

GlyphAgo demonstrated 6.8-fold increased bioavailability and 10-fold reduced variability versus unmodified agomelatine in healthy volunteers at doses projected to mitigate liver exposure

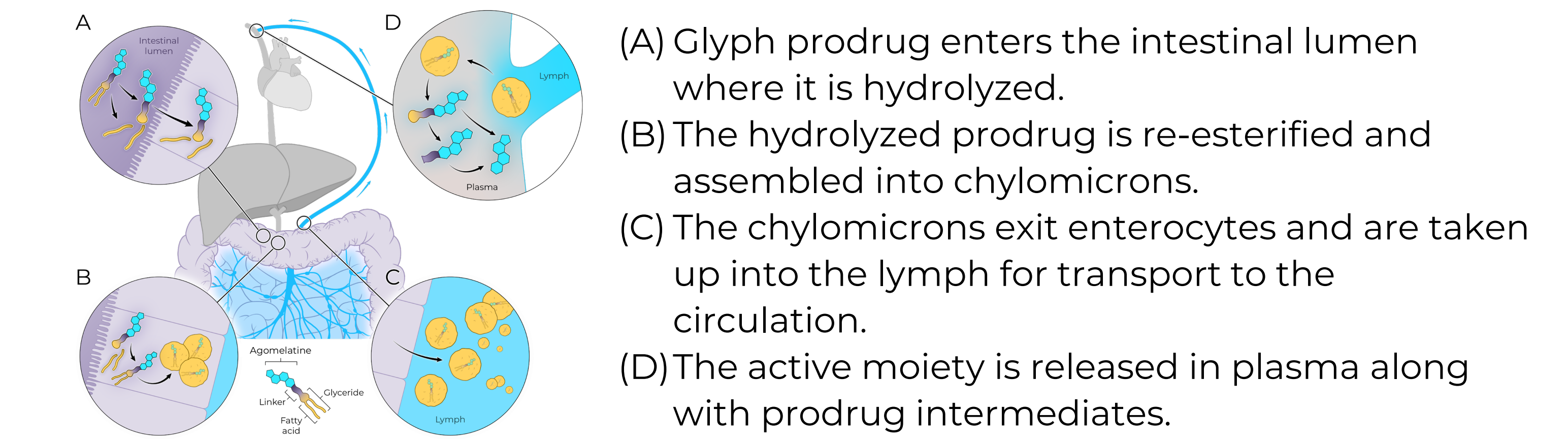
SEAPORT
THERAPEUTICS

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Background

- Agomelatine, a MT₁/2 agonist and 5-HT_{2C} antagonist, is effective in GAD and MDD with lower rates of the typical side effects of many anxiolytic and antidepressant drugs or the dependence risk of benzodiazepines¹
- However, agomelatine undergoes extensive first-pass hepatic metabolism (over 90%) which can lead to dose-dependent liver enzyme elevations and requires routine liver monitoring which has been cited as a barrier to clinical use^{2,3}
- GlyphAgoTM (SPT-320 or Glyph Agomelatine) is an oral prodrug of agomelatine designed with the GlyphTM platform to avoid first-pass hepatic metabolism and reduce or eliminate liver enzyme elevations
- The Glyph platform is a lymphatic-targeting prodrug technology that reversibly links a drug of interest to a dietary fat molecule, redirecting intestinal absorption from the liver to the gut-draining lymphatics



- **Objective:** Here, we present proof-of-concept pharmacokinetic (PK) data from a first-in-human, phase 1 trial of GlyphAgo in healthy volunteers

Methods

- The safety, tolerability, and PK of agomelatine following oral GlyphAgo administration was evaluated in a multipart, phase 1 trial of 174 healthy adult (18-55 years) volunteers:

Trial Part	Treatment		Agomelatine Equivalent Doses
Part A: Agomelatine	Agomelatine	25 mg	25 mg
Part B: SAD	GlyphAgo	8.1 mg	2.5 mg
		16.2 mg	5.0 mg
		32.3 mg	10 mg
		80.8 mg	25 mg
		161.5 mg	50 mg
Part C: Crossover	Placebo	NA	NA
	GlyphAgo	32.3 mg (fed and fasted)	10 mg
Part D: MAD	Agomelatine	25 mg (fed or fasted)	25 mg
	GlyphAgo	16.2 mg	5.0 mg
		32.3 mg	10 mg
		80.8 mg	25 mg
	Placebo	NA	NA

- Blood samples for PK analyses were collected at predefined time points pre and post dose
- Data are represented as geometric mean (geometric CV%) and plotted on a semi-logarithmic scale

Abbreviations: Ago, agomelatine; AUC, area under the plasma concentration time curve; C_{max}, maximum observed concentration; GAD, generalized anxiety disorder; IMP, investigational medicinal product; MAD, multiple ascending dose; MDD, major depressive disorder; PK, pharmacokinetics; SAD, single ascending dose.

Results

Figure 1. Single oral administration of GlyphAgo dose-dependently increased plasma agomelatine concentration (A), AUC₀₋₂₄ (B), and C_{max} (C) in healthy volunteers.

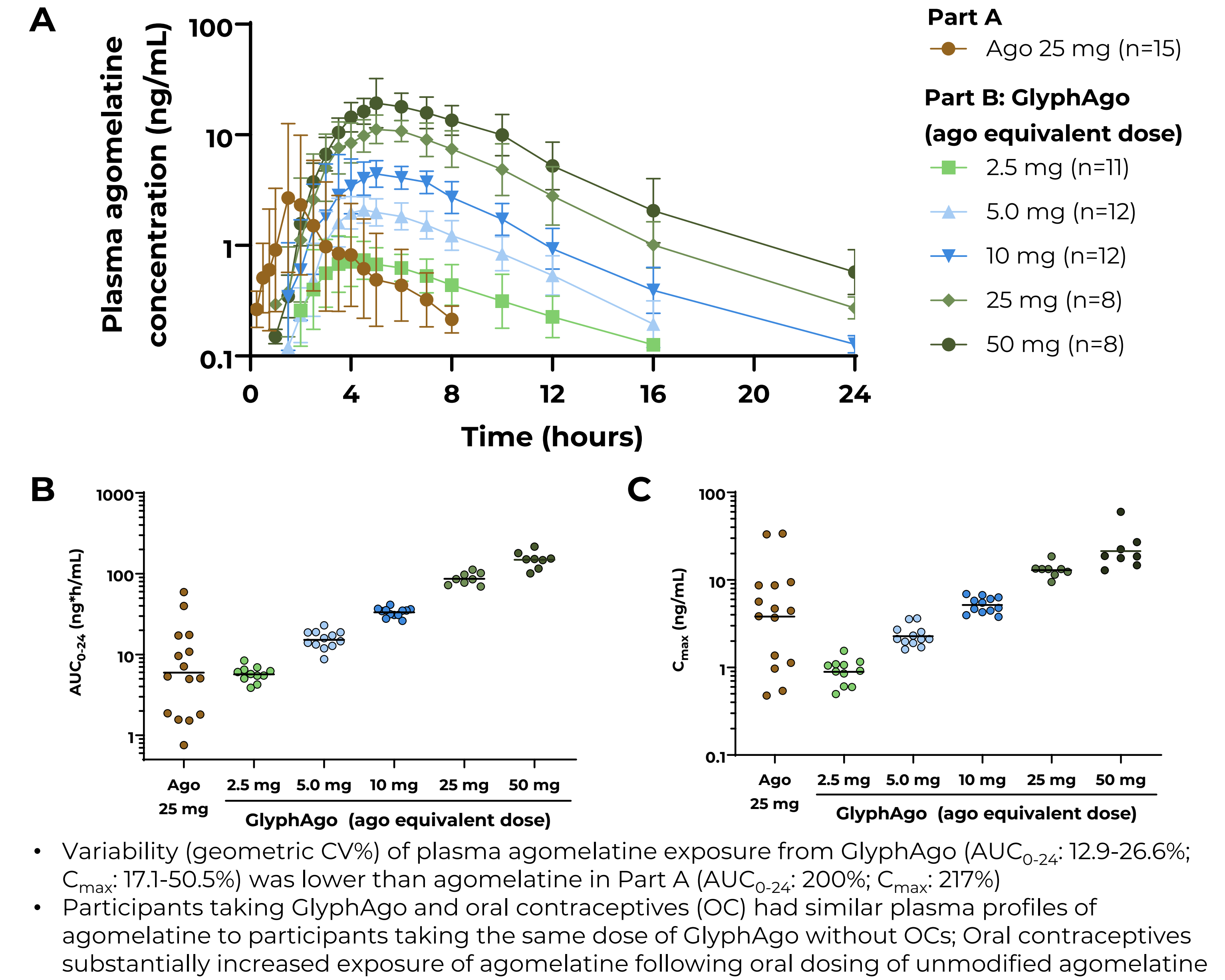


Figure 2. There was no observed food effect on agomelatine exposure after dosing with GlyphAgo in Part C.

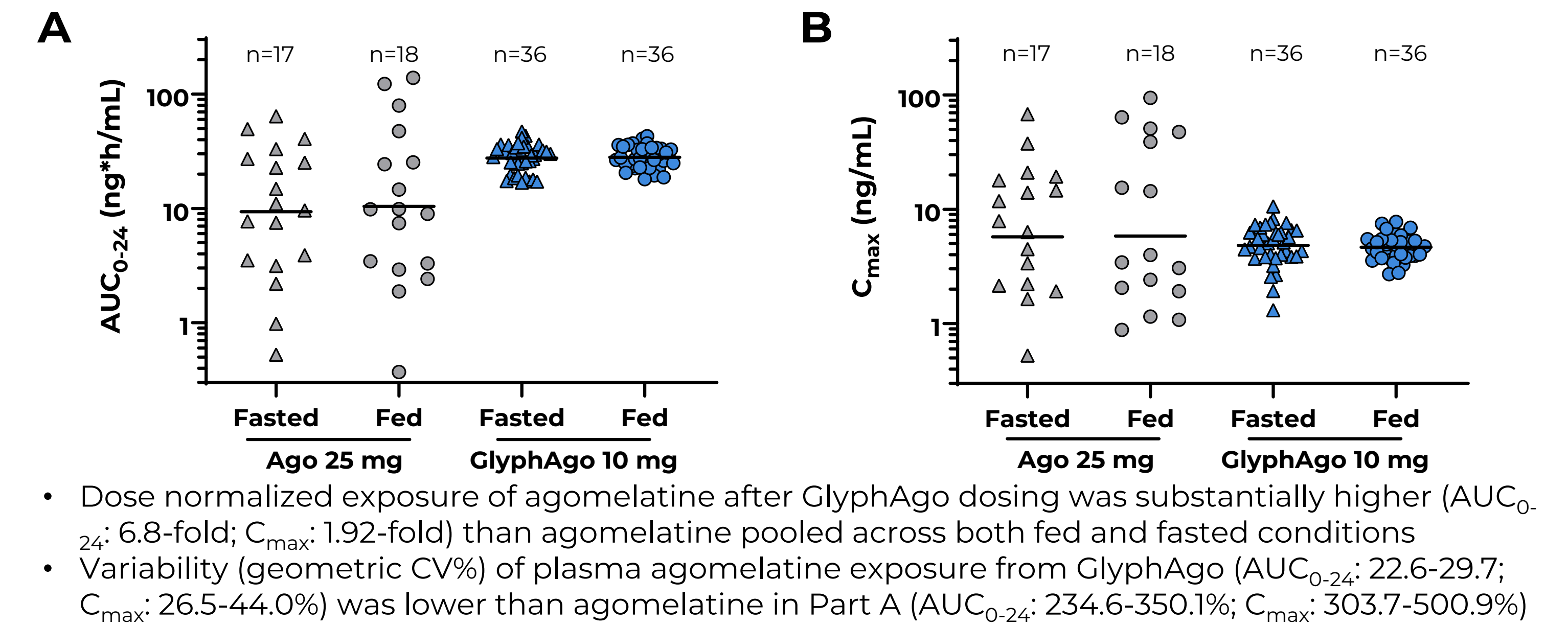
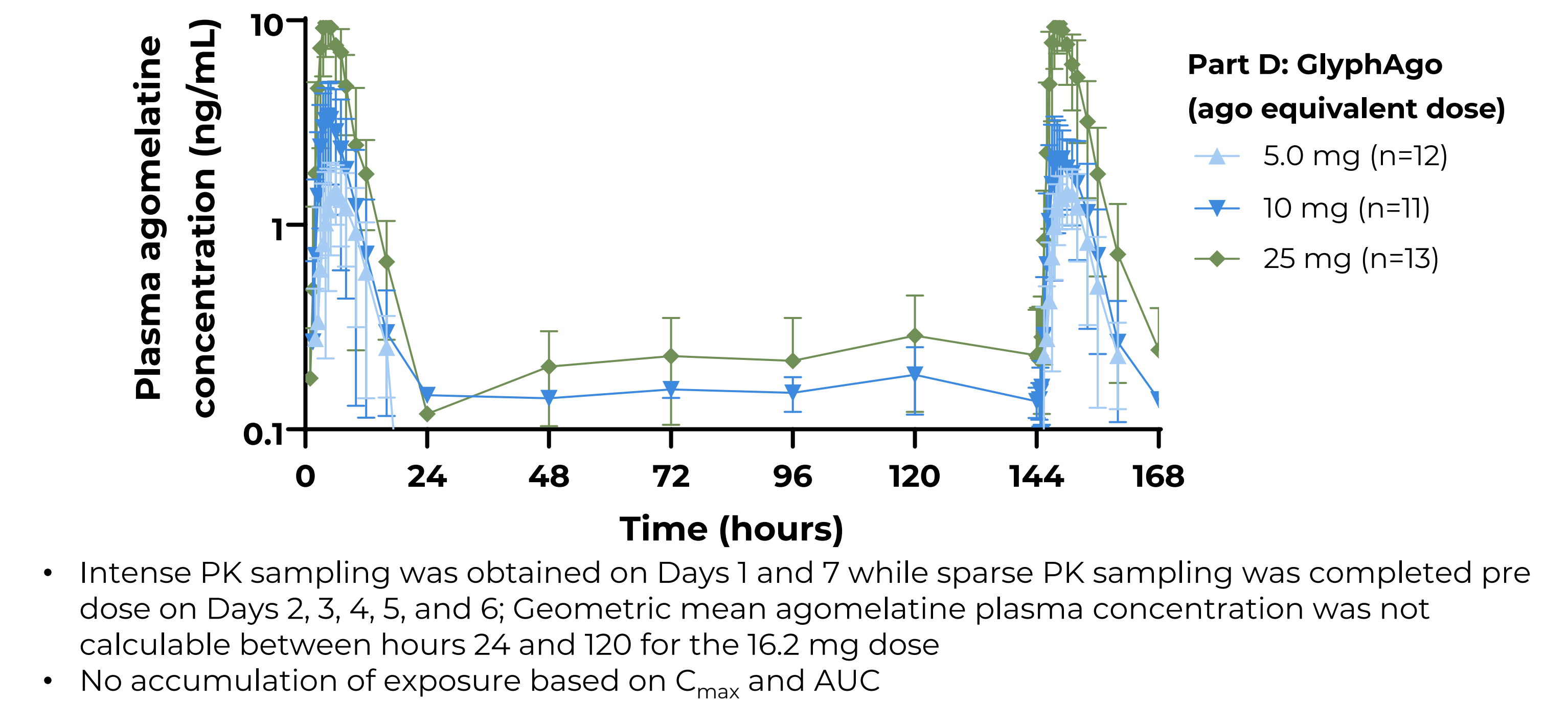


Figure 3. Multiple-ascending doses of GlyphAgo showed no accumulation of exposure over seven days of administration.



Conclusions

- In a phase 1 trial of healthy volunteers, oral GlyphAgo administration achieved 6.8-fold greater dose-normalized agomelatine exposure compared to unmodified agomelatine administration
- GlyphAgo demonstrated a 10-fold reduction in agomelatine PK variability compared to unmodified agomelatine, which may improve the consistency of exposures and clinical outcomes in patients
- There was no observed effect of estrogen-containing oral contraceptives on agomelatine exposure after dosing with GlyphAgo, further supporting the ability of GlyphAgo to bypass first-pass metabolism and avoid drug-drug interactions that occur in the liver
- GlyphAgo achieved therapeutic exposures of agomelatine at doses projected to avoid liver enzyme elevations and reduce or eliminate the need for liver function testing, supporting further clinical development of GlyphAgo for psychiatric indications

	Dose	Route of Absorption	Liver Exposure	Liver Function Tests	
Agomelatine • Unique and validated mechanism: GAD (Australia) & MDD (Australia/EU) • No weight gain, sexual dysfunction, or emotional blunting	25-50 mg	Hepatic portal vein	Extensive first-pass metabolism High liver exposure	Dose-dependent ALT elevations & liver monitoring required	Limitations: First-pass metabolism and liver monitoring required
GlyphAgoTM • Oral, lymphatic-targeted prodrug of agomelatine using the Glyph platform	<25 mg	Intestinal lymphatics	Avoids first-pass metabolism Reduces liver exposure	No ALT elevations predicted above placebo	Potential to overcome agomelatine limitations by bypassing first-pass metabolism, reducing liver exposure and thus hepatotoxicity