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Galaxy Publication

Population Pharmacokinetic Study of GB-5001, a Long-Acting Injectable Donepezil Formulation, in Healthy Korean Subjects: Phase 1 Trial

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ABSTRACT

Donepezil is an acetylcholinesterase inhibitor widely used in Alzheimer's disease, but its clinical effectiveness can be limited by the need for daily oral administration and associated adherence issues. To address this limitation, long-acting injectable (LAI) formulations such as GB-5001 have been developed to enable less frequent dosing. This Phase 1, open-label, active-controlled, dose-escalation study was designed to characterize the safety profile, tolerability, pharmacokinetics, and pharmacodynamics of GB-5001 in healthy adult men. Participants were assigned to receive either GB-5001A or GB-5001D via intramuscular or subcutaneous injection, or oral donepezil (Aricept®). Safety assessments were conducted alongside pharmacokinetic sampling and pharmacodynamic evaluation based on acetylcholinesterase inhibition. The potential influence of CYP2D6 metabolic phenotype on drug exposure was also explored, supported by pharmacokinetic modeling and simulation approaches. Fifty healthy male volunteers completed the study. After intramuscular administration, GB-5001A (70, 140, and 280 mg) showed a clear dose-dependent increase in systemic exposure (AUCinf and Cmax), with substantially prolonged drug exposure compared with oral donepezil 10 mg. No serious safety concerns were identified. The most frequently reported adverse events were mild injection-site reactions, observed in all groups except the GB-5001A 70 mg intramuscular cohort and the oral donepezil group. Sustained inhibition of acetylcholinesterase activity was also observed with GB-5001A. Overall, GB-5001A demonstrated acceptable tolerability, predictable dose-exposure relationships, and extended pharmacokinetic persistence, with an estimated 3–4 times longer half-life than oral donepezil. These findings, together with modeling results, support its potential as a long-acting once-monthly intramuscular therapeutic option for Alzheimer's disease.

Keywords: Pharmacodynamics, Phase 1, Safety, Tolerability, Donepezil, Long-acting injectable

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Introduction

Dementia refers to a progressive decline in cognitive abilities, such as memory, reasoning, and judgment, severe enough to interfere with independent functioning in daily life. In addition to cognitive impairment, patients may develop changes in mood regulation and personality traits. The disorder typically evolves from mild cognitive impairment, which may only subtly disrupt everyday activities, to advanced stages in which individuals become fully dependent on others for basic care, including eating and personal hygiene [1]. Alzheimer's disease, the most prevalent type of dementia, is defined by characteristic neuropathological changes, including extracellular deposition of β-amyloid plaques and intracellular accumulation of hyperphosphorylated tau protein forming neurofibrillary tangles. These pathological processes impair neuronal communication and network integrity, eventually leading to synaptic degeneration and widespread neuronal loss [2].

In 2021, the global number of people living with dementia was estimated at 57 million, with the majority—over 60%—residing in low- and middle-income countries. Each year, roughly 10 million new cases are added worldwide [3].

By 2024, unpaid care provided by family members and informal caregivers to individuals with Alzheimer's disease and other dementias was estimated at 19.2 billion hours, valued at approximately $413.5 billion. The projected lifetime cost per affected individual reached about $405,262, with nearly 70% of this burden attributed to unpaid caregiving and direct out-of-pocket family expenditures [4]. Furthermore, the overall global economic impact of dementia, including both direct healthcare costs and indirect societal costs, is expected to increase sharply from $1.33 trillion in 2020 to approximately $9.12 trillion by 2050 [5].

Donepezil, an acetylcholinesterase inhibitor originally introduced in 1996 under the trade name Aricept®, has become a standard therapeutic option for Alzheimer's-type dementia. It is typically prescribed as a once-daily oral medication, with common dosing regimens of 5 mg or 10 mg for mild-to-moderate disease, and 10 mg or 23 mg for more advanced stages [6]. In an effort to overcome limitations associated with oral administration, including first-pass metabolism and patient adherence issues, alternative drug delivery systems have been investigated to improve convenience and enable more flexible administration. A transdermal formulation was initially introduced in 2010 but was subsequently discontinued by the U.S. FDA. More recently, a revised transdermal delivery system for donepezil was developed and approved in 2022 [7, 8].

Donepezil undergoes extensive hepatic biotransformation, yielding several metabolites, and is eliminated primarily via the kidneys [9]. The metabolic process is mainly mediated by cytochrome P450 enzymes, particularly CYP3A4 and CYP2D6 [10]. Among its metabolites, 6-O-desmethyl donepezil is considered the principal active form and exhibits acetylcholinesterase inhibitory activity comparable to that of donepezil itself [11].

In patients with cognitive decline, the ability to independently manage medication therapy is often compromised. Difficulties such as forgetting doses, improper handling of medication containers, or refusal to take prescribed drugs can significantly reduce treatment adherence. As the disease progresses, responsibility for medication administration is frequently transferred to caregivers. This transition, together with the worsening cognitive status associated with dementia, plays an important role in determining adherence patterns, which vary according to disease severity [12].

Medication adherence is a key determinant of therapeutic effectiveness and overall disease control. Long-acting injectable (LAI) drug delivery systems are designed to replace daily oral dosing with infrequent injections, thereby improving convenience by extending dosing intervals to weeks or even months. Compared with conventional oral regimens, LAI formulations have been associated with improved adherence, as patients are more likely to maintain consistent treatment and demonstrate reduced discontinuation rates [13].

To overcome the limitations of daily administration and suboptimal adherence observed with standard therapies, the development of a long-acting injectable form of donepezil represents a potential advancement in Alzheimer's disease management. GB-5001 is a once-monthly intramuscular formulation of donepezil designed for this purpose. The present study was conducted to assess the safety profile and tolerability, as well as the pharmacokinetics of donepezil and its active metabolite, 6-O-desmethyl donepezil, in healthy adult subjects. Furthermore, exploratory pharmacodynamic evaluations and pharmacokinetic simulations after repeated dosing were performed to support its future clinical application in patients with Alzheimer's disease, ranging from mild to severe stages.

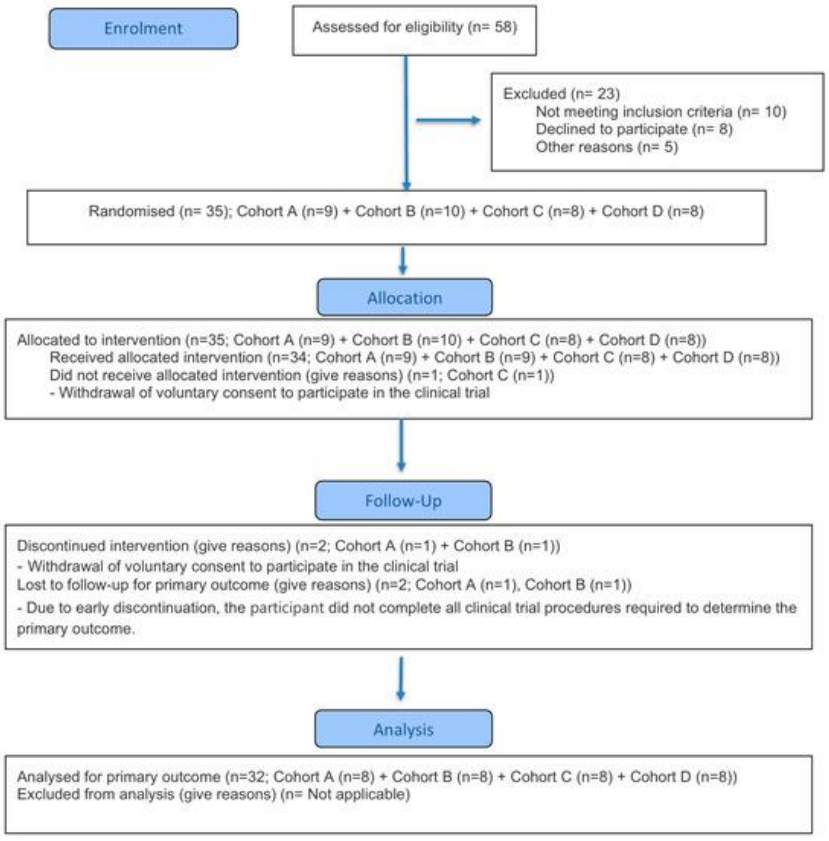
Materials and Methods

Ethics

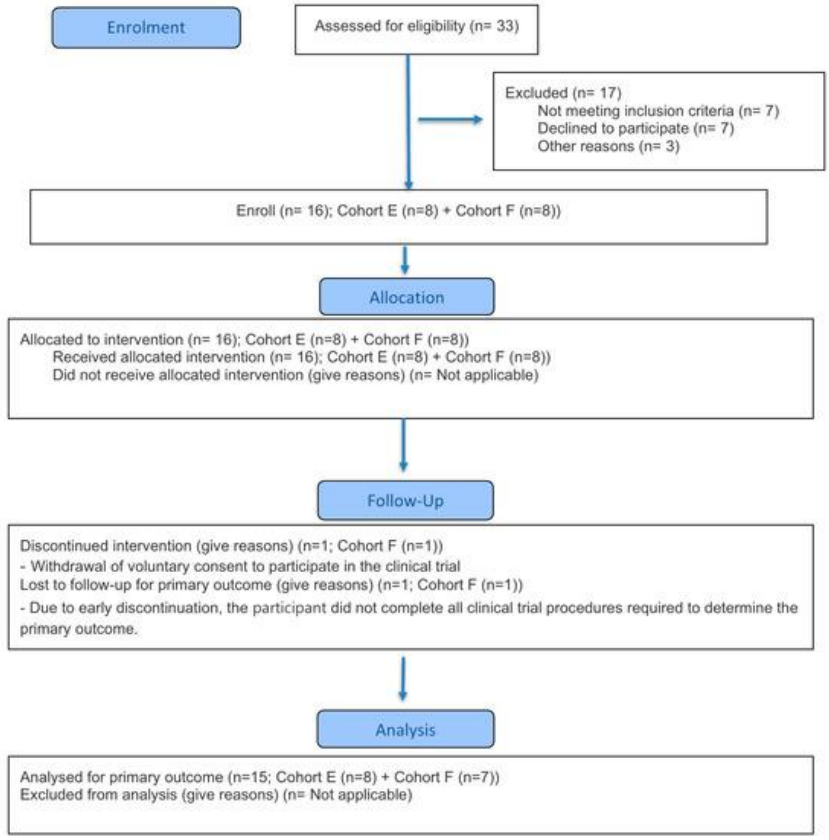
Ethical and regulatory compliance for this clinical investigation was ensured before patient enrollment began. The protocol was reviewed and authorized by both national and institutional authorities, including the Korea Ministry of Food and Drug Safety and the Institutional Review Board of Chungnam National University Hospital (approval No. CNUH 2023-08-088; 12 October 2023).

The study was conducted in accordance with Good Clinical Practice (ICH-GCP) and the principles of the Declaration of Helsinki. Trial design, conduct, and reporting followed CONSORT recommendations, as illustrated in **Figure 1.**

Prospective registration of the study was completed on ClinicalTrials.gov (NCT06127368; 7 November 2023).



a)



b)

Figure 1. CONSORT study flow chart: (a) Cohort A and (b) Cohort B.

Study design

This Phase 1 investigation was designed as an open-label, active-controlled, parallel-group, dose-escalation study and conducted at the Clinical Trial Center of Chungnam National University Hospital. Recruitment of participants began on 3 January 2024, and the final participant completed follow-up on 16 October 2024. The study protocol was implemented in two sequential phases. The first phase (Part A) comprised multiple dose cohorts alongside an oral active comparator group. Participants assigned to the comparator arm received oral donepezil (Aricept® 10 mg once daily). In the investigational arms of Part A, three groups were evaluated at the 70 mg dose level: one received GB-5001A by intramuscular injection, another received GB-5001A by subcutaneous injection, and a third received GB-5001D by subcutaneous injection. The second phase (Part B) focused on dose escalation of GB-5001A delivered intramuscularly, evaluating two higher dose levels of 140 mg and 280 mg in separate cohorts.

Investigational products

GB-5001A and GB-5001D, developed by G2GBIO (Cheongju, Republic of Korea), are long-acting injectable formulations of donepezil and were investigated as study drugs in this trial. Administration strategies differed by formulation and cohort. GB-5001A was delivered at 70 mg/0.55 mL in Cohorts A and B via intramuscular (IM) and subcutaneous (SC) injection, respectively, while larger IM doses of 140 mg/1.1 mL and 280 mg/2.2 mL were used in Cohorts E and F. GB-5001D was evaluated only at 70 mg/0.4 mL and administered subcutaneously in Cohort C, in accordance with prior nonclinical findings suggesting that SC delivery provides a more suitable pharmacokinetic profile for long-acting systems compared with IM injection. All IM injections were applied to the right ventrogluteal site, whereas SC injections were administered in the right abdominal region. Participants were instructed not to massage or exert pressure on the injection site following dosing to avoid potential alteration of drug absorption.

Participants

All participants provided voluntary written informed consent before enrollment, in accordance with procedures approved by the Institutional Review Board. The study enrolled healthy Asian male adults aged 19–55 years with a body weight of ≥ 55 kg and a body mass index (BMI) of 18.5-30.0 kg/m². Eligibility required the absence of clinically relevant medical conditions, no history of significant systemic disease, and no evidence of viral infection, alcohol abuse or dependence, or drug abuse or dependence. Participants were also required to demonstrate normal findings on screening evaluations, including physical examination, vital signs, and routine clinical laboratory tests. For Part B, individuals identified as CYP2D6 poor metabolizers were excluded due to the risk of increased systemic exposure and delayed elimination of donepezil associated with long-acting injectable administration.

Study objectives

This clinical investigation was designed with a hierarchical set of objectives. The primary endpoint focused on the safety and tolerability of a single dose of long-acting donepezil administered by intramuscular or subcutaneous injection. As a secondary aim, the study characterized the pharmacokinetics of 6-O-desmethyl donepezil, the active metabolite of donepezil, following a single IM or SC dose of GB-5001, compared with oral Aricept®.An additional exploratory component evaluated pharmacodynamic responses to a single intramuscular dose of GB-5001A. Moreover, population-based pharmacokinetic modeling and simulation were performed using data from IM GB-5001A and oral Aricept® to project drug exposure profiles under repeated dosing scenarios.

Pharmacokinetic and pharmacodynamic parameters

To describe the pharmacokinetics of donepezil following single-dose administration of GB-5001A, GB-5001D, and oral Aricept®, multiple exposure and disposition parameters were analyzed. These included AUClast, AUCinf, AUC0–720, Cmax, CL/F, Vd/F, t1/2, Tmax, and Tlag. For the active metabolite 6-O-desmethyl donepezil, the same PK metrics (AUClast, AUCinf, AUC0–720, Cmax, CL/F, Vd/F, t1/2, Tmax, and Tlag) were evaluated in participants receiving GB-5001A at the 280 mg dose level. Pharmacodynamic assessment was based on acetylcholinesterase (AChE) inhibition. The maximal effect (Emax) was defined as the highest observed percentage of AChE inhibition, and overall pharmacodynamic exposure was quantified using AUElast, along with Emax, after a single 280 mg dose of GB-5001A. To better characterize drug exposure, three AUC-derived

measures were applied. AUC0–720 captured early exposure within the first 30 days post-dose and reflected the long-acting properties of GB-5001A. AUClast represented observed exposure based on measurable concentrations, whereas AUCinf estimated total systemic exposure, including extrapolated values beyond the last sampling point. In the pharmacokinetic modeling and simulation component, steady-state exposure parameters were derived from simulated profiles, including Cmax, ss, Cmin, ss, AUCτ, Cav, ss, and Swing_tau, to describe concentration–time behavior under repeated-dosing conditions.

Blood sampling and preparation

PK and PD evaluations were performed using blood samples collected after donepezil administration, with all measurements aligned with predefined sampling time points. For PK assessment, Cohorts A, B, E, and F underwent extensive serial blood collection beginning at pre-dose (0 h) and continuing at multiple post-dose time points up to 2352 h (D99), including dense early sampling within the first 24 h. Cohort C followed an identical schedule but with sampling completed at 1512 h (D64). In contrast, Cohort D used a more intensive early-phase schedule extending to 240 h (D11), with additional frequent sampling within the first 6 h after dosing. PD evaluation was restricted to Cohort F and utilized the same samples collected for PK analysis. For PK processing, blood specimens were centrifuged within 1 h of collection at 600× g for 10 min at 4 °C using a refrigerated centrifuge to obtain plasma. The resulting plasma was aliquoted and stored at ≤ −70 °C until bioanalysis. For PD processing, red blood cells were isolated from the lower fraction of the centrifuged blood samples. A defined volume (2 mL) of RBCs was transferred to a conical tube, diluted threefold with sterile normal saline, and gently mixed. The suspension was centrifuged under the same conditions, and the supernatant was discarded. This washing procedure was repeated twice to ensure adequate purification. The final RBC fraction was then stored at ≤ −70 °C until PD analysis.

Pharmacokinetics and pharmacodynamics analysis

Plasma levels of donepezil and its active metabolite, 6-O-desmethyl donepezil, were quantified using a validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) assay for pharmacokinetic evaluation. Concentrations below the lower limit of quantification (BQL) were handled according to the time of occurrence: values detected before Tmax were set to zero, whereas those detected after Tmax were treated as missing and excluded from analysis. Pharmacokinetic parameters were derived using non-compartmental analysis implemented in Phoenix WinNonlin® (version 8.5; Certara, L.P., Princeton, NJ, USA). Observed data were used to determine Cmax and Tmax, and the area under the concentration–time curve (AUC) was calculated using the linear trapezoidal method. For pharmacodynamic assessment, acetylcholinesterase (AChE) activity was measured using a spectrophotometric method based on a commercial assay kit (SIGMA-ALDRICH®, St. Louis, MO, USA). Reagents supplied with the kit were prepared according to the manufacturer's instructions, with a working solution freshly prepared at 10 mg/mL and used within 30 minutes to ensure stability. Any unused reagent was discarded immediately and not stored. Control samples, including water and a 200 U/L calibrator, were processed in parallel using identical procedures. For RBC samples, sequential dilutions were performed before analysis, and measurements were carried out within the assay's linear range (10–600 U/L); additional dilutions were applied when values exceeded the upper limit. The enzymatic reaction was quantified using a 96-well plate format in duplicate, and changes in AChE activity from baseline were calculated. Pharmacodynamic parameters, including Emax and AUE, were estimated using non-compartmental analysis in Phoenix WinNonlin® (version 8.5; Certara, L.P., Princeton, NJ, USA), with AUE determined using the linear trapezoidal approach.

Safety and tolerability analysis

Safety evaluations in this study included a systematic review of all reported clinical and laboratory data. This comprised adverse events (AEs), adverse drug reactions (ADRs), serious AEs/ADRs (SAE/SADRs), unexpected ADRs (UADRs), and injection-site reactions (ISRs), as well as documentation of concomitant and prior medication use. Additional safety parameters included vital signs (blood pressure, pulse rate, and tympanic body temperature), physical examination findings, routine laboratory test results, and 12-lead electrocardiogram (ECG) recordings.

Tolerability of the investigational products was assessed based on the overall safety dataset collected throughout the study period.

Pharmacokinetic modeling and simulation

Pharmacokinetic modeling and simulation were performed using data obtained from subjects receiving intramuscular GB-5001A and oral Aricept® 10 mg, with incorporation of individual covariates including sex, age, body weight, and CYP2D6 metabolizer status. Model development and evaluation were carried out using NONMEM® version 7.5 (ICON plc, Dublin, Ireland), following a stepwise process that included structural model identification, implementation of inter-individual variability, and construction of a final model.

Structural model exploration was conducted to define an appropriate compartmental framework. For GB-5001A, a two-compartment model was selected, incorporating three parallel absorption processes. Drug input into the central compartment was described by one zero-order and two first-order absorption pathways originating from an intramuscular depot **(Figure 2).** In contrast, oral Aricept® was adequately described using a standard two-compartment model with first-order absorption kinetics.

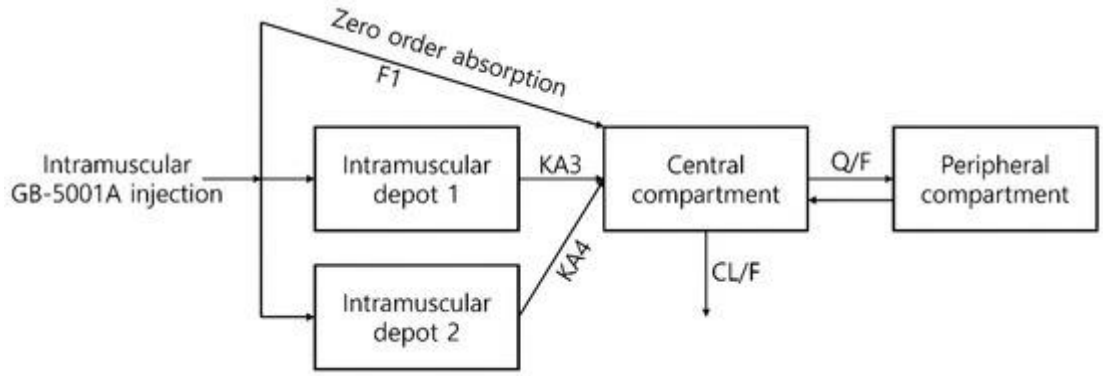


Figure 2. Structural model used for population pharmacokinetic analysis of GB-5001A. The model illustrates the disposition of GB-5001A following intramuscular administration, incorporating two depot compartments. Drug absorption into the central compartment occurs through two first-order processes (KA3 and KA4) and one zero-order pathway governed by the fraction absorbed (F1). The central compartment is linked to a peripheral compartment via intercompartmental clearance (Q/F), while systemic elimination is described by CL/F. The schematic arrows indicate the absorption, distribution, and elimination pathways, along with the corresponding pharmacokinetic parameters.

Within the basic structural framework, residual unexplained variability not captured by inter-individual differences was described using a combined error model. A single residual error term (ε) was applied to the model predictions (Y), incorporating both proportional (θ1) and additive (θ2) components to account for measurement and model-related variability (Eq. 1).

$$Y = F + \sqrt{F^2 * \theta_1^2 * \theta_2^2 * \varepsilon}, \qquad \varepsilon \sim N(0, 1^2) \tag{1}$$

In the final population pharmacokinetic model of GB-5001A, intercompartmental clearance (Q) was fixed at 100 L/h. Initial modeling efforts in which Q was estimated led to instability during model convergence. This issue was considered related to the formulation's flip-flop kinetics and to insufficient early sampling to adequately describe the distribution phase. The fixed value of 100 L/h was therefore selected based on preliminary estimates derived from the current dataset. It was also informed by previously reported values for an earlier formulation, where Q was approximately 185 L/h [14].

The final (full) model was defined as a model in which successful minimization was achieved while retaining as many covariates as possible identified during the screening process. Models were not excluded solely due to covariance step warnings or rounding issues, as these were not considered definitive indicators of model misspecification.

Model performance and adequacy were evaluated using diagnostic goodness-of-fit plots **(Figure 3)** as well as visual predictive checks (VPC).

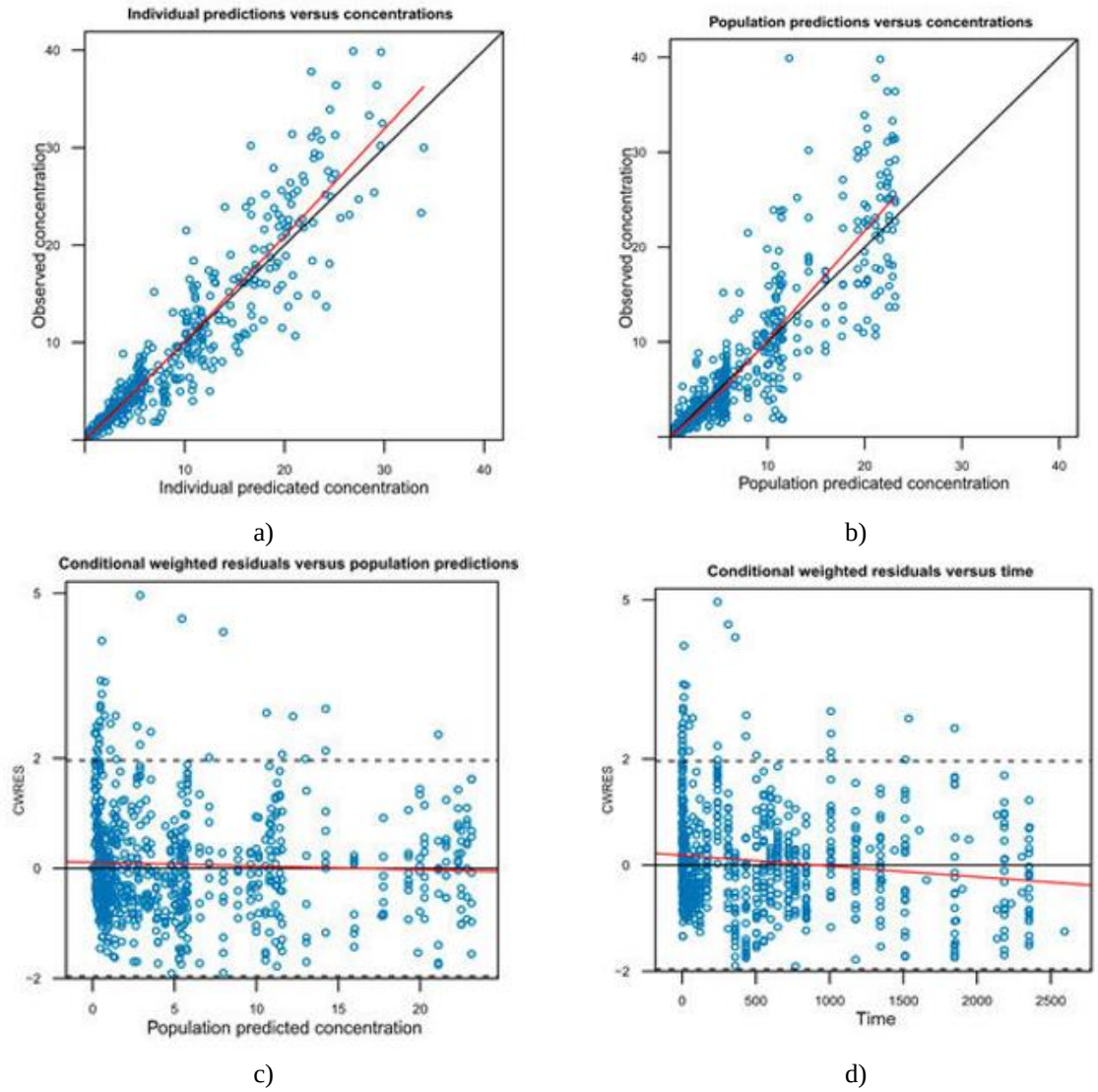


Figure 3. Goodness-of-fit diagnostics for the final population pharmacokinetic model of GB-5001A. The plots compare observed concentrations with both individual- and population-predicted values, alongside diagnostic assessments of conditional weighted residuals (CWRES) plotted against population predictions and time.

The solid black line in the upper panels represents the line of identity, while red curves indicate locally weighted smoothing (LOESS) trends. Horizontal dashed lines correspond to ±2 standard deviations, used to evaluate residual distribution and model performance.

Dose proportionality evaluation

Dose proportionality was examined in the intramuscular GB-5001A cohorts receiving 70 mg (Cohort A), 140 mg (Cohort E), and 280 mg (Cohort F). Each group was administered the same investigational formulation via the same route to allow direct comparison across dose levels.

To evaluate the relationship between dose and exposure, a regression approach was performed using SAS® (version 9.4; SAS Institute Inc., Cary, NC, USA). Both dose and key pharmacokinetic metrics (AUClast, AUCinf, and Cmax) were log-transformed before analysis, with exposure parameters treated as dependent variables and dose as the independent variable. The resulting slope estimates and their 95% confidence intervals were used to assess proportionality.

Additionally, dose-normalized values of AUClast, AUCinf, and Cmax were compared across cohorts using one-way analysis of variance (ANOVA), with $P < 0.05$ considered significant.

Statistical analysis

Statistical analyses were conducted using SAS® software (v9.4; SAS Institute Inc., Cary, NC, USA), and all hypothesis tests were two-sided with an alpha level of 0.05. P-values were reported to four decimal places, with values below 0.001 expressed as "< 0.0001."

For quantitative variables, cohort-wise summaries were generated. Depending on distributional assumptions, either one-way ANOVA (for normally distributed data) or the Kruskal–Wallis test (for non-normal data) was applied. Qualitative variables were summarized as counts and percentages, and intergroup differences were assessed using the Chi-square test. When expected cell counts were low (≥ 20% of cells ≤ 5), Fisher's exact test was used instead.

Adverse events were classified using MedDRA (version 27.1 or higher) and summarized by System Organ Class and Preferred Term. Safety outcomes were reported as the number and proportion of participants, the number of events, and 95% confidence intervals. For repeated events within the same participant, each subject was counted once per category, and the same individual could contribute to multiple categories if different event types occurred.

Results and Discussion

Study population and demographics

A total of 91 volunteers underwent screening, and 40 were excluded due to ineligibility. In the first part of the study, 35 subjects entered the trial; 34 of them were randomized and received study treatment, as one participant in Cohort B withdrew before dosing. During follow-up, early discontinuations occurred in Cohorts A and B (one case each), leaving 32 participants who completed Part A.

In the second part, 16 eligible volunteers were enrolled, and all were randomized and dosed. One participant in Cohort F discontinued after treatment, resulting in 15 completers across Part B (Cohort E: 8; Cohort F: 7).

For baseline analysis, only participants who received at least one dose of the investigational product were included. In Part A, this population consisted of 34 healthy male subjects. Mean age across the group was 29.53 ± 6.43 years, with cohort means of 29.22 ± 6.82 (A), 26.78 ± 4.76 (B), 30.25 ± 5.47 (C), and 32.25 ± 8.19 (D). Overall, the average body weight was 73.31 ± 8.72 kg, ranging from 70.00 ± 7.54 to 74.74 ± 10.75 kg across cohorts.

In Part B, 16 male participants were included in the safety and baseline set. The overall mean age was 31.00 ± 8.10 years, with cohort-specific means of 30.75 ± 10.21 (E) and 31.25 ± 6.02 (F). Mean body weight was 71.83 ± 10.43 kg, with values similar across cohorts.

A full summary of baseline characteristics is provided in **Table 1.**

Table 1. Demographic characteristics of the study population.

			Part A			
	P-value	**All (n = 34)**	**Aricept® 10 mg (n = 8)**	**GB-5001D 70 mg SC (n = 8)**	**GB-5001A 70 mg SC (n = 9)**	**GB-5001A 70 mg IM (n = 9)**
Sex						
Male	-	34 (100.00)	8 (100.00)	8 (100.00)	9 (100.00)	9 (100.00)
Age: (years)	0.3748	29.53 ± 6.43	32.25 ± 8.19	30.25 ± 5.47	26.78 ± 4.76	29.22 ± 6.82
Height :(cm)	0.5561	173.60 ± 6.20	176.23 ± 3.58	173.80 ± 7.95	172.33 ± 5.54	172.37 ± 7.13
Weight: (kg)	0.6403	73.31 ± 8.72	74.51 ± 8.25	74.74 ± 10.75	70.00 ± 7.54	74.28 ± 8.90
Body mass index: (kg/m^2)	0.6480	24.32 ± 2.56	23.94 ± 1.97	24.70 ± 2.84	23.61 ± 2.63	25.03 ± 2.88
			Part B			
	P-value	**All (n = 16)**	**GB-5001A 280 mg IM (n = 8)**	**GB-5001A 140 mg IM (n = 8)**		
Sex						
Male	-	16 (100.00)	8 (100.00)	8 (100.00)		
Age (years)	0.9067	31.00 ± 8.10	31.25 ± 6.02	30.75 ± 10.21		
Height (cm)	0.6029	173.11 ± 6.10	173.94 ± 5.02	172.28 ± 7.27		
Weight (kg)	0.7548	71.83 ± 10.43	70.98 ± 7.21	72.69 ± 13.39		

Body mass index (kg/m^2)	0.5480	23.92 ± 2.74	23.49 ± 2.61	24.35 ± 2.98

Notes: Continuous variables, including age, height, weight, and BMI, are reported as mean ± standard deviation (SD). In Part A, statistical comparisons among cohorts were conducted using one-way ANOVA, whereas in Part B, group differences were assessed using an independent t-test. Abbreviations: IM, intramuscular; SC, subcutaneous.

Pharmacokinetics

PK analyses were carried out in the per-protocol population, defined as participants who were exposed to the investigational product, complied with the study protocol without major deviations, and completed all planned pharmacokinetic sampling visits. In cases of early discontinuation, all PK data obtained before withdrawal were retained and included in the evaluation.

Donepezil

In Part A, participants receiving GB-5001A 70 mg via intramuscular injection exhibited the greatest systemic exposure to donepezil, with an AUClast (95% CI) of 6991.81 (4694.41–7978.01) h·ng/mL. The same group also demonstrated the highest peak concentration, with a Cmax (95% CI) of 5.28 (4.06–6.87) ng/mL. Detailed pharmacokinetic results for the remaining Part A cohorts are summarized in **Table 2 (Figure 4).**

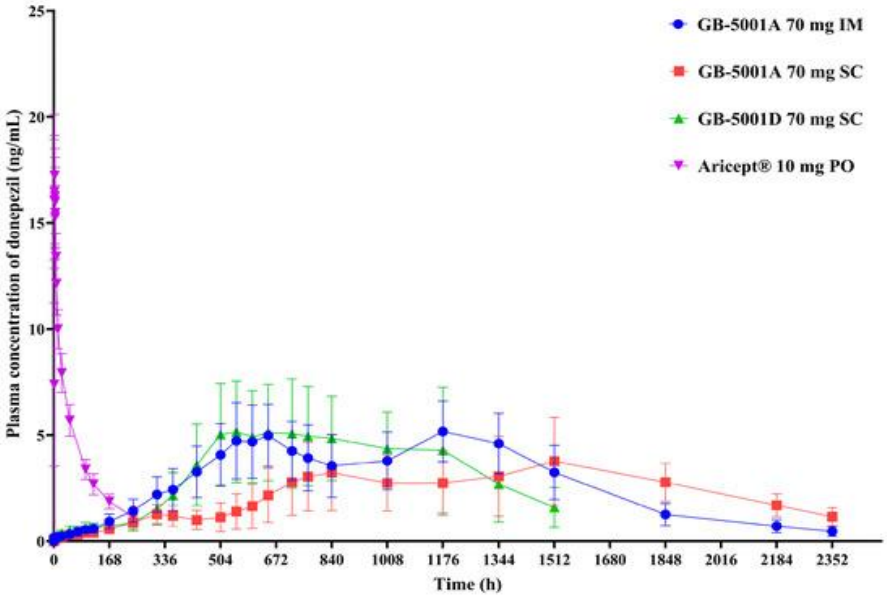


Figure 4. Presents the mean (± SD) plasma concentration–time curves of donepezil in Part A following single-dose administration in healthy participants. The figure compares GB-5001A 70 mg given subcutaneously (■), GB-5001A 70 mg administered intramuscularly (●), oral Aricept® 10 mg (▼), and GB-5001D 70 mg subcutaneously (▲).

Table 2. Summary of pharmacokinetic parameters for donepezil.

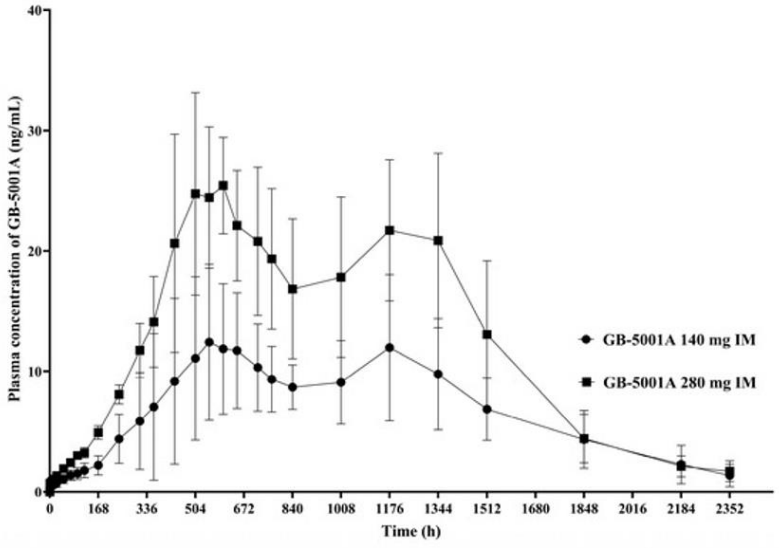
Pharmacokinetic parameters	**GB-5001A 280 mg IM**	**GB-5001A 140 mg IM**	**Aricept® 10 mg**	**GB-5001D 70 mg SC**	**GB-5001A 70 mg SC**	**GB-5001A 70 mg IM**
n	7	8	8	8	8	8
C_{max} (ng /mL)	29.12 (23.66, 35.84)	13.71 (10.46, 17.97)	17.54 (15.66, 19.63)	5.23 (2.85, 9.6)	3.78 (2.43, 5.88)	5.28 (4.06, 6.87)
T_{max} (h)	619.19 (442.79, 865.85)	816.72 (519.12, 1284.93)	2.50 (1.50, 3.00)	924.00 (504.00, 1176.00)	1512.00 (768.00, 1512.02)	1176.00 (552.00, 1344.00)
T_{lag} (h)	-	0.5	-	0.71 (0.01, 57.80)	1.86 (0.21, 16.34)	6.00
AUC $_{inf}$ (h·ng/mL)	29,693.07 (24,705.24, 35,687.92)	16,803.08 (13,076.75,	1078.73 (978.21, 1189.59)	4414.72 (2115.25,	5653.52 (3907.87, 8178.96)	6326.81 (4841.49, 8267.8)

		21,591.25) [n = 7]		9213.95) [n = 7]		
AUC last (h·ng/mL)	28,981.27 (24,212.79, 34,688.86)	15,523.91 (12,179.46, 19,786.74)	927.53 (857.93, 1002.78)	4219.61 (2249.72, 7914.38)	4831.61 (3244.52, 7195.02)	6119.81 (4694.41, 7978.01)
AUC 0–720 (h·ng/mL)	10,028.22 (8342.81, 12,054.12)	4341.46 (2638.35, 7143.94)	1073.26 (974.65, 1181.84)	1583.34 (777.48, 3224.49)	711.37 (440.19, 1149.63)	1773.33 (1282.41, 2452.19)
CL /F (L/h)	9.43 (7.85, 11.33)	8.33 (6.48, 10.71) [n = 7]	9.27 (8.41, 10.22)	15.86 (7.60, 33.09) [n = 7]	12.38 (8.56, 17.91)	11.06 (8.47, 14.46)
V_d/F (L)	3937.14 (3170.05, 4889.85)	3448.76 (2746.38, 4330.77) [n = 7]	1200.55 (1058.64, 1361.49)	6159.31 (3048.22, 12,445.66) [n = 7]	7587.24 (4433.43, 12,984.56)	5016.88 (3953.75, 6365.88)
$t_{1/2}$ (h)	289.4 (240.32, 348.52)	286.91 (251.35, 327.51) [n = 7]	89.77 (76.19, 105.77)	269.25 (161.48, 448.96) [n = 7]	424.75 (306.08, 589.43)	314.3 (276.31, 357.52)

Notes: Pharmacokinetic variables were summarized using geometric mean and 95% confidence interval, while Tmax is described as median (range). In the GB-5001D 70 mg SC cohort, one subject was excluded from analyses involving elimination-phase–dependent metrics (AUCinf, CL/F, Vd/F, and t1/2) due to insufficient definition of the terminal elimination phase.

Abbreviations: AUClast = exposure from time zero to last measurable concentration; AUCinf = exposure extrapolated to infinity; AUC0–720 = exposure from 0 to 720 h; Cmax = observed peak concentration; CL/F = apparent clearance; Vd/F = apparent distribution volume; t1/2 = terminal half-life; Tmax = time of peak concentration; Tlag = delay before first measurable concentration; IM = intramuscular; SC = subcutaneous.

Within Part B, the highest exposure to donepezil was observed in the GB-5001A 280 mg intramuscular group, showing an AUClast of 28,981.27 (24,212.79–34,688.86) h·ng/mL and a Cmax of 29.12 (23.66–35.84) ng/mL. Other pharmacokinetic findings from Part B are presented in **Table 2 (Figure 5).**



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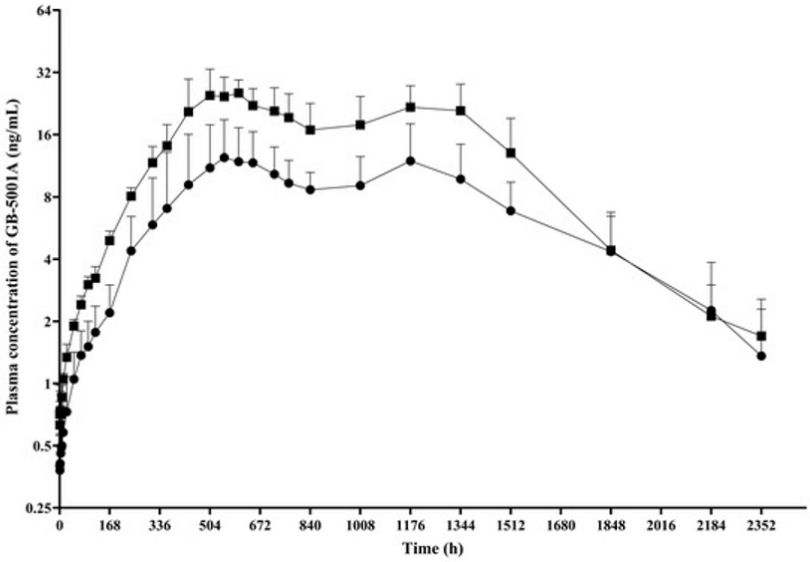


b)

Figure 5. Presents the average (± SD) concentration–time curves of GB-5001A in Part B following IM administration in healthy volunteers. Profiles are 280 mg (■) displayed and for the 140 mg (●) dose cohorts using both linear (a) and semi-logarithmic (b) axes.

6-O-desmethyl donepezil

Pharmacokinetic assessment of the active metabolite 6-O-desmethyl donepezil was restricted to participants who received GB-5001A at the 280 mg intramuscular dose level. The metabolite showed high systemic exposure, with a geometric mean AUClast of 80,078.69 h·ng/mL (95% CI: 54,625.31–117,392.42) and an AUCinf of 85,087.25 h·ng/mL (95% CI: 58,899.81–122,917.90).

Exposure within the first 720 hours (AUC0–720) was 31,156.10 h·ng/mL (95% CI: 22,682.70–42,794.84), and peak plasma concentration reached 100.12 ng/mL (95% CI: 66.73–150.20). The metabolite demonstrated a prolonged elimination phase, with a mean terminal half-life of 223.16 hours (95% CI: 178.41–279.14).

Time to maximum concentration occurred late and was highly variable across individuals, with a median Tmax of 552.03 hours (range: 432.03–1344.00). Full data are provided in **(Figure 6).**

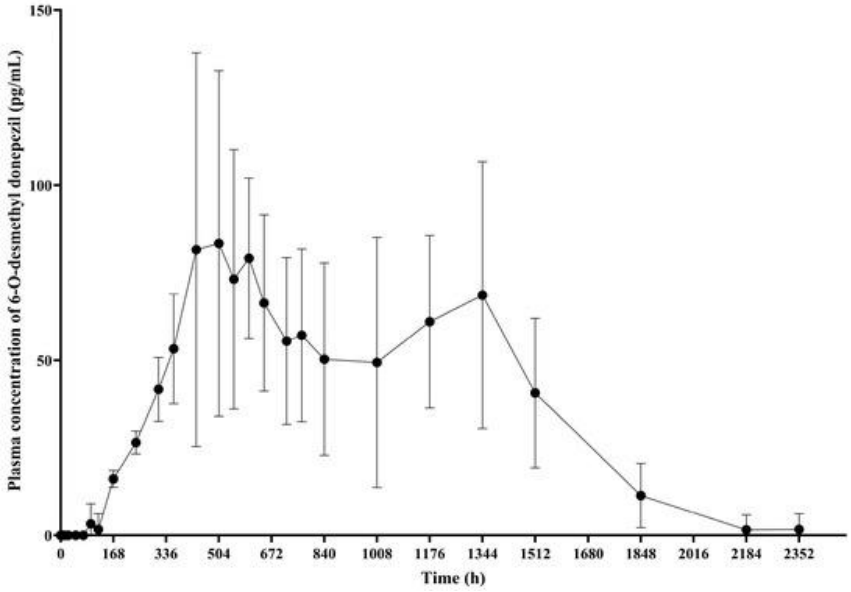


Figure 6. Illustrates the mean (± SD) plasma concentration–time profile of 6-O-desmethyl donepezil following intramuscular administration of GB-5001A at a dose of 280 mg in healthy participants.subcutaneously (■), GB-5001A 70 mg administered intramuscularly (●), oral Aricept® 10 mg (▼), and GB-5001D 70 mg subcutaneously (▲).

Pharmacodynamics

Pharmacodynamic evaluation of donepezil, assessed through acetylcholinesterase (AChE) inhibition, was performed in participants from Cohort F. The AUElast showed a geometric mean of 52,373.11 h (95% CI: 41,037.97–66,839.15), while the maximal inhibitory effect (Emax) reached 37.06% (95% CI: 28.94–47.44) as summarized in **Table 3.**

Table 3. Summary of pharmacodynamic parameters following GB-5001A 280 mg administration.

Variables	Values
n	7
E_{max} (%)	37.06 (28.94, 47.44)
AUE_{last} (h·{%})	52,373.11 (41,037.97, 66,839.15)

Note: Results are expressed as geometric mean values with 95% confidence intervals. AUElast refers to the area under the AChE inhibition–time curve from baseline to the last measurable effect, while Emax represents the peak percentage of acetylcholinesterase inhibition observed.

Safety and tolerability

Participants in the safety set were those who received at least 1 dose of study medication, totaling 34 in Part A and 16 in Part B.

For Part A, 25 of 34 participants experienced at least one adverse event, giving an overall incidence of 73.53% and a total of 60 events. By cohort, AEs were observed in 77.78% (7/9; 18 events) of the GB-5001A 70 mg IM group, 88.89% (8/9; 21 events) of the GB-5001A 70 mg SC group, 100% (8/8; 18 events) of the GB-5001D 70 mg SC group, and 25.00% (2/8; 3 events) of the Aricept® 10 mg group. Drug-related events were recorded in 17 participants overall (50.00%), mainly arising from the SC formulations, while none were reported in the IM GB-5001A group. No serious safety events or treatment discontinuations occurred.

In Part B, 14 of 16 participants (87.50%) reported AEs, totaling 31 events. Incidence was 75.00% in the 140 mg IM cohort and 100% in the 280 mg IM cohort. Drug-related AEs were observed in 13 participants (81.25%), with no serious cases or withdrawals.

Regarding system organ class distribution in Part A, the most frequently affected categories were General disorders and administration site conditions, followed by Investigations, with smaller proportions in Nervous system disorders and Respiratory-related disorders. The most common preferred terms included injection site pain, injection site induration, and elevated creatine phosphokinase.

In Part B, the leading SOCs were General disorders and administration site conditions, Investigations, and Infections and infestations. Frequently reported preferred terms included injection site discomfort, increased creatine phosphokinase, elevated bilirubin, and upper respiratory tract infection. Full AE classification is shown in **Table 4.**

Table 4. Summary of adverse events observed during the study.

System organ class/Preferred term	GB-5001A 280 mg IM	GB-5001A 140 mg IM	Aricept® 10 mg	GB-5001D 70 mg SC	GB-5001A 70 mg SC	GB-5001A 70 mg IM
General disorders and administration site conditions	6 (75.00), {6}	5 (62.50), {5}	0	7 (87.50), {11}	8 (88.89), {12}	0
Injection site pain	1 (12.50), {1}	0	0	7 (87.50), {8}	8 (88.89), {8}	0
Injection site induration	0	0	0	3 (37.50), {3}	4 (44.44), {4}	0
Injection site discomfort	5 (62.50), {5}	5 (62.50), {5}	0	0	0	0
Investigations (laboratory findings)	5 (62.50), {10}	3 (37.50), {3}	0	1 (12.50), {1}	0	0
Alanine aminotransferase elevation	1 (12.50), {1}	0	0	1 (12.50), {1}	0	0
Increased blood bilirubin	2 (25.00), {4}	1 (12.50), {1}	0	0	0	0

Elevated creatine phosphokinase	4 (50.00), {4}	0	0	0	0	0
Cardiac disorders	2 (25.00), {2}	0	0	0	1 (11.11), {1}	0
Arrhythmia	–	–	0	0	1 (11.11), {1}	0
Bradycardia	1 (12.50), {1}	0	0	0	0	0
Tachycardia	1 (12.50), {1}	0	0	0	0	0
Infections and infestations	2 (25.00), {3}	1 (12.50), {1}	2 (25.00), {3}	0	0	0
Upper respiratory tract infection	2 (25.00), {2}	1 (12.50), {1}	2 (25.00), {2}	0	0	0
Nasopharyngitis	1 (12.50), {1}	0	1 (12.50), {1}	0	0	0
Gastrointestinal disorders	0	1 (12.50), {1}	1 (12.50), {1}	1 (12.50), {1}	0	0
Nausea	0	0	1 (12.50), {1}	0	0	0
Vomiting	0	0	0	1 (12.50), {1}	0	0
Abdominal discomfort	0	1 (12.50), {1}	0	0	0	0
Nervous system disorders	0	0	1 (12.50), {1}	1 (12.50), {1}	0	0
Dizziness	0	0	1 (12.50), {1}	0	0	0
Headache	0	0	0	1 (12.50), {1}	0	0
Ear and labyrinth disorders	0	0	0	1 (12.50), {2}	0	0
Tinnitus	0	0	0	1 (12.50), {2}	0	0

Note: Values are expressed as n (%) for participants, with the corresponding total number of adverse events shown in braces { }. Abbreviations: IM, intramuscular; SC, subcutaneous.
No study withdrawal was attributed to adverse events following administration of GB-5001.

Dose proportionality

Dose proportionality was assessed in the intramuscular GB-5001A cohorts receiving 70 mg (Cohort A), 140 mg (Cohort E), and 280 mg (Cohort F). The association between administered dose and exposure was examined using log–log linear regression for AUClast, AUCinf, and Cmax. Estimated slope values (95% confidence intervals) were 1.13 (0.91–1.34), 1.12 (0.90–1.34), and 1.24 (1.01–1.46), respectively **(Table 5).**In addition, intergroup comparisons across dose levels were evaluated using analysis of variance (ANOVA), with detailed outcomes summarized in **Table 5.**

Table 5. Evaluation of dose proportionality for GB-5001A following intramuscular administration.

	Linear regression				
Variable	**Parameter estimate**	**Standard error**	**t-value**	**P-value**	**95% confidence intervals (Lower, Upper)**
C_{max}					
Intercept	−3.55	0.54	−6.61	< 0.0001	
Dose	1.24	0.11	11.37	< 0.0001	(1.01, 1.46)
AUC_{last}					
Intercept	3.98	0.52	7.72	< 0.0001	
Dose	1.13	0.10	10.80	< 0.0001	(0.91, 1.34)
AUC_{inf}					
Intercept	4.05	0.52	7.78	< 0.0001	

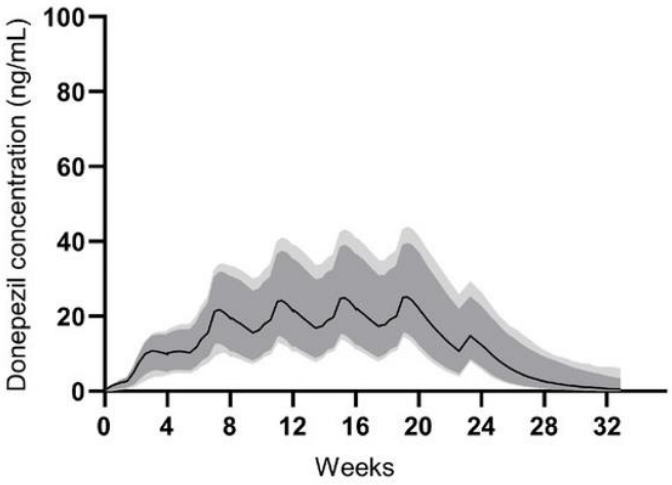
Dose	1.12	0.11	10.65	< 0.0001	(0.90, 1.34)
Analysis of covariance					
Pharmacokinetic parameters	**Num DF**	**Den DF**	**F value**	**p value**	
AUC_{last} (h·ng/mL)	2	20	1.57	0.2333	
C_{max} (ng/mL)	2	20	2.61	0.0985	
AUC_{inf} (h·ng/mL)	2	19	2.07	0.1538	

Note: Dose proportionality was evaluated based on intramuscular GB-5001A dose groups of 70 mg, 140 mg, and 280 mg. The analysis included PK exposure metrics across these cohorts. Abbreviations: AUClast, area under the concentration–time curve to the last measurable point; AUCinf, area under the concentration–time curve extrapolated to infinity; Cmax, peak plasma concentration observed.

Pharmacokinetic modeling and simulation

Modeling and simulation analyses were performed using data from Cohorts A, E, and F (GB-5001A administered intramuscularly), while Cohort D data were used to characterize oral Aricept® 10 mg. Overall, 32 participants were included in the modeling dataset. Covariates incorporated into the model included sex, age, body weight, and measured plasma concentrations of donepezil; CYP2D6 metabolizer status was additionally considered for participants in Cohorts E and F.

The estimated pharmacokinetic parameters for both GB-5001A and Aricept® derived from the final model are presented in **Table 6.** Simulation analyses assumed repeated intramuscular dosing of GB-5001A every 28 days over four administrations. Plasma concentration–time profiles were generated through 1000 simulation runs, and the resulting trajectories with corresponding 90% and 95% confidence intervals are shown in **Figure 7.**



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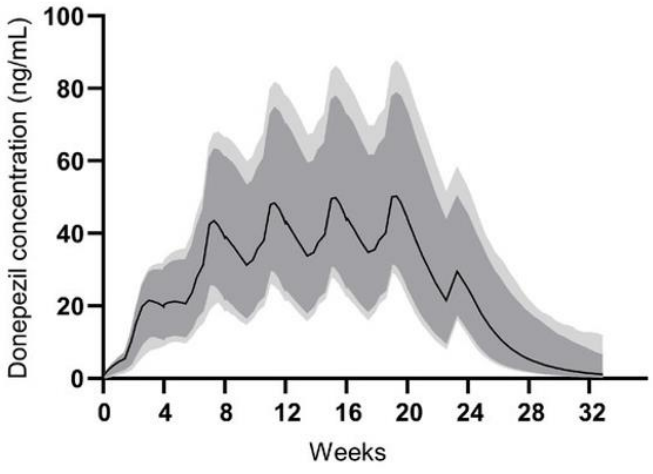

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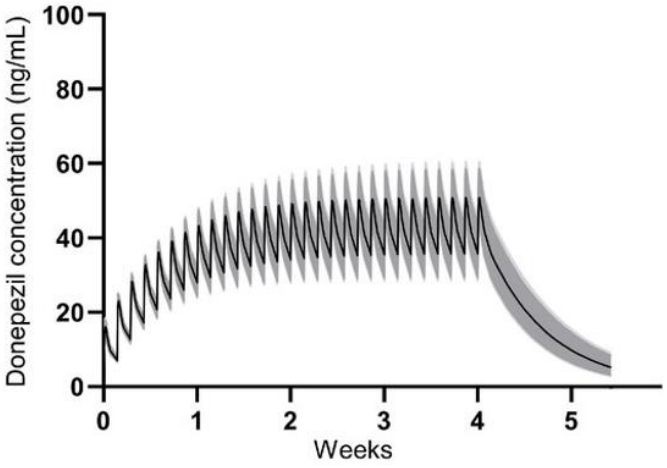

c)

Figure 7. The simulated pharmacokinetic profiles of GB-5001A under multiple-dose administration conditions. Median model predictions are indicated by solid black lines, while the dark grey band corresponds to the 90% prediction interval and the light grey band represents the 95% prediction interval. Panel (a) shows results for intramuscular GB-5001A 140 mg, panel (b) for intramuscular GB-5001A 280 mg, and panel (c) for oral Aricept® 10 mg administered once daily.

Table 6. Population parameter estimates for the final pharmacokinetic model of GB-5001A.

Parameter	Point estimate	95% confidence interval	Standard error
V_1, L	58.2	−35.684–152.084	47.9
ALAG4	1130	1075.708–1184.292	27.7
IIV_{V1}	6.97		1.69
V_2, L	2050	1456.12–2643.88	303
D1	497	485.436–508.564	5.9
F3	0.657	0.623–0.691	0.0172
F4	0.195	0.167–0.223	0.0142
Q	100 FIX		
ALAG3	299	285.456–312.544	6.97
IIV_{CL}	0.0945		0.0334
ε_2 (proportional) [a]	0.271	0.237–0.305	0.0174
ε_1 (additive), ng/mL	0.0713	0.0307–0.112	0.0207
CL, L/h	9.57	8.453–10.687	0.57
KA_4, 1/h	0.0113	0.00187–0.0207	0.00481
KA_3, 1/h	0.00173	0.00145–0.00201	0.000141

Notes: This table presents results from the population pharmacokinetic model, including parameter point estimates, standard errors, and 95% confidence intervals. Sources of variability are also reported, consisting of inter-individual variability (IIV) and residual unexplained variability. The structural model incorporates multiple kinetic components, including clearance (CL), distribution spaces for the central and peripheral compartments (V1 and V2), dual absorption processes (KA3, KA4), fractional bioavailability terms (F3, F4), intercompartmental transfer (Q), absorption delay terms (ALAG3, ALAG4), and a zero-order input duration parameter (D1). IIV was estimated only for CL and V1. Residual error was modeled using a combined structure with additive (ε1) and proportional (ε2) components. During model development, Q was fixed at 100 L/h due to instability in the estimation.

Abbreviations: IIV = inter-individual variability; CV = coefficient of variation (%), defined as CV = $\sqrt{(\exp(\omega) - 1)} \times 100$; CL = systemic clearance; V1 = central compartment volume; V2 = peripheral compartment volume; KA3 = absorption rate constant for first IM depot; KA4 = absorption rate constant for second IM depot; F3 = bioavailability from first IM depot; F4 = bioavailability from second IM depot; Q = intercompartmental clearance; D1 = duration of zero-order absorption; ALAG3 = absorption lag time for first depot; ALAG4 = absorption lag time for second depot.

The estimate of central compartment volume was associated with relatively wide uncertainty **(Table 6),** consistent with the kinetic characteristics of long-acting injectable formulations, in which absorption processes largely govern the observed concentration–time behavior. In addition, the limited availability of samples during the early post-dose period likely reduced the resolution of the distribution phase. Despite this limitation, the main exposure metrics remained robust. Overall, variability in clearance and distribution parameters was low, reflecting the

controlled, homogeneous nature of the study population, which comprised healthy male volunteers with strict eligibility criteria. The exclusion of CYP2D6 poor metabolizers in the higher-dose cohort may have further minimized inter-subject pharmacokinetic variability.

In the simulation for oral Aricept® 10 mg administered once daily for 28 days, 1000 Monte Carlo replicates were generated to construct concentration–time profiles and corresponding 90% and 95% prediction intervals **Figure 7**. Steady-state parameters were derived from these simulations and reported as mean values with coefficients of variation (CV%). The fluctuation index (Swing_tau) was calculated using ($C_{max,ss} - C_{min,ss}$) divided by Cav, ss.

For GB-5001A 140 mg IM, the simulated steady-state results were: $C_{max,ss}$ 26.2 ng/mL (28.0%), $C_{min,ss}$ 18.3 ng/mL (35.9%), AUCτ 15,111.5 h·ng/mL (31.5%), Cav, ss 22.5 ng/mL (31.5%), and Swing_tau 0.37 (33.2%), for the 280 mg IM dose, values were: $C_{max,ss}$ 52.4 ng/mL (28.0%), $C_{min,ss}$ 36.8 ng/mL (36.1%), AUCτ 30,259.2 h·ng/mL (31.6%), Cav, ss 45.0 ng/mL (31.6%), and Swing_tau 0.37 (32.5%). In comparison, oral Aricept® 10 mg showed: $C_{max,ss}$ 51.4 ng/mL (8.9%), $C_{min,ss}$ 36.0 ng/mL (12.2%), AUCτ 1120.9 h·ng/mL (9.4%), Cav, ss 46.7 ng/mL (9.4%), and Swing_tau 0.33.

CYP2D6

CYP2D6 phenotyping was performed only in participants enrolled in Part B. Based on metabolic capacity, individuals were categorized as ultrarapid (UM), extensive (EM), intermediate, or poor metabolizers (PM).

Within the GB-5001A 140 mg intramuscular cohort, most subjects were classified as extensive metabolizers (62.5%, 5/8), while the remaining 37.5% (3/8) were intermediate metabolizers. No UM or PM phenotypes were detected in this group.

In the GB-5001A 280 mg intramuscular cohort, the majority of participants were extensive metabolizers (87.5%, 7/8), with a small proportion identified as intermediate metabolizers (12.5%, 1/8). Other CYP2D6 phenotypes were not observed in this cohort.

The injectable formulation of donepezil is administered intramuscularly and subcutaneously. In addition, the active metabolite profile and exploratory multiple-dose pharmacokinetics were characterized using modeling and simulation approaches.

Each cohort was planned to include eight participants, and this enrollment target was achieved before dosing. However, one participant in Cohort F discontinued after the administration, leaving seven completers in that group. Baseline demographic characteristics were generally comparable across cohorts, with similar distributions in age and body weight among healthy male subjects.

Pharmacokinetic findings demonstrated a clear increase in systemic exposure with increasing intramuscular doses of GB-5001A (70 mg, 140 mg, and 280 mg). Exposure metrics, including AUClast, AUCinf, and Cmax, increased consistently across dose levels. Dose proportionality assessment supported a largely linear relationship for AUClast and AUCinf, whereas Cmax showed a slightly greater-than-proportional increase at higher doses. ANOVA results did not indicate statistically significant differences among dose groups for AUClast, AUCinf, or Cmax, suggesting a low likelihood of nonlinear kinetics within the studied range and predictable exposure behavior across doses.

Both intramuscular and subcutaneous formulations of GB-5001 exhibited slow absorption, with gradual increases in plasma concentrations after administration. In contrast, oral Aricept® demonstrated rapid absorption and elimination. Long-acting formulations of GB-5001A and GB-5001D produced prolonged exposure profiles with sustained concentrations over several weeks and a biphasic peak pattern, consistent with depot-based drug release. Overall, the observed pharmacokinetic pattern is consistent with absorption-limited disposition, in which absorption governs the terminal phase rather than elimination. Given the depot nature of the formulations and the extended release from tissue reservoirs, absorption is likely the rate-determining step shaping the concentration–time profile. The prolonged Tmax and extended apparent half-life observed in both IM and SC groups further support this interpretation and suggest a potential flip-flop kinetic behavior for GB-5001 formulations.

The pharmacokinetic profile of GB-5001 indicates an absorption-rate–limited, flip-flop kinetic behavior, with important consequences for both model structure and parameter interpretation. In contrast to oral donepezil—characterized in our model by rapid first-order absorption ($ka = 0.7\ h^{-1}$)—the intramuscular and subcutaneous formulations of GB-5001 showed substantially slower input rates, with estimated $KA3 = 0.00173\ h^{-1}$ and $KA4 = 0.0113\ h^{-1}$, respectively.

A distinctive feature of GB-5001 was the presence of a biphasic peak pattern in the concentration–time profiles. To appropriately represent this behavior, the model incorporated two delayed absorption processes with separate

rate constants, which improved the structural fit and were supported during model evaluation. Consequently, the terminal phase for GB-5001 was not driven by systemic elimination but instead reflected sustained release from the depot site. Failure to incorporate this absorption-limited mechanism would lead to mischaracterization of elimination and distribution parameters.

Accordingly, the final population PK model for GB-5001A included a depot-driven structure with a zero-order input and dual first-order absorption pathways. This formulation correctly attributed the prolonged terminal slope to slow absorption processes and minimized bias in elimination-related estimates.

Intramuscular administration of GB-5001A also resulted in a substantially longer apparent half-life compared with oral donepezil, indicating prolonged systemic exposure. This extension was approximately three- to four-fold, supporting the feasibility of GB-5001 as a long-acting injectable option for Alzheimer's disease therapy.

To further evaluate absorption behavior, lag time (Tlag) was determined from the first measurable plasma concentration. In the 70 mg and 140 mg intramuscular cohorts, 7 of 8 participants exhibited detectable concentrations at the first sampling point, resulting in a Tlag of 0 h in most cases. If assay sensitivity or sampling design were the main factors influencing this observation, a consistent delay would be expected across multiple participants. Instead, delayed Tlag was observed only in isolated cases, potentially reflecting inter-individual variability in injection-site tissue composition such as muscle and adipose distribution. Nevertheless, additional investigations are required to confirm this explanation.

The influence of CYP2D6 metabolic phenotype on donepezil pharmacokinetics was explored in this study. In Cohort E, concentration–time profiles were examined according to CYP2D6 classification, comparing extensive metabolizers (EMs) and intermediate metabolizers. EM subjects tended to show slightly lower early exposure, whereas a relatively slower decline in plasma concentrations was observed at later time points (after approximately 1512 h) compared with intermediate metabolizers. This tendency aligns with prior literature describing genotype- or phenotype-dependent variability in donepezil disposition [15, 16].

However, the limited number of participants substantially restricted interpretability. In Cohort F, the only identified intermediate metabolizer discontinued participation on Day 64 for personal reasons, resulting in incomplete pharmacokinetic sampling. As a result, PK evaluation in this cohort was restricted to EM subjects only. Overall, the small sample size precluded meaningful statistical comparison between metabolizer groups, and these findings should be regarded as exploratory. Larger studies will be required to clarify the role of CYP2D6 phenotype in this setting.

Regarding the metabolite 6-O-desmethyl donepezil, systemic exposure and peak concentrations were substantially lower than those of the parent drug. This observation is consistent with earlier reports indicating that metabolite levels are often near or below the lower limit of quantification (0.2 ng/mL) [17].

For pharmacodynamic evaluation, acetylcholinesterase inhibition was used as the primary biomarker. Because the study population consisted of healthy volunteers, clinical efficacy outcomes in patients with Alzheimer's disease were not assessed. Previous research has suggested that approximately 65% or greater AChE inhibition may correlate with cognitive improvement as measured by ADAS-cog scores [18]. In the present study, the observed inhibition level (~37%) was below that threshold and therefore insufficient to infer clinical efficacy. Nevertheless, the PD response was broadly consistent with that reported after a single oral dose of donepezil in earlier studies [19].

No participants discontinued treatment due to adverse events, and no serious or clinically meaningful safety issues were observed. A single Grade 3 elevation in blood creatine phosphokinase occurred after intramuscular administration of GB-5001A, but it resolved spontaneously without any medical intervention. Overall, most treatment-related adverse reactions were mild in severity and mainly involved local injection-site symptoms. Interestingly, such injection-site reactions were not observed in the intramuscular cohorts in Part A but were observed in Part B, despite the same formulation being administered. This discrepancy is most likely related to the higher injection volumes used in the higher-dose cohorts, suggesting that local tolerability may be influenced by administered volume. Nevertheless, all injection-site reactions were transient and self-limiting, indicating that GB-5001A is generally well tolerated when administered intramuscularly.

Model-based simulations suggested that repeated intramuscular dosing of GB-5001A every 28 days results in near steady-state conditions after approximately three administrations, with sustained plasma exposure thereafter. The 280 mg intramuscular dose achieved steady-state Cmax and AUCτ values that were broadly comparable to those observed with daily oral administration of Aricept® 10 mg, supporting its potential as a long-acting therapeutic alternative.

When compared with a previous GB-5001 study, the current investigation showed lower peak concentrations and a delayed time to peak exposure for GB-5001A [14]. This longer Tmax may reflect further optimization of the long-acting injectable formulation. Given the known association between donepezil exposure and dose-dependent adverse events, the reduced Cmax observed here may improve tolerability [20]. Importantly, despite these pharmacokinetic differences, overall exposure remained similar across studies, reinforcing the feasibility of GB-5001A as a long-acting formulation candidate. However, given that the present study was conducted exclusively in healthy male volunteers rather than the typical elderly, mixed-sex patient population, further clinical studies are required before translation into routine clinical practice.

Conclusion

GB-5001A demonstrated an overall acceptable safety and tolerability profile, accompanied by largely dose-proportional pharmacokinetics and a substantially extended elimination profile relative to oral donepezil. While Cmax showed a modestly greater-than-proportional increase with dose escalation, total systemic exposure remained consistent across the investigated dose range.
Collectively, these results support the potential of GB-5001A as a long-acting injectable formulation that could replace daily oral donepezil with a once-monthly dosing regimen.

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Conflict of Interest: Eunyoung Seol and Jongmi Lee are employees of G2GBIO, Inc. The other authors report no financial or commercial ties that could be considered a conflict of interest in relation to this work.

Financial Support: The clinical trial received financial backing from G2GBIO, Inc., which also supplied all investigational drug materials used in the study.

Ethics Statement: Ethical approval for the study was obtained from both the Korea Ministry of Food and Drug Safety and the Institutional Review Board of Chungnam National University Hospital. The protocol was authorized under approval number CNUH 2023-08-088 on 12 October 2023.
All participants provided voluntary written consent before taking part in the study.

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