

Phase 1 Study and Population Pharmacokinetic Characterization of GB-5001, a Long-Acting Intramuscular Donepezil

P3-01

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- ◆ GB-5001 was well tolerated in healthy male volunteers, with injection-site reactions being the most common adverse events and generally mild in severity.
- ◆ Following the single intramuscular administration, GB-5001 demonstrated approximately dose-proportional donepezil exposure over the 70-280 mg dose range.
- ◆ The prolonged absorption profile, characterized by delayed T_{max} and extended apparent half-life, supports the feasibility of once-monthly intramuscular dosing.
- ◆ At steady-state, monthly GB-5001 maintained sustained plasma donepezil exposure with lower peak-to-trough fluctuation than daily oral donepezil.
- ◆ An integrated population pharmacokinetic model, informed by both the phase 1 study and the Indonesian pilot study, supported predictable accumulation and steady-state exposure comparable to oral donepezil.

INTRODUCTION

Symptomatic pharmacotherapy for Alzheimer's disease (AD) — including donepezil, rivastigmine, galantamine, and memantine — requires **daily oral administration** and is frequently complicated by gastrointestinal adverse events and impaired adherence in patients with cognitive decline.

GB-5001 is a novel long-acting injectable (LAI) microsphere formulation of donepezil designed for **once-monthly intramuscular (IM) administration**, with the goal of improving adherence while maintaining a therapeutic exposure window comparable to oral donepezil.

This poster integrates evidence from the completed **Single Ascending Dose (SAD)** phase, the ongoing **Multiple Ascending Dose (MAD)** phase, and a **population pharmacokinetic (PopPK)** model-based analysis of GB-5001 in healthy male volunteers.

Objective. To characterize the safety, tolerability, and PK of GB-5001 across single and repeated IM doses and to support predictable accumulation and steady-state exposure via PopPK modeling and simulation.

METHODS

Design. Open-label, active-controlled, parallel, dose-escalation Phase 1 study in healthy adult male volunteers, with SAD and MAD phases.

SAD GB-5001A IM single doses: **70, 140, 280 mg**. Comparator arm: oral Aricept® 10 mg.
MAD GB-5001A IM **140 mg every 4 weeks** × 4 administrations (D1, D29, D57, D85) vs. oral Aricept®. Dense PK sampling through ~D204 to characterize accumulation and steady-state.

PopPK modeling and simulation NONMEM® v7.5 (FOCE-INTER); two-compartment disposition with parallel IM depot pathways (zero-order + two first-order absorption with lag) to capture observed double-peak. Model adequacy assessed by GOF, VPC, and NPDE; integrated SAD + MAD posthoc predictions.

Indonesian clinical trial An open-label, randomized, multiple-dose, three-arm parallel pilot PK study was conducted in 28 healthy Indonesian male volunteers. Participants received GB-5001A IM 280 mg, oral Aricept® followed by GB-5001A IM 280 mg, or oral Aricept® only.

All plasma donepezil concentrations were quantified by validated liquid chromatography-tandem mass spectrometry.

RESULTS

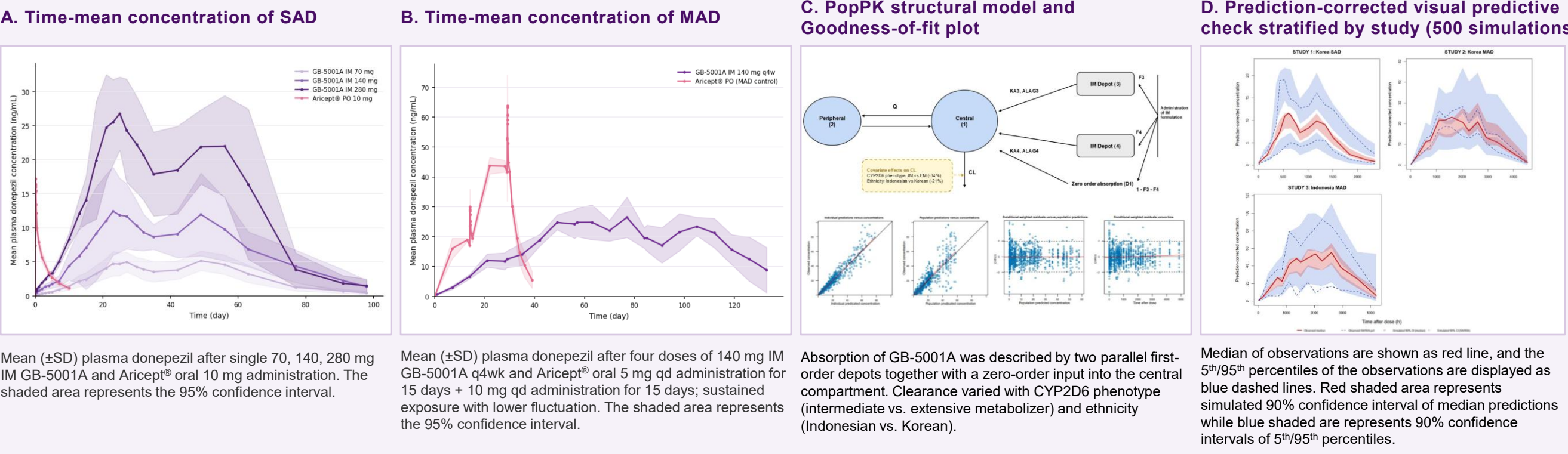


Table 1. SAD PK parameters of donepezil				
Parameter	GB-5001A 70 mg IM	GB-5001A 140 mg IM	GB-5001A 280 mg IM	Aricept® 10 mg PO
n	8	8	7	8
C _{max} (ng/mL)	5.28 (4.06, 6.87)	13.71 (10.46, 17.97)	29.12 (23.66, 35.84)	17.54 (15.66, 19.63)
T _{max} (h)	1176.00 (552, 1344)	816.72 (519.1, 1284.9)	619.19 (442.8, 865.9)	2.50 (1.50, 3.00)
T _{lag} (h)	6.00	0.5	—	—
AUC _{last} (h·ng/mL)	6119.81 (4694, 7978)	15,523.91 (12,179, 19,787)	28,981.27 (24,213, 34,689)	927.53 (858, 1003)
AUC _{inf} (h·ng/mL)	6326.81 (4841, 8268)	16,803.08 (13,077, 21,591) [n=7]	29,693.07 (24,705, 35,688)	1078.73 (978, 1190)
CL/F (L/h)	11.06 (8.47, 14.46)	8.33 (6.48, 10.71) [n=7]	9.43 (7.85, 11.33)	9.27 (8.41, 10.22)
V _d /F (L)	5016.88 (3954, 6366)	3448.76 (2746, 4331) [n=7]	3937.14 (3170, 4890)	1200.55 (1059, 1361)
t _{1/2} (h)	314.3 (276, 358)	286.91 (251, 328) [n=7]	289.4 (240, 349)	89.77 (76, 106)
Geometric mean (95% confidence interval). T _{max} as median (min, max).				

Table 2. MAD PK parameters of donepezil		
Parameter	GB-5001A 140 mg IM (test)	Aricept® 5 mg PO (control) ¹
Single dose (first administration)		
n	8	2
C _{max} (ng/mL)	12.42 (10.06, 15.33)	—
T _{max} (h)	603.00 (532.6, 682.7)	—
AUC ₀₋₆₇₂ (h·ng/mL)	4204.28 (3264, 5415)	—
Multiple dose (steady-state)		
n	7	2
C _{max,ss} (ng/mL)	24.58 (21.21, 28.49)	32.08 (14.25, 72.22)
C _{min,ss} (ng/mL)	16.09 (12.35, 20.96)	17.10 (12.70, 23.01)
C _{av,ss} (ng/mL)	20.32 (16.40, 25.17) [n=6]	22.65 (15.75, 32.59)
T _{max,ss} (h)	2370.85 (2142.16, 2623.95)	338.50 (332.21, 344.91) **Based on the last dose: 2.50
AUC _{τ,ss} (h·ng/mL)	13,652.6 (11,020, 16,914) [n=6]	543.67 (377.90, 782.15)
t _{1/2} (h)	343.71 (315.5, 374.4) [n=6]	42.11 (1.98, 893.80)
Geometric mean (95% confidence interval). Test = GB-5001A IM 140 mg q4wk; Control = oral Aricept® 5 mg qd. [*] Due to participant dropout, data from the time of dropout onward were treated as missing; consequently, these data were excluded from the analysis population for certain PK parameters. ¹ Due to the limited sample size of only two participants, caution is required when interpreting the numerical analysis.		

Table 3. Final PopPK parameter estimates of GB-5001A		
Parameter	Point estimate	RSE (%)
Structural model parameters		
CL/F (L/h)	10.4	5.1
V1 (L)	30.0	25.8
V2 (L)	3250	10.6
Q (L/h)	147	10.2
KA, IM depot-3 (1/h)	0.00281	30.2
KA, IM depot-4 (1/h)	0.00638	22.9
F, IM depot-3	0.431	13.4
F, IM depot-4	0.316	8.7
ALAG, IM depot-3 (h)	302	3.0
ALAG, IM depot-4 (h)	992	1.6
D1 (h)	653	7.4
Covariate effects on CL (exponential)		
CYP2D6 IM vs EM	-0.423	28.6
Indonesian vs Korean	-0.237	53.6
Variability		
IV CL (CV%)	28.0	39.6
IV V1 (CV%)	266.2	36.8
IV V2 (CV%)	33.3	42.5
IV KA depot-3 (CV%)	83.6	63.6
IV KA depot-4 (CV%)	62.1	39.6
Proportional error (CV%)	22.3	6.7
Additive error	0.0001 (FIXED)	-
CL = 10.4 × exp(-0.423 × [IM] - 0.237 × [Indonesian]) L/h. RSE, relative standard error. Interindividual variability (IV) reported as CV% = 100 × sqrt(exp(omega^2) - 1). RSE% of IV refers to the variance (omega^2) estimate. Proportional residual error reported as CV%.		

GB-5001 was **well tolerated** in healthy male volunteers; injection-site reactions were the most common AEs and were generally mild.

SAD demonstrated **linear, approximately dose-proportional PK** over 70–280 mg IM, with a **flip-flop profile** (median T_{max} 619.19–1176.00 h; mean t_{1/2} 286.91–314.3 h).

MAD steady-state data confirm **sustained plasma exposure** (C_{av,ss} ≈ 20 ng/mL at 140 mg q4w) with markedly lower fluctuation than daily oral donepezil.

The integrated PopPK model (two-compartment, parallel IM depots) supports GB-5001 as a once-monthly IM alternative providing **predictable accumulation** and steady-state exposure.

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