text{-last}}$/D, area under the curve from 0 time to last measurable concentration dose corrected; $AUC_{0\text{-inf}}$/D, area under the curve from 0 time extrapolated to infinity dose corrected.
[a]From model.
[b]Ratio of adjusted geometric mean, ie, ND0701/APO-go® (Regimen C/Regimen B).
[c]CI = confidence interval for ratio of adjusted geometric means.

- Statistical analysis confirmed peak and total exposures were similar for ND0701 and APO-go®. Differences were not statistically significant at the 10% level for any of the dose-corrected C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ parameters; P = 0.60, 0.28, and 0.99, respectively
- Statistical analysis of dose-corrected parameters confirmed peak and total exposures were similar for ND0701 doses with GMRs (90% CIs) for 24.00 mg/12.00 mg of 99.84% (87.87%, 113.43%), 113.65% (92.46%, 139.71%), and 114.13% (92.14%, 141.38%), for C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$, respectively, indicating close to dose proportional increase. Difference was not statistically significant at the 10% level for any of these dose-corrected parameters; P = 0.98, 0.29, and 0.29, respectively.

Safety

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

Table 3: Subjects Reporting TEAEs by Severity

	Subjects Reporting Treatment-Emergent Adverse Events (Severity), n (%)			
Regimen	Mild	Moderate	Severe	Total
A (n=18)	13 (72.2)	2 (11.1)	0	15 (83.3%)
B (n=17)	6 (35.3)	5 (29.4)	0	11 (64.7%)
C (n=16)	6 (37.5)	2 (12.5)	0	8 (50.0%)

Regimen A = ND0701 1 mg/h (12.00 mg apomorphine), Regimen B = APO-go® 2 mg/h (24.28 mg apomorphine), Regimen C = ND0701 2 mg/h (24.00 mg apomorphine); n = number of subjects.
Subjects received Regimen A on Day 1 followed by Regimen B or C on Days 2 and 3 in a randomized order. The incidence of subjects reporting adverse events overall, by system organ class, is calculated counting multiple occurrences once per subject for each regimen.

- General
  - Overall incidence of TEAEs was highest following ND0701 1 mg/h, as expected, because of the initial exposure to apomorphine and respective absence of tolerance; 15 (83.3%) subjects reported 32 TEAEs
  - Lowest incidence of TEAEs was observed following ND0701 2 mg/h with 8 (50.0%) subjects reporting 13 TEAEs; 11 (64.7%) subjects reported 29 TEAEs following APO-go® 2 mg/h. Majority of TEAEs were assessed as treatment related
  - TEAEs were most frequently reported in the gastrointestinal and nervous system disorders system organ classes. The most frequently reported events within these categories were nausea, vomiting, dizziness, and somnolence; the lowest incidence was observed following ND0701 2 mg/h
  - Majority of TEAEs were mild in severity and no subject experienced a severe TEAE
  - Majority of vital signs assessments were not considered to be clinically significant; across regimens, hypotension and orthostatic hypotension were reported for 2 subjects each, which all resolved within 2 hours of onset
  - All postdose physical examinations were normal except for a muscle spasm associated with a predose AE
  - There were no clinically significant findings in any laboratory assessments or ECGs
- Local
  - Erythema, swelling, and pain were noted at infusion sites for a few subjects across regimens, with no notable difference in incidence or severity between the ND0701 2 mg/h sites and the APO-go® 2 mg/h sites; all incidents resolved by the 28-day follow-up visit
  - Infusion site nodules were reported more frequently and their incidence and severity were higher at sites administered APO-go® 2 mg/h (10 small, 1 medium, and 1 severe nodule) compared with sites administered ND0701 2 mg/h (6 small nodules)
    - More nodules were still evident at the 28-day follow-up visit following administration of APO-go® 2 mg/h (n=4) compared with N0701 2 mg/h (n=1)
  - No subject experienced a TEAE associated with clinically significant erythema, swelling, pain, or nodules at any infusion sites, except for 1 subject who experienced a severe nodule (44 mm × 8 mm in size) at the APO-go® 2 mg/h site
  - These results align with findings from previous preclinical studies that demonstrated greater local safety and tolerability with comparable PK to APO-go®[2]

Conclusions

- Under the experimental conditions, ND0701 exhibited similar bioavailability and good safety and tolerability when compared with APO-go®
- The findings of this pilot study suggest that ND0701 may offer a convenient, easier-to-use, and more tolerable alternative to available apomorphine-HCl drug products
- Further clinical studies with ND0701 are planned

References

1. APO-go®. Summary of Product Characteristics, 2017. https://www.apo-go.com/hcp/apo-go-pump.
2. Shaltiel-Karyo R, Tsarfati Y, Rubinski A, et al. Magnetic resonance imaging as a noninvasive method for longitudinal monitoring of infusion site reactions following administration of a novel apomorphine formulation. *Toxicol Pathol*. 2017 Jan 1:192623317706111. Epub ahead of print.

Disclosures

Liat Adar, Cécile Durlach, 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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