Population Pharmacokinetics of GB-5001, a Long-acting Intramuscular Injection of Donepezil, in Healthy Participants

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BACKGROUND

- Alzheimer's disease (AD) is a neurodegenerative disorder marked by a progressive decline in cognitive or behavioral impairment.
- Donepezil, characterized by a non-competitive and reversible inhibitor of Acetylcholinesterase (AChE), alleviates AD symptoms by inhibiting the hydrolysis of AChE, which enhances cholinergic neurotransmission.
- GB-5001 is a sustained-release intramuscular (IM) injectable of donepezil for a monthly treatment interval under development for the treatment of AD.
- Compared to daily oral treatment, GB-5001 is expected to improve patient compliance and treatment adherence, which is a major concern among the elderly population affected by AD.

OBJECTIVE

- The aim of this study was to develop a population pharmacokinetic (PK) model for donepezil in both IM and oral formulation, and to optimize the dose of the IM formulation to achieve systemic exposure comparable to that of the oral formulation following multiple administration.

METHODS

- Data from a Phase 1, randomized, double-blind, placebo-controlled, dose-escalation study (NCT05525780) were used for the population PK analysis.
- Data consisted of plasma donepezil concentrations from 27 participants who received a single dose of the IM formulation (GB-5001 injection 70 mg, 140 mg, or 280 mg), and 12 participants who received a single dose of the oral formulation (Aricept tablet 10 mg).
- A population PK model of donepezil for the IM and oral formulation was developed using NONMEM software version 7.5.1.
- The model was evaluated based on goodness-of-fit plots, conditional weighted residuals, and visual predictive check (VPC).
- Based on the final PK model, bootstrapping with 1000 replications was conducted for the validation of the parameter estimates.
- The final PK model was used for Monte Carlo simulations (N=200) of plasma donepezil concentrations, simulating three administrations of different doses of an IM formulation at four-week intervals and daily administrations of a 10 mg oral formulation for 84 days.
- Simulation results were analyzed using R version 4.2.1 NonCompart package to calculate the maximum plasma concentration (C_{max}) and the area under the concentration-time curve (AUC) at steady state.

RESULTS

- A total of 39 subjects with 853 concentration data of donepezil were used for population PK modeling.
- The PKs of donepezil were best described by a two-compartment model.
- Distinct absorption compartments were defined for the IM (dual first-order absorption with lag time and a simultaneous zero-order absorption) and oral formulation (first-order absorption).
- The volume of distribution, clearance, inter-compartmental clearance, and residual errors of donepezil concentrations were separately modeled for each formulation, considering the different distribution and elimination profiles between the oral and IM formulation (Figure 1, Table 1).

Table 1. Parameter estimates of the population pharmacokinetic model of donepezil for oral and intramuscular formulation.

		Final model		Bootstrap*	
Parameter		**Estimate**	**RSE**	**Median**	**95% CI**
Oral formulation					
Oral bioavailability	F1	1 (fixed)	-	-	-
Absorption rate constant (depot 1)	KA	0.203 h^{-1}	11.40%	0.21	(0.165 - 0.257)
Clearance	CL	14.3 L/h	6.50%	14.35	(12.602 - 16.282)
Volume of distribution (central)	V2	39.5 L	36.50%	40.737	(19.526 - 73.488)
Intercompartmental clearance	Q	84.9 L/h	9.60%	86.514	(70.362 - 103.327)
Volume of distribution (peripheral)	V3	1080 L	5.90%	1073.55	(957.33 - 1202.795)
Absorption lag time (depot 1)	ALAG1	0.931 h	1.70%	0.93	(0.887 - 0.956)
IIV on clearance		0.0475 (22.1%)†	39.20%	0.045	(0.009 - 0.08)
IIV on volume of distribution (central)		1.59 (197.6%)†	31.10%	1.498	(0.636 - 2.525)
Covariance clearance vs volume of distribution (central)		-0.144 (-52.0%)†	68.60%	-0.131	(-0.311 - 0.024)
IIV volume of distribution (peripheral)		0.0153 (12.4%)†	44.10%	0.015	(0.002 - 0.031)
IIV oral bioavailability		0.0162 (12.8%)†	28.60%	0.013	(0.003 - 0.023)
Proportional error		0.137	11.50%	0.132	(0.106 - 0.162)
Additive error		138 pg/mL	13%	137.786	(85.692 - 202.99)
Intramuscular formulation					
Fraction of dose (depot 4)	F4	0.748	1.90%	0.748	(0.719 - 0.778)
Fraction of dose (depot 5)	F5	0.145	11.20%	0.144	(0.106 - 0.172)
Absorption rate constant (depot 4)	KA4	0.00402 h^{-1}	6.70%	0.004	(0.004 - 0.005)
Absorption rate constant (depot 5)	KA5	0.0134 h^{-1}	17.20%	0.015	(0.011 - 0.034)
Clearance	CL	10.3 L/h	6.10%	10.295	(9.112 - 11.595)
Volume of distribution (central)	V2	503 L	29%	511.553	(259.082 - 834.504)
Intercompartmental clearance	Q	185 L/h	18.10%	183.88	(128.741 - 250.004)
Volume of distribution (peripheral)	V3	1160 L	8.30%	1176.22	(1026.616 - 1357.204)
Duration of zero order absorption	D2	648 h	0.20%	647.833	(574.904 - 820.454)
Absorption lag time (depot 4)	ALAG4	235 h	0.50%	234.934	(231.951 - 236.813)
Absorption lag time (depot 5)	ALAG5	645 h	0.20%	644.194	(637.819 - 709.858)
IIV on clearance		0.0936 (31.3%)†	24%	0.088	(0.053 - 0.137)
IIV on volume of distribution (central)		1.13 (144.8%)†	39.70%	1.06	(0.496 - 2.37)
Covariance clearance vs volume of distribution (central)		0.113	55.20%	0.118	(-0.02 - 0.239)
Proportional error		0.223	5%	0.219	(0.196 - 0.241)
Additive error		23.5 pg/mL	14.40%	23.353	(15.668 - 30.726)

*605 successful bootstrap runs were included (307 runs with minimization terminated were skipped when calculating the bootstrap results, and 88 runs with estimates near a boundary were skipped when calculating the bootstrap results)

†Coefficient of variation calculated as $\sqrt{e^{\omega^2}-1} \times 100$

Abbreviations: CI, confidence interval; RSE, relative standard error; IIV, inter-individual variability.

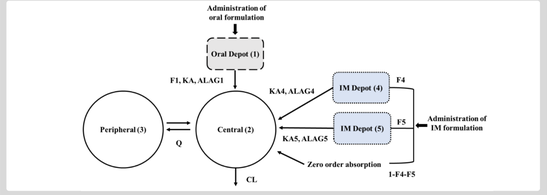

Figure 1. Structure for population pharmacokinetic model of donepezil for oral and intramuscular formulation.

Abbreviations: ALAG1, Absorption lag time (depot 1); ALAG4, Absorption lag time (depot 4); ALAG5, Absorption lag time (depot 5); CL, Clearance; IM, Intramuscular; F1, Oral bioavailability; F4, Fraction of dose (depot 4); F5, Fraction of dose (depot 5); KA, Absorption rate constant (depot 1); KA4, Absorption rate constant (depot 4); KA5, Absorption rate constant (depot 5); Q, Intercompartmental clearance.

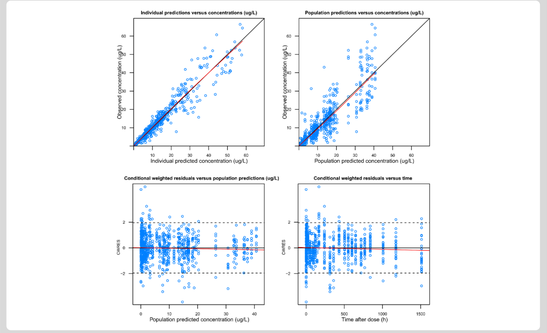

Figure 2. Diagnostic plots of the final population PK model.

Abbreviation: CWRES, conditional weighted residuals.

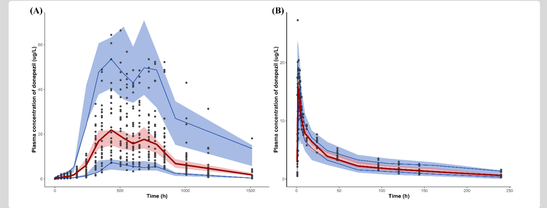

Figure 3. Visual predictive plot of the population pharmacokinetic model for donepezil (A) IM and (B) oral formulation.

Notes: Dots are observed concentrations. The blue solid lines are the 5% and 95% percentile of the observed concentrations, and the blue shaded area are the 95% confidence intervals of the simulated 5% and 95% percentile. The red solid line is the 50% percentile of the observed concentrations, and the red shaded area is the 95% confidence intervals of the simulated 50% percentile.

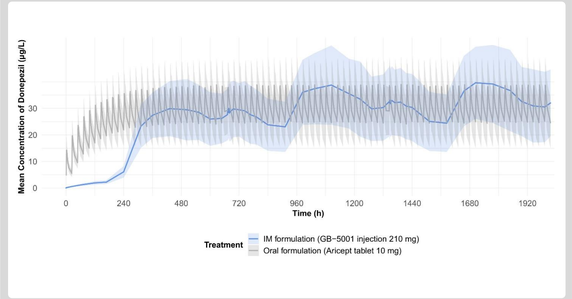

Figure 4. Simulated mean concentration-time profile of donepezil following intramuscular (GB-5001 injection 210 mg) and oral (Aricept Tablet 10 mg) administration.

- The diagnostic plots (Figure 2), VPC results (Figure 3), and bootstrapping analysis (Table 1) indicated that the PK model adequately described the observed data.
- The simulated steady state systemic exposure of a daily oral dose of donepezil 10 mg was comparable to that of a 210 mg IM dose administered at four-week intervals (Figure 4).
- In this scenario, the mean ± standard deviation (SD) of the simulated steady-state C_{max} for the IM and the oral formulation were 49.00 ± 16.02 and 45.34 ± 10.83 μg/L, respectively.
- The mean ± SD of the simulated steady state AUC for the IM formulation (observed over 28 days following the third administration) and the oral formulation (observed AUC on day 84 multiplied by 28) were 21834.57 ± 7288.64 and 20265.28 ± 5759.60 h·μg/L, respectively.

CONCLUSION

- Our population PK model of donepezil well explained the PKs of both the IM and oral formulation.
- This study will inform the decision-making process in the design and dose selection of future clinical trials.
- A pivotal bioequivalence (BE) study is planned to be conducted on a selected dose based on this modeling study to demonstrate the BE of the PKs and safety profiles of the IM formulation compared to the oral formulation in patients with AD.

CONFLICTS OF INTEREST

- This study was sponsored by G2GBIO, Inc.
- Eunyoung Seol and Heeyong Lee are employees of G2GBIO, Inc.
- The other authors do not have any conflicts of interest in this study.