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ORIGINAL RESEARCH ARTICLE

A Novel Once-Daily Fixed-Dose Combination of Memantine Extended Release and Donepezil for the Treatment of Moderate to Severe Alzheimer's Disease: Two Phase I Studies in Healthy Volunteers

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Abstract

Background Combining two standard-of-care medications for Alzheimer's disease (AD) into a single once-daily dosage unit may improve treatment adherence, facilitate drug administration, and reduce caregiver burden. A new fixed-dose combination (FDC) capsule containing 28 mg memantine extended release (ER) and 10 mg donepezil was evaluated for bioequivalence with co-administered commercially available memantine ER and donepezil, and for bioavailability with regard to food intake.

Methods Two phase I, single-dose, randomized, open-label, crossover studies were conducted in 18- to 45-year-old healthy individuals. In MDX-PK-104 study, fasting participants ($N = 38$) received co-administered memantine ER and donepezil or the FDC. In MDX-PK-105 study, participants ($N = 36$) received three treatments: intact FDC taken while fasting or after a high-fat meal, or FDC contents sprinkled on applesauce while fasting. Standard pharmacokinetic parameters for memantine and donepezil were calculated from the plasma concentration time-curve using non-compartmental analyses. Linear mixed-effects models were used to compare: (a) FDC versus co-administered individual drugs; (b) FDC fasted versus with food; and (c) FDC sprinkled on applesauce versus FDC intact, both fasted. Safety parameters were also evaluated.

Results The FDC capsule was bioequivalent to co-administered memantine ER and donepezil. There was no significant food effect on the bioavailability of the FDC components. There were no clinically relevant differences in time to maximum plasma concentration or safety profiles across treatments.

Conclusions An FDC capsule containing 28 mg memantine ER and 10 mg donepezil is bioequivalent to commercially available memantine ER and donepezil, and bioavailability is not affected by food intake or sprinkling of capsule contents on applesauce.

Key Points

A fixed-dose combination consisting of memantine extended-release and donepezil is bioequivalent to the commercially available component drugs.

This can be administered with or without food, the capsule swallowed intact or with its contents sprinkled on soft food.

The use of this fixed-dose combination in patients with moderate to severe Alzheimer's disease may facilitate drug administration, improve treatment adherence, and reduce caregiver burden.

1 Introduction

The most recent best-practice models of care in Alzheimer's disease (AD) favor a team-based approach that focuses on both the patient and the caregiver [1] and includes strategies

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aimed at better medication management and improved adherence [2, 3]. Non-adherence in patients with AD, reported in up to 42 % of patients [4], is caused by several factors, including forgetfulness, high caregiver burden, high pill burden, complex medication regimens, and swallowing difficulties (dysphagia) [4–7]. Patients with moderate to severe AD take on average six different medications per day [4], which frequently includes two anti-dementia agents: memantine, a non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist [8], and a cholinesterase inhibitor (ChEI: donepezil, galantamine, or rivastigmine) [9].

Memantine is approved for patients in the moderate to severe stages of the disease in the USA and around the world, while donepezil, the most frequently prescribed ChEI, is approved for the entire severity range of AD in the USA, Canada, Japan, and several other countries (in the EU, however, it is approved only for mild to moderate AD). In clinical practice, treatment is usually initiated with a ChEI (most frequently donepezil) and memantine is added as the disease progresses. In randomized, placebo-controlled trials, both drugs were shown to improve cognition, behavior, daily functioning, and global clinical status [8, 9], and trials using both immediate-release [10] and extended-release (ER) memantine [11] demonstrated efficacy and good tolerability in patients already receiving donepezil. Co-prescribing memantine and donepezil has been shown to increase medication persistence [12], but co-administration of these two drugs also increases pill burden. Availability of a once-daily fixed-dose combination (FDC) consisting of memantine and donepezil, in a formulation that could be sprinkled on soft food (e.g., applesauce) if needed, could reduce pill burden, simplify medication management, improve patient safety for those who have swallowing difficulties, and facilitate caregiving.

We report the results of two phase I clinical trials (MDX-PK-104 and MDX-PK-105), conducted to determine: (a) whether a once-daily FDC consisting of 28 mg memantine ER and 10 mg donepezil is bioequivalent to co-administered commercially available memantine ER and donepezil; (b) whether bioavailability of FDC components is affected by food intake; and (c) whether the intact FDC capsule is bioequivalent to capsule contents sprinkled on applesauce. To the best of our knowledge, this represents the first assessment of an FDC consisting of two approved medications for AD.

2 Methods

2.1 Study Population

Participants in both trials were healthy men and women between 18 and 45 years of age. Inclusion criteria included an agreement to use an effective method of contraception and not become pregnant or have their partners become pregnant during the study, nonsmoker status (never smoked or had not smoked within the previous 2 years), body mass index (BMI) $\geq$18 and $\leq$30 kg/m^2, and sitting pulse rate $\geq$50 and $\leq$100 beats/min during vital signs assessments. Exclusion criteria included known hypersensitivity to memantine, donepezil, or other ChEI or NMDA receptor antagonists, clinically significant disease state in any body system or abnormal and clinically significant results at screening, sitting systolic BP $\geq$140 or $\leq$90 mmHg, or a sitting diastolic BP $\geq$90 or $\leq$50 mmHg at screening, abnormal ECG results at screening, a history of alcohol or substance abuse within the previous 5 years or a positive test for alcohol or drugs of abuse at screening, consumption of any grapefruit-containing products within 14 days, caffeine within 48 h, or alcohol within 72 h before investigational product administration, taking of any concomitant medications, including over-the-counter medications, within 14 days or hormonal drug products within 30 days before study, or prior exposure to memantine or donepezil, or previous participation in an investigational study of memantine or donepezil.

2.2 Study Design

MDX-PK-104 was a phase I, single-center, randomized, open-label, crossover study. Fasting participants ($N = 38$) were randomly assigned to one of two treatment sequences (AB or BA) with a 21-day washout period between treatments. Treatment groups were defined as Treatment A (co-administered commercially available memantine HCl ER [Namenda XR® 28 mg, Actavis, Inc., St Louis, MO, USA] and donepezil HCl [Aricept® 10 mg, Eisai, Inc., Research Triangle Park, NC, USA]) and Treatment B (FDC consisting of 28 mg memantine ER and 10 mg donepezil: approved in the USA as Namzaric™ and manufactured by Actavis, Inc., St Louis, MO, USA).

MDX-PK-105 was a phase I, single-center, randomized, open-label, three-period crossover study in which participants ($N = 36$) were randomized to one of six treatment sequences (ABC, ACB, BAC, BCA, CAB, or CBA) with a 21-day washout period between each treatment. The 21-day duration of the washout was determined based on the terminal elimination half-lives of 60–80 h and 70 h for memantine and donepezil, respectively, and based on clinical experience to avoid carryover effects. Treatment A was defined as the intact FDC capsule taken while fasting, Treatment B as the intact FDC capsule taken following a high-fat meal, and Treatment C as FDC capsule contents sprinkled on applesauce and administered while fasting.

2.3 Sample Collection and Analysis

For both studies, blood samples were collected starting on Day 1 of each treatment period at hour 0 (pre-dose) and at 1, 2, 3, 4, 6, 8, 10, 12, 14, 24, 30, 36, 48, 72, 96, 120, 168, 216, and 264 h after dosing. Plasma samples were analyzed for memantine and donepezil concentrations using high-performance liquid chromatography coupled with tandem mass spectrometry (HPLC MS/MS), with a lower limit of quantification of 0.5 ng/mL for both analytes. Briefly, plasma samples (100 μL) were combined with 25 μL of internal standard spiking solution (75/75 ng/mL of [2H6] memantine/[2H7] donepezil in 0.01 N hydrochloric acid) and 200 μL of ammonium hydroxide in 96-well plate wells, and thoroughly mixed in ThermoMixer® (Eppendorf, Germany) for 5 min. The analytes and their internal standards were then extracted using methyl *tert*-butyl ether (MTBE). After evaporation of the isolated organic layer, the dry residue was reconstituted in 200 μL of formic acid-water-methanol acetonitrile solution (2:1200:500:300, by volume). The addition of MTBE, mixing in support of extraction, MTBE organic layer transfer, and dry residue reconstitution were all accomplished using Tomtec® liquid handler (Hamden, CT, USA). A 20-μL aliquot of the final solution was directly injected into the HPLC-MS/MS system. Chromatographic separation was achieved using an Agilent Zorbax XDB-C18 column (50 × 4.6 mm; 1.8 μm; Agilent Technologies, Santa Clara, CA, USA) under isocratic conditions with a mobile phase of formic acid-water-methanol-acetonitrile (2:1000:600:400, by volume) and a flow rate of 0.5 mL/min. Memantine and donepezil were detected using an MDS Sciex API 3000 mass spectrometer (Applied Biosystems/Life Technologies, Grand Island, NY, USA). Standard pharmacokinetic parameters for memantine and donepezil, calculated from the plasma concentration-time data using non-compartmental analyses, included area under the plasma concentration-time curve (AUC) from time zero to time of last quantifiable concentration (AUC_{0-t}; calculated using the linear trapezoidal rule), AUC from time zero to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), and terminal elimination half-life ($t_{½}$).

Safety and tolerability evaluations consisted of adverse event (AE) monitoring, vital signs and clinical laboratory evaluations (hematology, blood chemistry, urinalysis), electrocardiogram (ECG) parameters, physical examinations, and results of the Columbia-Suicide Severity Rating Scale (C-SSRS) [13], a clinician-administered survey on suicidal ideation and behavior that was assessed at baseline and on day 4 of each treatment period, and at the end of the study. AEs were monitored for up to 30 days after the last dose received. AE severity was assessed by the Principal Investigator or Sub-Investigator according to the following scale:

Mild: Minor awareness of signs or symptoms that are easily tolerated without specific medical intervention.

Moderate: Discomfort that interferes with usual activities and may require minimal intervention.

Severe: Significant signs or symptoms that are incapacitating with an inability to work or perform routine activities and/or that require medical intervention.

2.4 Statistical Analyses

In both studies, two populations were considered for statistical analyses. The pharmacokinetic population included all participants who completed the study and had evaluable pharmacokinetic parameters. Individuals who vomited within 24 h from investigational product administration were excluded from pharmacokinetic analyses of memantine; those who vomited within twice the median t_{max} of donepezil were excluded from the analyses of donepezil. The safety population included all participants who received at least one dose of any treatment. C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for memantine and donepezil were compared by means of a linear mixed-effects model. Bioequivalence of memantine and donepezil delivered via different formulations or modes of administration (study MDX-PK-104: Treatment B vs. A; study MDX-PK-105: Treatment B vs. A, and Treatment C vs. A) was established if the 90 % confidence intervals (90 % CIs) for the ratio of geometric least squares means (GLSM) of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were contained within the range 0.80–1.25. The differences in median t_{max} values were compared using the Wilcoxon signed-rank test.

3 Results

3.1 Baseline Characteristics and Trial Discontinuations

Thirty-eight individuals were enrolled in the MDX-PK-104 trial, of which 31 (81.6 %) completed the study. Two (5.3 %) participants discontinued the trial due to AEs, one (2.6 %) withdrew consent, one (2.6 %) was lost to follow-up, and three (7.9 %) discontinued for other reasons. In MDX-PK-105, out of 36 individuals enrolled, 33 (91.7 %) completed the study. The three discontinuations were due to AEs, protocol violation, and other reasons (one [2.8 %] for each). Demographic characteristics at baseline were similar between the two trials (Table 1), with the majority of participants being male, White, and with a mean age close to 30 years.

Table 1 Baseline characteristics (safety population)

Parameter	MDX-PK-104 ($N = 38$)	MDX-PK-105 ($N = 36$)
Age, years	29.8 ± 7.7[a]	27.3 ± 5.3[a]
Women, *n* (%)	13 (34.2)	11 (30.6)
Men, *n* (%)	25 (65.8)	25 (69.4)
White, *n* (%)	22 (57.9)	25 (69.4)
Hispanic, *n* (%)	12 (31.6)	16 (44.4)
BMI, kg/m^2	25.9 ± 3.7[a]	25.4 ± 2.9[a]

BMI body mass index

[a] Mean ± standard deviation

3.2 Study MDX-PK-104

In the trial MDX-PK-104, the number of participants excluded from the pharmacokinetic analysis of memantine and donepezil was 15 and 14, respectively. Seven were excluded due to trial discontinuation (Treatment A, $n = 5$; Treatment B, $n = 2$), eight experienced vomiting within pre-specified time windows for both memantine and donepezil (see Sect. 2.4, Methods), of which one also discontinued the trial, and one experienced vomiting within the pre-specified time window for memantine only.

The mean plasma concentration-time profiles for both memantine and donepezil were similar between treatments (Fig. 1), as were the pharmacokinetic parameters for both drugs (Table 2). For plasma memantine, median t_{max} values were 14 h for Treatment A (co-administration) and 24 h for Treatment B (FDC), but the difference was not statistically significant ($P = 0.27$; Table 2). In addition, the 90 % CI values for GLSM ratios of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ indicate bioequivalence between commercially available, co-administered drugs and the FDC.

The total treatment-emergent adverse event (TEAE) rates were similar between treatments (co-administration

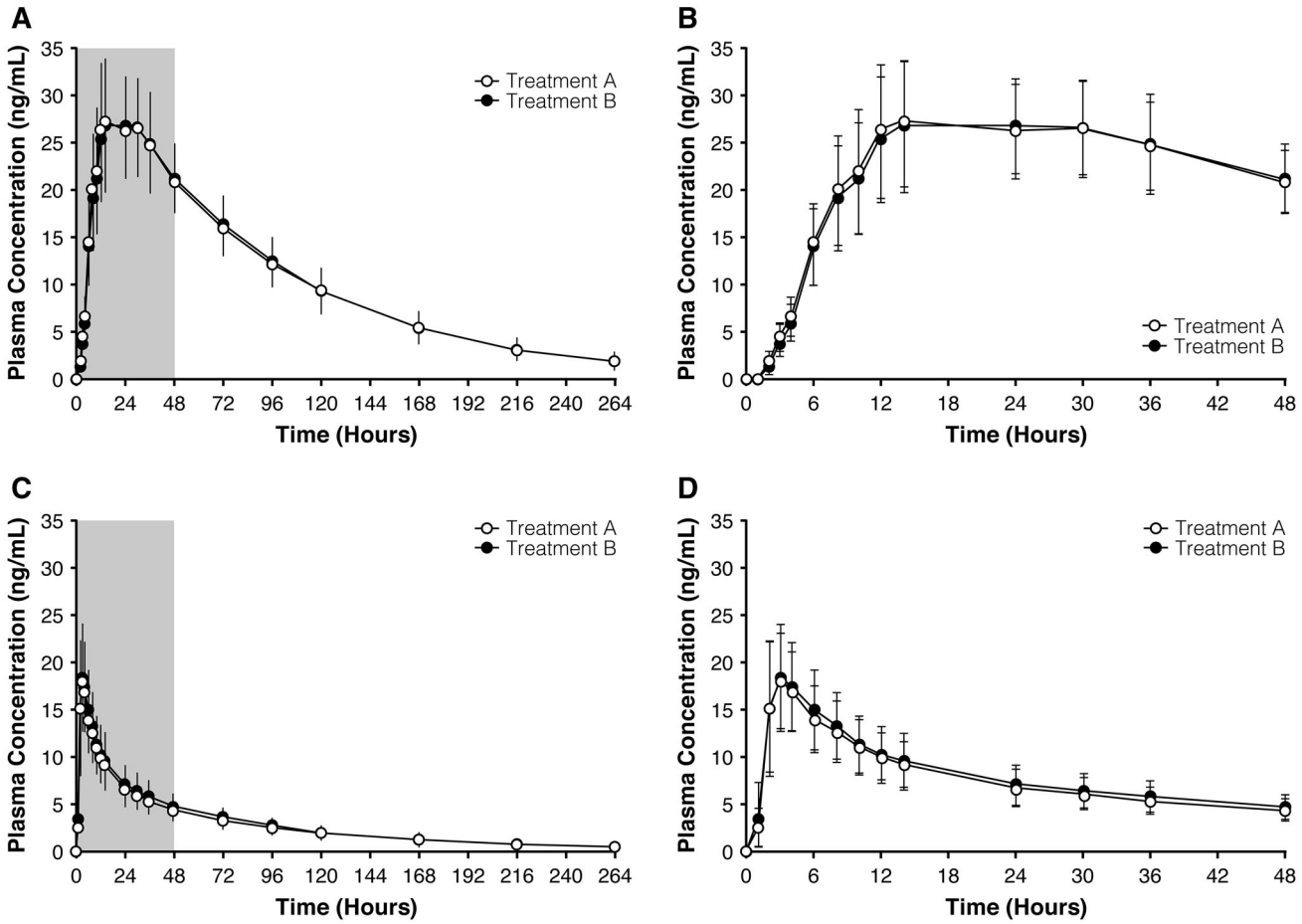

Fig. 1 Study MDX-PK-104: memantine and donepezil concentration profiles following a single dose of memantine extended release (ER) plus donepezil (Treatment A) or a fixed-dose combination (FDC) (Treatment B). **a**, **b** Mean memantine plasma concentration-time profile and **c**, **d** mean donepezil plasma concentration-time profile. *Panels* on the *left* **a**, **c** represent plasma concentrations ranging from 0 to 264 h; the *shaded areas* indicate the time windows augmented in *panels* **b**, **d** on the *right* (0–48 h)

Table 2 Study MDX-PK-104: pharmacokinetic parameters of memantine and donepezil (pharmacokinetic population)

Parameter		Memantine		Donepezil	
		Treatment A[a] ($n = 23$)	Treatment B[a] ($n = 23$)	Treatment A[a] ($n = 24$)	Treatment B[a] ($n = 24$)
C_{max}	ng/mL, mean ± SD	28.5 ± 6.3	28.5 ± 6.3	19.3 ± 5.5	19.1 ± 5.3
	GLSM ratio (90 % CI)	1.00 (0.97–1.04)		0.99 (0.93–1.04)	
AUC_{0-t}	ng·h/mL, mean ± SD	2782 ± 553	2798 ± 536	748 ± 227	791 ± 230
	GLSM ratio (90 % CI)	1.01 (0.98–1.04)		1.06 (1.04–1.08)	
$AUC_{0-\infty}$	ng·h/mL, mean ± SD	2966 ± 643	2966 ± 609	838 ± 278	881 ± 269
	GLSM ratio (90 % CI)	1.00 (0.97–1.04)		1.06 (1.03–1.08)	
t_{max}	h, median (min, max)	14 (12, 36)	24 (12, 36)	3.0 (2.0, 4.1)	3.0 (2.0, 6.0)
	Differences in median (P value)[b]	10 (0.27)		0 (0.99)	
$t_{½}$	h, mean ± SD	62 ± 9.3	60 ± 8.8	69 ± 24	69 ± 21

AUC area under the plasma concentration-time curve, AUC_{0-t} AUC from time zero to time of last quantifiable concentration, $AUC_{0-\infty}$ AUC from time zero to infinity, C_{max} maximum plasma concentration, *CI* confidence interval, *FDC* fixed-dose combination, *GLSM ratio* geometric least squares mean ratio of Treatments B/A, *max* maximum, *min* minimum, *SD* standard deviation, $t_{½}$ terminal elimination half-life, t_{max} time to C_{max}

[a] Treatment A indicates commercially available memantine extended release (28 mg) and donepezil (10 mg); Treatment B indicates the FDC

[b] P value calculated using the Wilcoxon signed-rank test

Table 3 Study MDX-PK-104: most common treatment-emergent adverse events (TEAEs) (>10 % of participants receiving either treatment; safety population), n (%)

Adverse event	Treatment A[a] ($n = 36$)	Treatment B[a] ($n = 34$)
Any TEAE	28 (77.8)	26 (76.5)
Nausea	19 (52.8)	22 (64.7)
Dizziness	13 (36.1)	14 (41.2)
Vomiting	7 (19.4)	8 (23.5)
Feeling hot	2 (5.6)	6 (17.7)
Abdominal pain	3 (8.3)	4 (11.8)
Headache	5 (13.9)	4 (11.8)

[a] Treatment A indicates commercially available memantine ER (28 mg) and donepezil (10 mg); Treatment B indicates the fixed-dose combination

77.8 %; FDC 76.5 %), with the most common TEAEs being nausea, dizziness, vomiting, feeling hot, abdominal pain, and headache (Table 3). All TEAEs were mild (80.7 %) or moderate (19.3 %) in severity. A feeling of body temperature change was reported in 8.3 % of participants receiving memantine-donepezil co-administration (Treatment A) and in none of the participants receiving the FDC (Treatment B; data not shown), although feeling hot was reported in 5.6 and 17.7 % of participants, respectively (Table 3). All other TEAEs were reported in no more than two individuals per treatment. No deaths or serious adverse events (SAEs) were reported. Additionally, no clinically meaningful differences were observed in vital sign, clinical laboratory, ECG, and physical examination parameters. The C-SSRS evaluations did not indicate suicidal ideation or behavior in any of the participants.

3.3 Study MDX-PK-105

In the trial MDX-PK-105, 23 participants were included in the pharmacokinetic analysis of food effects (intact capsule administered with or without food) and 21 in the analysis of intact capsule versus sprinkled contents. Three individuals were excluded from pharmacokinetic analyses due to trial discontinuation (one from each treatment). Because of vomiting (based on both memantine and donepezil criteria: see Sect. 2.4, Methods), ten were excluded from the Treatment A versus Treatment B comparison and 12 from the Treatment A versus Treatment C comparison.

The mean plasma concentration-time profiles for both memantine and donepezil were similar between treatments (Fig. 2), as were the pharmacokinetic parameters of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ (Table 4). For memantine, median t_{max} values associated with Treatment B (intact capsule, high-fat meal) and Treatment C (capsule contents sprinkled on applesauce, fasted condition) were both significantly shorter (14 h for both) than the value observed with Treatment A (intact capsule, fasted condition; 24 h;

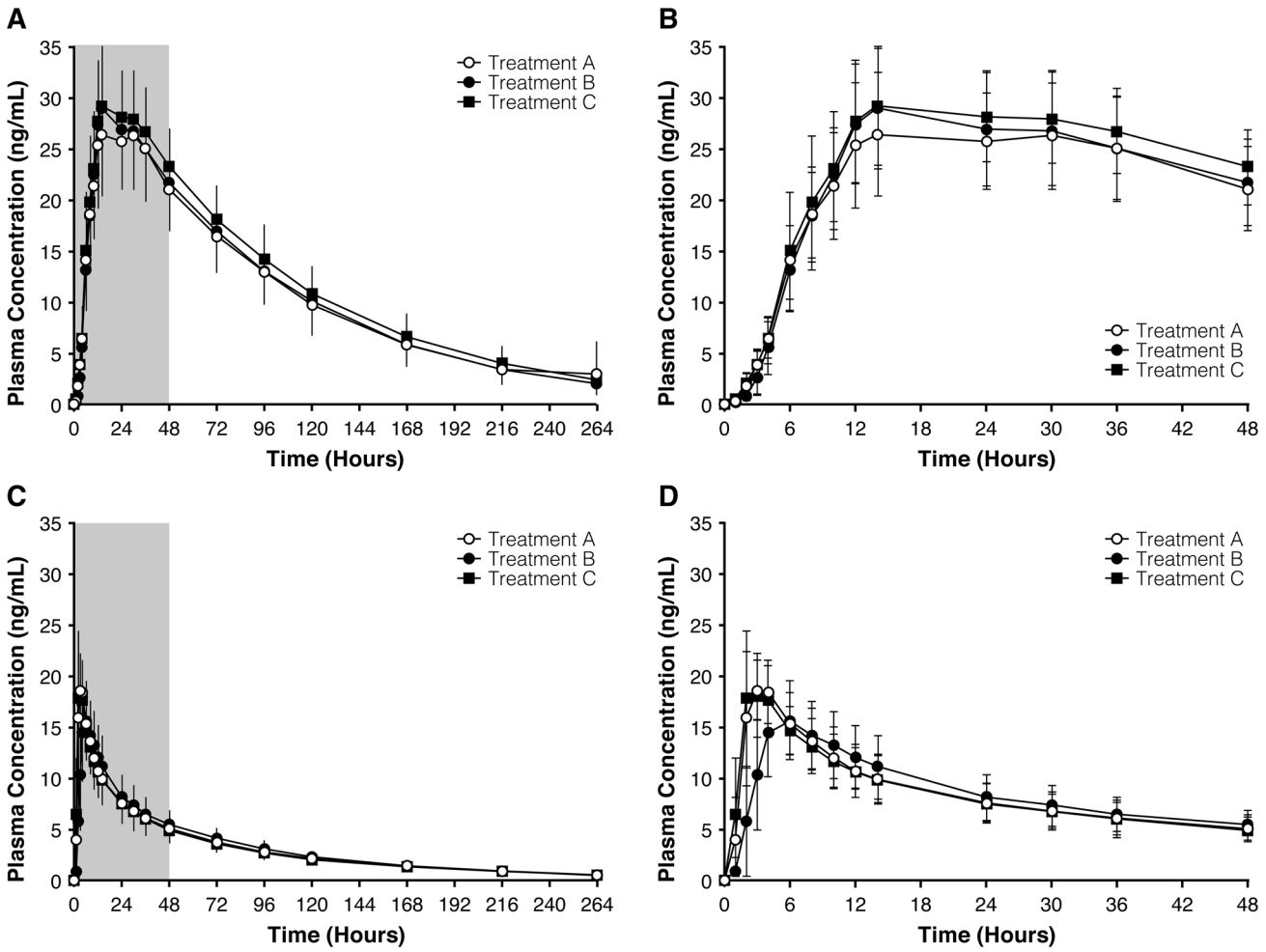

Fig. 2 Study MDX-PK-105: memantine and donepezil concentration profiles following a single dose of memantine extended release (ER) plus donepezil fixed-dose combination (FDC) taken while fasting (Treatment A), after a high-fat meal (Treatment B), or capsule contents sprinkled on applesauce while fasting (Treatment C). **a**, **b** Mean memantine plasma concentration-time profile and **c**, **d** mean donepezil plasma concentration-time profile. *Panels* on the *left* **a**, **c** represent plasma concentrations ranging from 0 to 264 h; the *shaded areas* indicate the time windows augmented in *panels* **b**, **d** on the *right* (0–48 h)

$P = 0.014$ vs. Treatment B and $P = 0.012$ vs. Treatment C; Table 4). For donepezil, Treatment B was associated with a significantly longer t_{max} than Treatment A (6 vs. 3 h; $P < 0.001$; Table 4). The 90 % CI values for GLSM ratios of C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ indicate bioequivalence between the intact capsule taken while fasting or after a high-fat meal, and between the intact capsule and capsule contents sprinkled on applesauce, both taken while fasting (Table 4).

The overall TEAE rates ranged from 44.1 % (intact capsule, high-fat meal) to 67.6 % (capsule contents sprinkled on applesauce, fasted), with the most common TEAEs being nausea, dizziness, vomiting, headache, and abdominal discomfort (Table 5). All reported TEAEs were mild (74.7 %) or moderate (25.3 %) in severity. There were no deaths during the study; one SAE (ectopic pregnancy) was reported, but it was deemed not related to the investigational product. No clinically meaningful differences were observed in vital sign, clinical laboratory, ECG, and physical examination parameters, and C-SSRS evaluations did not indicate suicidal ideation or behavior in any of the participants.

4 Discussion

Results of these two phase I studies indicate that the memantine-donepezil FDC is bioequivalent with commercially available co-administered memantine ER (28 mg) and donepezil (10 mg), and that administration of the intact FDC capsule while fasting is bioequivalent with administration after a high-fat meal or after capsule contents were

Table 4 Study MDX-PK-105: pharmacokinetic parameters of memantine and donepezil (pharmacokinetic population)

Parameter		Memantine			Donepezil		
		Treatment A[a] ($n = 23$)	Treatment B[a] ($n = 23$)	Treatment C[a] ($n = 21$)	Treatment A[a] ($n = 23$)	Treatment B[a] ($n = 23$)	Treatment C[a] ($n = 21$)
C_{max}	ng/mL, mean ± SD	27.9 ± 5.6	30.0 ± 6.4	30.1 ± 5.4	20.1 ± 3.9	17.3 ± 3.0	20.3 ± 4.4
	GLSM ratio (90 % CI)		1.07[b,c] (0.99–1.15)	1.08[d,e] (1.01–1.16)		0.86[b] (0.83–0.90)	0.99[c] (0.93–1.05)
AUC_{0-t}	ng·h/mL, mean ± SD	2865 ± 617	2913 ± 671	3113 ± 633	803 ± 190	847 ± 205	803 ± 220
	GLSM ratio (90 % CI)		1.01[b,c] (0.94–1.09)	1.07[d,e] (0.99–1.15)		1.05[b] (1.01–1.10)	0.98[c] (0.94–1.03)
$AUC_{0-\infty}$	ng·h/mL, mean ± SD	3056 ± 736	3096 ± 762	3337 ± 798	875 ± 209	916 ± 219	874 ± 244
	GLSM ratio (90 % CI)		1.01[b,c] (0.94–1.10)	1.09[d,e] (1.00–1.19)		1.04[b] (1.00–1.09)	0.98[c] (0.94–1.03)
t_{max}	h, median (min, max)	24 (12, 36)	14 (12, 36)	14 (12, 36)	3.0 (2.0, 4.1)	6.0 (2.0, 10)	2.1 (2.0, 4.0)
	Differences in median (P value)[f]		10[c] (0.014)	10[c] (0.012)		3[e] (<0.001)	0.93[e] (0.278)
$t_{½}$	h, mean ± SD	62 ± 13[c]	60 ± 12	63 ± 16	67 ± 12	67 ± 10	65 ± 13

AUC area under the plasma concentration-time curve, AUC_{0-t} AUC from time zero to time of last quantifiable concentration, $AUC_{0-\infty}$ AUC from time zero to infinity, C_{max} maximum plasma concentration, *CI* confidence interval, *FDC* fixed-dose combination, *GLSM* geometric least squares mean, *max* maximum, *min* minimum, *SD* standard deviation, $t_{½}$ terminal elimination half-life, t_{max} time to C_{max}

[a] Treatment A indicates intact memantine extended release (ER) plus donepezil FDC capsule taken while fasting; Treatment B indicates intact FDC capsule taken following a high-fat meal; Treatment C indicates FDC capsule contents sprinkled on applesauce and taken while fasting

[b] Ratio of Treatments B/A

[c] $n = 22$

[d] Ratio of Treatments C/A

[e] $n = 20$

[f] P value calculated using the Wilcoxon signed-rank test

Table 5 Study MDX-PK-105: most common treatment-emergent adverse events (TEAEs) (>10 % of participants receiving any treatment; safety population), *n* (%)

Adverse event	Treatment A[a] ($n = 35$)	Treatment B[a] ($n = 34$)	Treatment C[a] ($n = 34$)
Any TEAE	22 (62.9)	15 (44.1)	23 (67.6)
Nausea	20 (57.1)	12 (35.3)	19 (55.9)
Dizziness	15 (42.9)	4 (11.8)	9 (26.5)
Vomiting	10 (28.6)	2 (5.9)	8 (23.5)
Headache	4 (11.4)	3 (8.8)	6 (17.6)
Abdominal discomfort	3 (8.6)	2 (5.9)	2 (5.9)

FDC fixed-dose combination

[a] Treatment A indicates intact memantine extended release (ER) plus donepezil FDC capsule taken while fasting; Treatment B indicates intact FDC capsule taken following a high-fat meal; Treatment C indicates FDC capsule contents sprinkled on applesauce and taken while fasting

sprinkled on applesauce. It should be noted that the statistically significant differences in t_{max} values observed in study MDX-PK-105 (Table 4) were not associated with significant differences in C_{max}.

To the best of our knowledge, this FDC is the first consisting of two approved anti-dementia medications. Since memantine and donepezil are frequently co-prescribed in patients with moderate to severe AD, who are characterized by rapidly declining independence and an increasing caregiving burden [14], availability of such an FDC could reduce total pill burden and dosing frequency, which could potentially improve treatment adherence and reduce caregiving time and burden. For example, a patient taking immediate-release memantine and donepezil would reduce their anti-dementia pill burden from a total of three pills, administered twice a day, to one capsule once daily. Data from an observational study conducted in Germany suggest that switching from orally administered rivastigmine to a rivastigmine patch (i.e., to a drug formulation that reduces pill burden) is associated with improved adherence and with time savings for caregivers of up to 20 min/day [15]. Moreover, data from studies in other clinical conditions that require multiple medications (e.g., diabetes mellitus, cardiovascular disease) suggest that switching to an FDC is associated with better adherence [16, 17], clinical improvements [17], and a decrease in hospitalization risk and healthcare costs [18].

The ability to open the FDC capsule and sprinkle the contents on soft food (e.g., applesauce) may facilitate caregiving for patients who have swallowing difficulties [5, 19, 20], including choking [21], a condition that affects up to 57 % of patients with dementia [22] and constitutes a major challenge in nursing homes [23]. In addition, challenges with swallowing may be exacerbated by feeding tubes [25] and lead to aspiration pneumonia [26], a common cause of morbidity and death in patients with AD [27]. Currently, caregivers of patients with dysphagia rely on either liquid drug formulations or crushed pills mixed with soft foods [28], but the latter practice may be incompatible with many drug formulations (especially enteric-coated or extended-release ones) [28], leading to efficacy or safety issues, and may even amount to unlicensed drug use and be associated with legal ramifications [29]. Capsule manufacturers are aware of these issues and easy-to-open products are already available on the market [24].

Our data indicate that the memantine ER/donepezil FDC is generally safe in healthy individuals, and randomized-trial data suggest that the observed tolerability issues (particularly gastrointestinal, likely stemming from a known ChEI effect [9]) would be transient and less prominent in clinical practice, in which doses of both component drugs would be gradually up- titrated (recommended up-titration for donepezil: 4–6 weeks [30]; recommended up-titration for memantine ER: 4 weeks [31]). Similar to other phase I studies of anti-dementia medications, data have been obtained from healthy individuals who were on average 40 years younger than a typical patient, who would also be expected to have several co-morbidities. Therefore, pharmacokinetic parameters reported here are not necessarily representative of the parameters that would be observed in a population of patients with AD.

5 Conclusion

In conclusion, the memantine ER plus donepezil FDC capsule provides an additional treatment option for patients with moderate to severe AD and their caregivers. Introduction of a once-daily memantine ER/donepezil FDC which can be sprinkled may facilitate caregiving for patients with moderate to severe AD and potentially improve clinical outcomes, through increased treatment adherence. Our studies indicate that the FDC capsule containing memantine ER and donepezil is bioequivalent to co-administered commercially available memantine ER and donepezil, can be taken with or without food, and that its contents can be sprinkled on applesauce to facilitate drug intake.

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These clinical studies were designed to comply with International Conference on Harmonisation (ICH) Guidance on General Considerations for Clinical Trials (62 FR 66113, 1997), Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authority for Pharmaceuticals (75 FR 3471, 21 2010), and Good Clinical Practice (GCP): Consolidated Guidance (62 FR 25692, 1997). All participants provided a signed informed consent form at screening and had the mental capability to understand it.

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RB contributed to the design and conduct of the studies, data interpretation, and draft and review of the manuscript. LC was involved in study conduct, data analysis and interpretation, study report preparation, and helped to draft and review the manuscript. SRZ was the medical lead on the study and was responsible for medical analysis as well as review of all data, data analysis, and safety data interpretation. NMC participated in the study design, data interpretation, and draft and review of manuscript. RKH contributed to the design, data interpretation, and draft and review of the manuscript. AP participated in the study design, data interpretation, and draft and review of manuscript. All authors read and approved the final manuscript.

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