



Pharmacokinetics and Bioequivalence of Memantine Tablet and a New Dry Syrup Formulation in Healthy Japanese Males: Two Single-Dose Crossover Studies

Yutaro Maekawa · Setsuo Hasegawa · Tomoko Ishizuka · Kazuhito Shiosakai · Hitoshi Ishizuka

Received: June 24, 2019 / Published online: August 9, 2019
© The Author(s) 2019

ABSTRACT

Introduction: Memantine hydrochloride, an N-methyl-D-aspartate receptor antagonist, is used to treat Alzheimer's disease (AD). A new dry syrup formulation containing memantine hydrochloride has been developed to improve medication adherence in AD patients and to reduce family and caregiver burden. This study was conducted to assess the bioequivalence of this new formulation to the tablet.

Methods: Two single-dose, randomized, open-label, two-period, two-group, crossover studies were conducted to assess the bioequivalence of a test product [dry syrup, 2%, 1 g (containing 20 mg of memantine hydrochloride)] to a reference product (film-coated tablet) under two dosing conditions: administration of the test product as a suspension in water (Study I) and as granules taken with water (Study II). Blood samples were collected at specified time intervals, and memantine plasma concentrations were determined using a validated liquid

chromatography tandem mass spectrometry method. The pharmacokinetic parameters of memantine were calculated using non-compartmental analysis. The maximum concentration (C_{max}) and area under the concentration–time curve up to the last sampling time (AUC_{all}) were used to assess the bioequivalence of the two formulations.

Results: The geometric least square mean (GLSM) ratios [90% confidence interval (CI)] of the C_{max} and AUC_{all} of memantine for the test product to the reference product were 0.981 (0.943–1.020) and 0.978 (0.955–1.001) in Study I, and 0.973 (0.944–1.003) and 1.004 (0.983–1.025) in Study II, respectively. In both studies, the 90% CI values of the GLSM ratios of C_{max} and AUC_{all} were within the prespecified bioequivalence range (0.80–1.25). The safety of the test product under both dosing conditions and that of the reference product were not different.

Conclusions: The new dry syrup formulation containing memantine hydrochloride showed bioequivalence to the film-coated tablet under the two dosing conditions. Thus, the new dry syrup is suitable under either dosing condition for patients with AD.

Funding: Daiichi Sankyo Co., Ltd.

Enhanced Digital Features To view enhanced digital features for this article go to <https://doi.org/10.6084/m9.figshare.8982368>.

Y. Maekawa (✉) · T. Ishizuka · K. Shiosakai · H. Ishizuka
Daiichi Sankyo Co., Ltd., Tokyo, Japan
e-mail: maekawa.yutaro.jb@daiichisankyo.co.jp

S. Hasegawa
Pharmaspur Inc., Tokyo, Japan

Keywords: Bioequivalence; Dry syrup; Memantine; Pharmacokinetics

INTRODUCTION

Alzheimer's disease (AD) is a degenerative brain disease with multiple progressive symptoms, such as memory loss, communication impairment, disorientation, behavioral changes, and swallowing impairment, and is the most common cause of dementia [1, 2]. AD is a very burdensome disease, as it imposes a heavy burden on not only the patients but also their families and caregivers [2, 3]. Generally, dementia, including that associated with AD, is most prevalent in the elderly (> 65 years) [2]; therefore, due to the increasing global elderly population, its incidence is expected to increase [4, 5].

Memantine hydrochloride is an N-methyl-D-aspartate receptor antagonist indicated for the treatment of moderate to severe dementia in AD. Currently, two orally administered dosage formulations [a film-coated tablet and an oral disintegrating (OD) tablet] at three strengths (5, 10, and 20 mg) have been approved in Japan. OD tablets are easy to take, especially by patients with swallowing impairment [6]. In contrast, several factors other than cognitive impairment affect medication adherence by patients with dementia [7, 8]. Therefore, a new dry syrup formulation of memantine hydrochloride has been developed to add another option, which will improve medication adherence and reduce the family and caregiver burden.

After oral administration, memantine is highly absorbed, reaching the observed maximum concentration (C_{max}) in 3–8 h [9]. The pharmacokinetics (PK) of memantine is proportional in a wide dose range and the apparent elimination half-life ($T_{1/2}$) is approximately 60–70 h [9, 10]. Memantine is mainly excreted from the kidney, and hardly metabolized in the liver [9, 10]. Multidrug and toxin extrusion protein contributes to renal secretion of memantine [11].

The primary objective of this study was to assess the bioequivalence between the test (dry syrup containing 20 mg of memantine hydrochloride) and reference (20 mg film-coated tablet) products in healthy adult Japanese males.

METHODS

The study was conducted in accordance with the Good Clinical Practice guidelines, locally applicable laws and regulations, and ethical principles originating in or derived from the Declaration of Helsinki. The study protocol was developed per the guideline for Bioequivalence Studies of Generic Products [12], and the study was conducted at Tokyo Heart Center (Tokyo, Japan). The study protocol, its amendments, and the informed consent form were approved by the 124th Institutional Review Board of the study site on December 16, 2015 (Protocol number: SUN Y7017-G-J101). This study was not registered at any registry databases because at the time it was conducted, the registration of healthy subject trials was not required by the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases by the International Federation of Pharmaceutical Manufacturers and Associations. Prior to study execution, all subjects provided written informed consent.

Subjects

Healthy Japanese males aged 20–40 years with $25.0 \text{ kg/m}^2 > \text{BMIs} \geq 18.5 \text{ kg/m}^2$ at screening, were eligible for inclusion. The exclusion criteria included: (1) any medical history of central nervous, cardiovascular, respiratory, gastrointestinal, urinary, or blood/hematopoiesis system disorders, or hepatic/renal impairment, thyroid dysfunction, pituitary malfunction, adrenal dysfunction; (2) any clinically significant deviation from the normal range in a physical examination, vital signs (e.g., blood pressure, heart rate, and body temperature), 12-lead electrocardiogram, or clinical laboratory determinations; (3) history of epilepsy or convulsions; (4) incompletely healed oral cavity wound; (5) hypersensitivity or idiosyncratic reactions to any drug; (6) history of alcohol or drug abuse; (7) presence of an infection; (8) previous participation in a memantine hydrochloride clinical study; (9) current or planned receipt of any medical intervention after screening; (10) whole blood collection of

> 800 mL within 1 year, > 400 mL within 84 days, or > 200 mL within 28 days, or blood component collection within 14 days of the study; (11) previous clinical trial participation and investigational drug administration within 120 days of the study; (12) current or planned use of other drugs or supplements 14 days prior to hospitalization for the study and until study completion; (13) consumption of grapefruit (juice or pulp) within 7 days prior to hospitalization; (14) not consenting effective contraception use; and (15) investigator-determined ineligibility. Subjects could withdraw from the study at any time after a request.

Study Design

Two single-dose, randomized, open-label, two-period, two-group, crossover studies were conducted under two dosing conditions: test product [dry syrup, 2%, 1 g (containing 20 mg of memantine hydrochloride); Daiichi Sankyo, Tokyo, Japan] administration as a suspension in water (Study I) and as granules with water (Study II), because the dry syrup will be marketed to be administered in both conditions. Thirty days prior to treatment commencement, subjects were screened for eligibility. Subjects were confined to the study site for 5 days, from the day before treatment commencement (Day –1) until 72-h post-dosing (Day 4). After discharge, the 120- and 192-h post-dosing procedures were conducted during ambulatory visits to the study site on Days 6 and 9. On Day –1 of each treatment period, the study drugs were administered, with a 20- to 24-day washout period between administrations. On Day –1 of the first treatment period of each study, subjects were randomly assigned (1:1 ratio) to either a test–reference or reference–test sequence. The follow-up assessment was conducted after 20–24 days of the last administration in the second treatment period.

Randomization was conducted by the investigators in accordance with a randomization schedule, which was created using a computer-generated randomization scheme by the contract research organization.

Treatment and Subject Restrictions

In both studies, subjects fasted overnight (> 10 h) pre administration, and for 4 h post-administration. Water (150 mL) was used for each administration, and beverages were prohibited until 2 h post-dosing. Treatment administration compliance was assessed by a thorough oral cavity examination by the investigators. Standardized meals were served at appropriate times throughout the study. For 14 days before Day –1 of the first treatment period until study completion, the use of other drugs or supplements was prohibited.

Sample Collection and Bioanalytical Methods

Blood samples (5 mL) were collected in vacuum tubes containing the anti-coagulant, sodium heparin, at pre-dosing, and at 1, 3, 4, 5, 6, 8, 12, 24, 48, 72, 120, and 192 h post-dosing in each treatment period of both studies. Plasma was separated by centrifugation and stored at –20 °C until analysis.

Memantine was extracted from 100- μ L plasma samples via liquid–liquid extraction with diethyl ether. The organic layer was transferred and then evaporated under a nitrogen stream at approximately 40 °C. The remaining residue was reconstituted with 600 μ L of reconstitution solution [0.76:600:400:2 (ammonium formate/water/methanol/formic acid), v/v/v/v]. The final solution was analyzed using a validated liquid chromatography tandem mass spectrometry method. Chromatographic separation was performed using an Inertsil ODS-SP column (2.1 mm I.D. \times 50 mm, 3 μ m; GL Sciences, Tokyo, Japan). Detection was performed using an API 4000 or 4000 QTRAP (AB SCIEX, Framingham, MA, USA) tandem mass spectrometer with a TurboIonSpray source by electrospray ionization in the positive ion mode, and multiple-reaction monitoring of memantine (m/z 180–163) and its internal standard (memantined6, m/z 186–169). The intra-study assay precisions for 1.60, 8.00, and 80.0 ng/mL memantine were 2.6, 1.4, and 0.4%, respectively. Assay

accuracy ranged from -3.1 to -2.5% , with a lower limit of quantification of 0.500 ng/mL.

Pharmacokinetic Analysis

PK parameters were calculated from the plasma concentration–time data of memantine of each subject by a non-compartment analysis using Phoenix WinNonlin (v.6.3; Certara G.K, Tokyo, Japan).

The primary PK parameters were C_{\max} and area under the concentration–time curve (AUC) up to the last sampling time (AUC_{all}), whereas the secondary PK parameters were the observed time to C_{\max} (T_{\max}), $T_{1/2}$, and AUC up to infinity (AUC_{inf}).

Statistical Analysis

Logarithmically-transformed values of the primary PK parameters (C_{\max} and AUC_{all}) were compared for the two dosage formulations, and the test product versus the reference product. A mixed-effect model that included treatment group, treatment period, and formulation as fixed effects, and subject within sequence as random effect, was used for all comparisons. The ratios of geometric least-squares means (GLSM) of the primary PK parameters and their 90% confidence intervals (CIs) were calculated. Subjects whose AUC_{all} could not be properly calculated were excluded from the calculation of GLSM and their 90% CIs. Bioequivalence of the test and reference products was concluded if the 90% CIs of the ratios of GLSM of the primary PK parameters were within the predefined acceptance range of 0.80 – 1.25 . Statistical analyses were performed using SAS[®] (v.9.2; SAS Institute Japan, Tokyo, Japan).

The sample size for this study was calculated by the reported approach [13] using previous memantine studies (data on file). The intra-individual geometric coefficient of variations of C_{\max} and AUC_{all} of memantine were approximately 10%; thus, 18 evaluable subjects were necessary to provide a 90% power to demonstrate bioequivalence of the two dosage formulations in each study. To ensure that we obtained the PK data of ≥ 18 subjects at study

procedure completion, 24 subjects were enrolled in each study.

Safety Assessments

Drug safety was assessed using data of adverse events (AEs), vital signs (body temperature, blood pressure, and pulse rate), body weight, 12-lead electrocardiograms, and laboratory tests (including hematology, serum chemistry, and urinalysis). The intensity, duration, relationship to the study drugs, outcome, and severity of all AEs that occurred after the first administration of study drugs until study completion were recorded.

RESULTS

Disposition and Baseline Clinical characteristics

In Study I, 24 healthy subjects were enrolled; 19 completed the study and five withdrew after drug administration in the first treatment period (four due to AEs and one due to deviation from the exclusion criteria).

In Study II, 24 healthy subjects were enrolled; 21 completed the study and two dropped out during the first treatment period (one due to an AE and one due to deviation from the exclusion criteria) and one dropped out during the second treatment period after withdrawing consent.

The subject demographics and baseline characteristics of both studies are shown in Table 1.

Pharmacokinetics

Study I (Test Product Administration: Suspension in Water)

The mean plasma memantine concentration–time profile is shown in Fig. 1. A summary of memantine's PK parameters are presented in Table 2. The C_{\max} and AUC_{all} of memantine in the test and reference products were similar, with mean [standard deviation (SD)] values of 27.3 (3.89) ng/mL and 1890 (315) ng h/mL, and 27.9 (3.81) ng/mL and 1950 (288) ng h/mL, respectively. The T_{\max} , $T_{1/2}$, and AUC_{inf} of the

Table 1 Summary of subject demographic and baseline characteristics

	Study I, <i>n</i> = 24	Study II, <i>n</i> = 24
Age (years)		
Mean (SD)	26.4 (5.98)	26.3 (6.35)
Min, max	20, 39	20, 38
Body weight (kg)		
Mean (SD)	60.80 (7.958)	61.37 (6.147)
Min, max	51.0, 79.8	49.8, 76.2
BMI (kg/m ²)		
Mean (SD)	20.69 (1.660)	21.03 (1.662)
Min, max	18.6, 24.4	18.6, 24.2

BMI body mass index, *max* maximum, *min* minimum, *n* the number of subjects for whom the corresponding PK parameters were estimable, *SD* standard deviation

test and reference products were also similar. The GLSM ratios (90% CI) of the C_{\max} and AUC_{all} were 0.981 (0.943–1.020) and 0.978 (0.955–1.001), respectively (Table 3). Both 90% CIs of the ratios of GLSM were within the pre-specified bioequivalence range (0.80–1.25).

Study II (Test Product Administration: Granule with Water)

The mean plasma memantine concentration–time profile is shown in Fig. 2. A summary of memantine's PK parameters are presented in Table 2. The C_{\max} and AUC_{all} of memantine in the test and reference products were similar, with mean (SD) values of 27.7 (3.94) ng/mL and 1890 (266) ng h/mL, and 28.5 (3.70) ng/mL and 1880 (271) ng h/mL, respectively. The T_{\max} , $T_{1/2}$, and AUC_{inf} of the test and reference products were also similar. The GLSM ratios (90% CI) of the C_{\max} and AUC_{all} were 0.973 (0.944–1.003) and 1.004 (0.983–1.025), respectively (Table 3). Both 90% CIs of the ratios of GLSM were within the pre-specified bioequivalence range (0.80–1.25).

Safety

All AEs that occurred during this study are listed in Table 4.

In Study I, AEs of test and reference product were reported by six (27.3%) and five (23.8%) subjects, respectively. Of these, one event of dizziness observed after the administration of the test product was considered to be related to the study drug. Four subjects withdrew due to AEs: one each of influenza observed after the administration of the test product, increased aspartate aminotransferase (ALT) and gamma-glutamyl transferase observed after the administration of the test product, pharyngitis observed after the administration of the reference product, and increased blood bilirubin observed after the administration of the reference product.

In Study II, test and reference product AEs were reported by four (18.2%) and seven (29.2%) subjects, respectively. Of these, three events of dizziness, one of soft feces, one of increased ALT, and one of increased AST were considered to be related to the study drugs. One subject withdrew due to influenza observed after the administration of the reference product.

In both studies, all AEs reported were of mild or moderate intensity. Subjects recovered from all but one AE (increased blood cholesterol), which was relieved to the value before its onset.

No deaths, other serious AEs, or severe AEs were reported in either of the two studies. No notable differences were observed in the safety of the test product under both dosing conditions, compared to the reference product.

DISCUSSION

Various memantine hydrochloride products have been developed and marketed for administration as solutions, extended release capsules [14], fixed dose combination tablets with donepezil [15], and transdermal therapeutic systems [16]. Here, we evaluate the bioequivalence of a new dry syrup formulation containing memantine hydrochloride under two dosing conditions [i.e., administered as a suspension in water (Study I) or as granules with water (Study II)] to the film-coated tablet. No major differences in PK parameters in this study were observed as compared to those after a

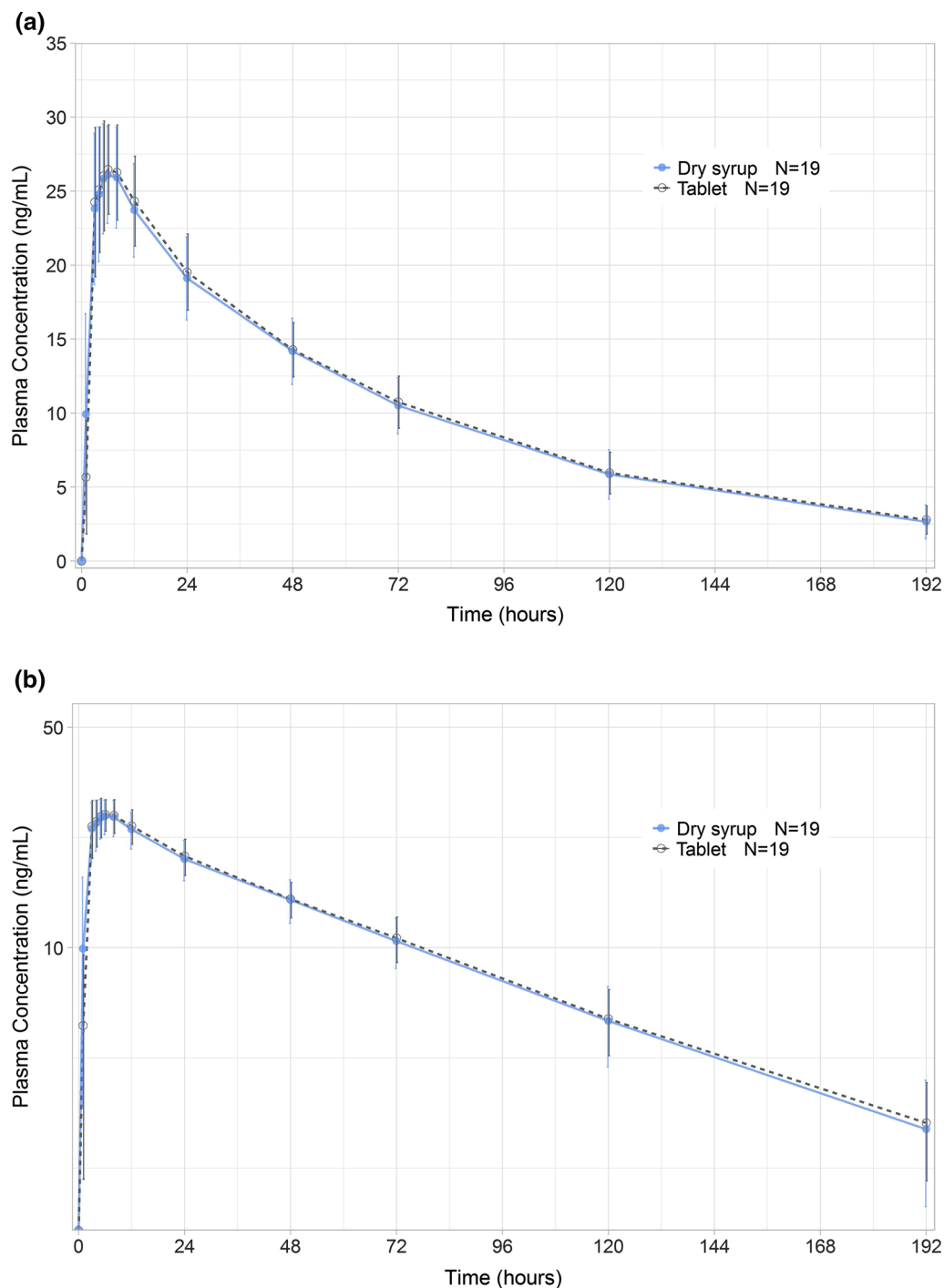


Fig. 1 Mean (standard deviation) plasma concentration–time profiles of memantine after a single oral administration of dry syrup 2%, 1 g (containing 20 mg of memantine hydrochloride) and a tablet with linear

(a) and semi-logarithmic (b) scales in Study I (administration of the dry syrup as a suspension in water). The mean plasma concentration of the dry syrup at 192-h post-dosing was calculated using $n = 18$

Table 2 Summary of pharmacokinetic (PK) parameters of memantine in Study I (administration of the dry syrup as a suspension in water) and Study II (administration of the dry syrup as granules with water)

	Dry syrup	Tablet
Study I ($n = 19$)		
C_{\max} (ng/mL)	27.3 (3.89)	27.9 (3.81)
AUC_{all} (ng h/mL)	1890 (315) ^b	1950 (288)
AUC_{inf} (ng h/mL)	2170 (459)	2200 (393)
T_{\max} (h) ^a	6.00 (1.00, 8.00)	6.00 (3.00, 8.00)
$T_{1/2}$ (h)	60.6 (12.5)	60.3 (10.1)
Study II ($n = 22$)		
C_{\max} (ng/mL)	27.7 (3.94)	28.5 (3.70)
AUC_{all} (ng h/mL)	1890 (266) ^c	1880 (271)
AUC_{inf} (ng h/mL)	2100 (319) ^c	2090 (327)
T_{\max} (h) ^a	5.00 (3.00, 8.00)	5.00 (1.00, 12.00)
$T_{1/2}$ (h)	57.1 (7.68) ^c	57.3 (8.07)

Data are presented as mean (SD)

AUC_{all} area under the concentration–time curve up to the last sampling time, AUC_{inf} area under the concentration–time curve up to infinity, C_{\max} observed maximum concentration, *max* maximum, *min* minimum, *SD* standard deviation, $T_{1/2}$ apparent elimination half-life, T_{\max} observed time to C_{\max}

^a Median (min, max)

^b $n = 18$ (number of subjects with reportable AUC_{all} ; one subject was excluded due to missing data)

^c $n = 21$ (number of subjects with reportable AUC_{all} , AUC_{inf} , and $T_{1/2}$; one subject was excluded due to missing data)

single dose of 20 mg of memantine in healthy Chinese subjects under fasting conditions [10]. In both Studies I and II, the 90% CIs of the GLSM ratios of C_{\max} and AUC_{all} for memantine were within the prespecified bioequivalence range, suggesting that patients with AD can take this new dry syrup under either dosing condition. These results are owed to the physicochemical properties of memantine

Table 3 Statistical analysis of pharmacokinetic (PK) parameters of memantine in Studies I and II

	GLSM ratio (dry syrup/tablet)	90% CI lower	90% CI upper
Study I ($n = 19$)			
C_{\max} (ng/mL)	0.981	0.943	1.020
AUC_{all} (ng h/mL) ^a	0.978	0.955	1.001
Study II ($n = 22$)			
C_{\max} (ng/mL)	0.973	0.944	1.003
AUC_{all} (ng h/mL) ^b	1.004	0.983	1.025

AUC_{all} area under the concentration–time curve up to the last sampling time, *CI* confidence interval, C_{\max} observed maximum concentration, *GLSM* geometric least squares mean

^a $n = 18$ (number of subjects with reportable AUC_{all})

^b $n = 21$ (number of subjects with reportable AUC_{all})

hydrochloride, classified as a class I (high solubility/permeability) drug, according to the Biopharmaceutical Classification System [17, 18]. Additionally, the results of the in vitro dissolution tests performed in accordance with local guidelines [19], using the paddle method at 50 rpm with 900 mL of Japanese Pharmacopoeia first Fluid for Dissolution Test (JP1, pH 1.2), diluted McIlvaine buffer (pH 4.0), Japanese Pharmacopoeia second Fluid for Dissolution Test (JP2, pH 6.8), and water, elucidated the similarity between the dry syrup and the film-coated tablet (data on file). These findings suggest that the dissolution of memantine hydrochloride from each formulation in the gastrointestinal tract was similar, and that the fraction absorbed after oral administration of each formulation was comparable.

With regards to the safety of the formulations, all reported AEs were of mild or moderate intensity, with no deaths, and subjects recovered or relieved from all AEs. The AEs after administration of the dry syrup under both dosing conditions were not notably different

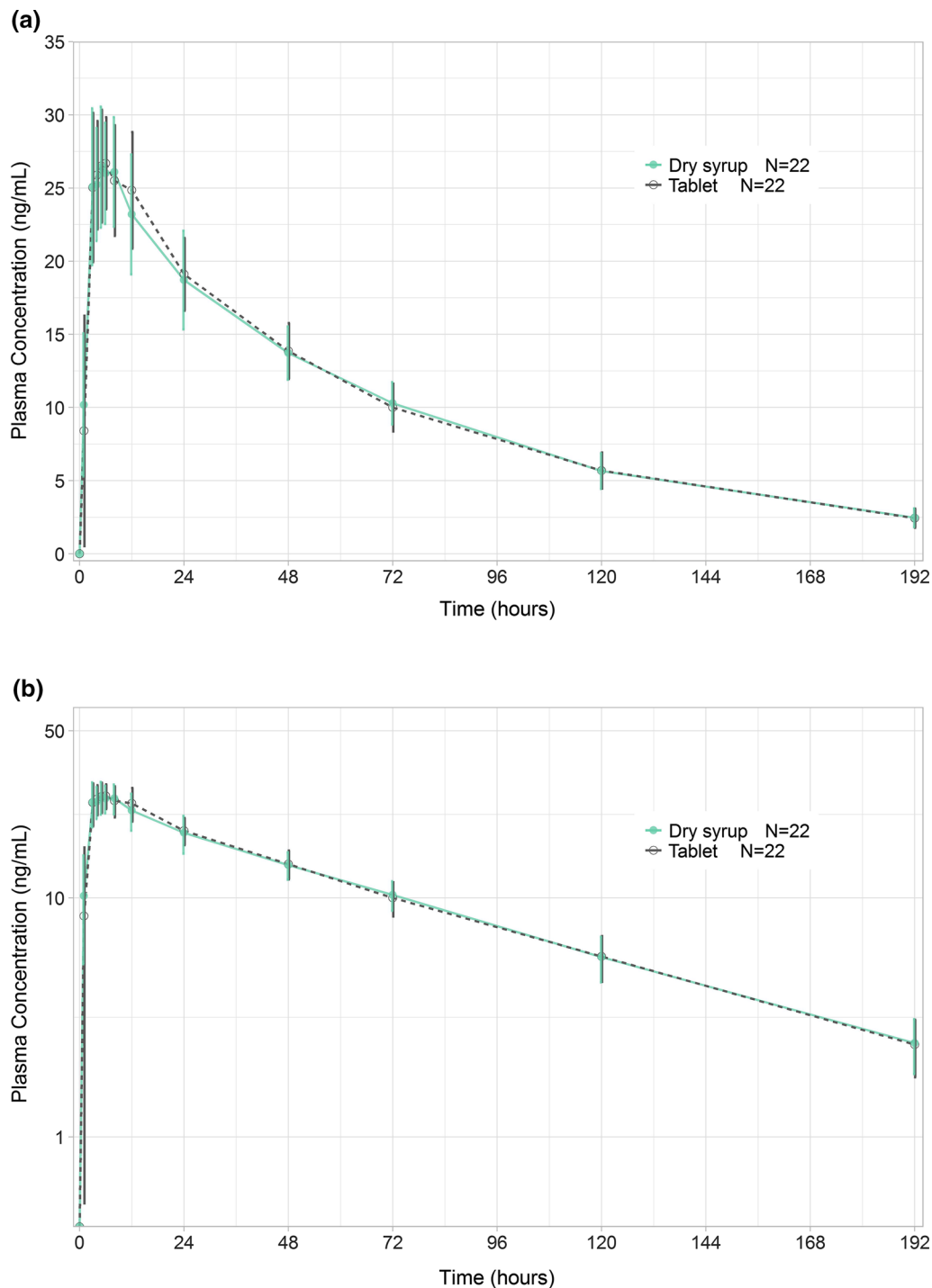


Fig. 2 Mean (standard deviation) plasma concentration–time profiles of memantine after a single oral administration of dry syrup 2%, 1 g (containing 20 mg of memantine hydrochloride) and a tablet with linear

(a) and semi-logarithmic (b) scales in Study II (administration of the dry syrup as granules with water). The mean plasma concentration of the dry syrup at 120- and 192-h post-dosing was calculated using $n = 21$

Table 4 Summary of Study I and II adverse events (AEs)

	Study I		Study II	
	Dry syrup	Tablet	Dry syrup	Tablet
No. of subjects evaluated	<i>n</i> = 22	<i>n</i> = 21	<i>n</i> = 22	<i>n</i> = 24
No. of subjects with AEs	6 (27.3)	5 (23.8)	4 (18.2)	7 (29.2)
Infections and infestations				
Influenza	1 (4.5)	0	0	1 (4.2)
Pharyngitis	0	1 (4.8)	0	0
Nervous system disorders				
Dizziness	1 (4.5)	0	1 (4.5)	2 (8.3)
Gastrointestinal disorders				
Diarrhoea	1 (4.5)	0	0	0
Toothache	2 (9.1)	0	0	0
Faeces soft	0	0	0	1 (4.2)
Stomatitis	0	0	0	1 (4.2)
Investigations				
Alanine aminotransferase increased	1 (4.5)	0	1 (4.5)	0
Blood bilirubin increased	0	1 (4.8)	0	0
Blood cholesterol increased	0	1 (4.8)	0	0
Blood triglycerides increased	2 (9.1)	2 (9.5)	0	1 (4.2)
Gamma-glutamyltransferase increased	1 (4.5)	0	0	0
Aspartate aminotransferase increased	0	0	1 (4.5)	0
Blood creatine phosphokinase increased	0	0	1 (4.5)	0
Myoglobin blood increased	0	0	1 (4.5)	0
Neutrophil count increased	0	0	0	1 (4.2)
White blood cell count increased	0	0	1 (4.5)	1 (4.2)

n (%), MedDRA/J v.19.0

from those of the conventional film-coated tablet [20].

Easy to administer formulations are desirable for patients with AD because of the associated low medication compliance [6]. OD tablets were developed for improved medication compliance compared with traditional tablets. Similarly, the dry syrup was developed to further improve medication compliance in patients with AD, and reduce family and caregiver burden. The

dry syrup formulation containing donepezil hydrochloride has been approved for AD treatment in Japan [21], as it is relatively easier to administer to some patients than tablets.

The existence of few limitations in this study is owed to the study design, subjects, PK sample points, bioanalytical method, and PK analysis being planned and performed in accordance with the Guideline for Bioequivalence Studies of Generic Products [12]. However, because all

study subjects were healthy, it remains unclear whether the new dry syrup formulation is beneficial to actual AD patients, and their families and caregivers. Notwithstanding, because of the benefits of the dry syrup formulation containing donepezil hydrochloride, we believe the memantine hydrochloride dry syrup will also be beneficial in AD treatment.

CONCLUSION

The new dry syrup formulation containing memantine hydrochloride is bioequivalent to the marketed film-coated tablet in healthy adult Japanese males, and is expected to improve patient medication adherence and to reduce family and caregiver burden.

ACKNOWLEDGEMENTS

The authors would like to thank the participants of this study. In addition, the authors are grateful to Tsunenori Nakazawa for supporting the bioanalysis.

Funding. Sponsorship for this study and article processing charges were funded by Daiichi Sankyo Co., Ltd. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Authorship. All authors of this article meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, and take responsibility for the work as a whole, including the integrity of the data and accuracy of the data analysis. All named authors approve the publication of this version.

Disclosures. Yutaro Maekawa is an employee of Daiichi Sankyo Co. Tomoko Ishizuka is an employee of Daiichi Sankyo Co. Kazuhito Shiosakai is an employee of Daiichi Sankyo Co. Hitoshi Ishizuka is an employee of Daiichi Sankyo Co., Ltd. Setsuo Hasegawa has nothing to disclose.

Compliance with Ethics Guidelines. All procedures performed in this study were in accordance with local regulations, Good Clinical Practice guidelines, and the Declaration of Helsinki and its later amendments. Informed consents were obtained from all eligible and willing study subjects.

Data Availability. All generated and/or analyzed study data are available upon reasonable request from the corresponding author.

Open Access. This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits any non-commercial use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

REFERENCES

1. Liang J, Li J, Jia R, et al. Identification of the optimal cognitive drugs among Alzheimer's disease: a Bayesian meta-analytic review. *Clin Interv Aging*. 2018;13:2061–73.
2. Alzheimer's Association. Alzheimer's disease facts and figures. *Alzheimers Dement*. 2018;2018(14):367–429.
3. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement*. 2011;7(3):270–9.
4. Alzheimer's disease International. World Alzheimer report. The global impact of dementia: an analysis of prevalence, incidence, cost and trends. London: Alzheimer's Disease International; 2015. <https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf>. Accessed 10 Jul 2019.
5. Sado M, Ninomiya A, Shikimoto R, et al. The estimated cost of dementia in Japan, the most aged society in the world. *PLoS ONE*. 2018;13(11):e0206508.

6. Sunada H, Bi Y. Preparation, evaluation and optimization of rapidly disintegrating tablets. *Powder Technol.* 2002;122:188–98.
7. Lima S, Gago M, Garrett C, Pereira MG. Medication adherence in Alzheimer's disease: the mediator role of mindfulness. *Arch Gerontol Geriatr.* 2016;67:92–7.
8. Noguchi Y, Saito S. Needs for dosage forms required in dementia patients. *Pharm Stage.* 2011;10(10):32–6 [in Japanese].
9. Noetzli M, Eap CB. Pharmacodynamic, pharmacokinetic and pharmacogenetic aspects of drugs used in the treatment of Alzheimer's disease. *Clin Pharmacokinet.* 2013;52(4):225–41.
10. Liu MY, Meng SN, Wu HZ, Wang S, Wei MJ. Pharmacokinetics of single dose and multiple-dose memantine in healthy chinese volunteers using an analytic method of liquid chromatography-tandem mass spectrometry. *Clin Ther.* 2008;30(4):641–53.
11. Müller F, Weitz D, Derdau V, et al. Contribution of MATE1 to renal secretion of the NMDA receptor antagonist memantine. *Mol Pharm.* 2017;14(9):2991–8.
12. Japanese Pharmaceutical and Food Safety Bureau. Guideline for bioequivalence studies of generic products, dated February 29, 2012. [http://www.nihs.go.jp/drug/be-guide\(e\)/Generic/GL-E_120229_BE.pdf](http://www.nihs.go.jp/drug/be-guide(e)/Generic/GL-E_120229_BE.pdf). Accessed 10 Jul 2019.
13. Chow SC, Liu JP. Design and analysis of bioavailability and bioequivalence studies. New York: Marcel Dekker; 1992.
14. Plosker GL. Memantine extended release (28 mg once daily): a review of its use in Alzheimer's disease. *Drugs.* 2015;75(8):887–97.
15. Boinpally R, Chen L, Zukin SR, McClure N, Hofbauer RK, Periclou A. 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. *Clin Drug Invest.* 2015;35(7):427–35.
16. Del Río-Sancho S, Serna-Jiménez CE, Sebastián-Morelló M, et al. Transdermal therapeutic systems for memantine delivery. Comparison of passive and iontophoretic transport. *Int J Pharm.* 2017;517(1):104–11.
17. Ono A, Tomono T, Ogihara T, Terada K, Sugano K. Investigation of biopharmaceutical and physicochemical drug properties suitable for orally disintegrating tablets. *ADMET DMPK.* 2016;4(4):335–60.
18. European Medicines Agency. Memantine film-coated tablets 5, 10, 15 and 20 mg, oral solution 5 mg product-specific bioequivalence guidance, dated 26 Mar, 2015. https://www.ema.europa.eu/documents/scientific-guideline/memantine-film-coated-tablets-5-10-15-20-mg-oral-solution-5-mg-product-specific-bioequivalence_en.pdf. Accessed 10 Jul 2019.
19. Japanese Pharmaceutical and Food Safety Bureau. Guideline for different oral solid dosage forms, dated February 29, 2012. [http://www.nihs.go.jp/drug/be-guide\(e\)/GL-E_120229_zaikei.pdf](http://www.nihs.go.jp/drug/be-guide(e)/GL-E_120229_zaikei.pdf). Accessed 10 Jul 2019.
20. Matsunaga S, Kishi T, Nomura I, et al. The efficacy and safety of memantine for the treatment of Alzheimer's disease. *Expert Opin Drug Saf.* 2018;17(10):1053–61.
21. Aricept® (donepezil hydrochloride) Dry syrup package insert . <https://medical.eisai.jp/content/000000315.pdf>. Accessed 10 Jul 2019. [in Japanese].