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Quantitative medicine analyses of zanidatamab dose regimens in patients with HER2-positive locally advanced/metastatic gastro-oesophageal adenocarcinoma

Filip Van Herpe[1], Josep Tabernero[2], Geoffrey Ku[3], Jaffer Ajani[4], Kohei Shitara[5], Elena Elimova[6], Lin Shen[7], Sun Young Rha[8], Sheryl Trueman[9], Liviawati Wu[9], Daniela Conrado[9], Mingguang Li[9], Honghui Zhou[10], Mengfan Yue[11], Jonathan Grim[9], Robert Iannone[10], Suzette Girgis[10], Joanne Ma[10]

[1]University Hospitals Leuven (UZ Leuven), Leuven, Belgium; [2]Vall d'Hebron Hospital Campus & Institute of Oncology (VHIO), IR-HUVH, UVic-UCC, Barcelona, Spain; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [5]National Cancer Center Hospital East, Kashiwa, Japan; [6]Princess Margaret Cancer Centre, ON, Canada; [7]State Key Laboratory of Holistic Integrative Management of Gastrointestinal Cancers, Beijing Key Laboratory of Cell & Gene Therapy for Solid Tumor, Department of GI Oncology, Peking University Cancer Hospital & Institute, Beijing, China; [8]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; [9]Jazz Pharmaceuticals, Palo Alto, CA, USA; [10]Jazz Pharmaceuticals, Philadelphia, PA, USA; [11]BeOne Medicines, Ltd., Beijing, China

Objective

- To characterize zanidatamab pharmacokinetics (PK) in patients with human epidermal growth factor receptor 2–positive (HER2+) advanced or metastatic gastro-oesophageal adenocarcinoma (mGEA) in HERIZON-GEA-01 following the recommended dosing regimen (every 3 weeks [Q3W]), and to predict PK of dosing every 2 weeks (Q2W) using modelling and simulation to support combination therapy with other chemotherapy (CT) agents that are administered Q2W

Conclusions

- This analysis showed that both zanidatamab dosing regimens (1800 mg [<70 kg]/2400 mg [≥70 kg] Q3W and 1200 mg [<70 kg]/1600 mg [≥70 kg] Q2W) are comparable and expected to be safe and effective, with clinical benefit in patients with first-line (1L) HER2+ mGEA
- Zanidatamab PK was well characterized by a 2-compartment model, with body weight identified as a significant covariate affecting exposure, supporting a 2-tiered weight-based dosing regimen
  - Exposure was unaffected by treatment-emergent antidrug antibodies (ADAs)
  - Zanidatamab PK was not impacted by mild or moderate renal or hepatic impairment, age, sex, race, or HER2 status, indicating that dose adjustments are not necessary in any of these groups
- The alternative Q2W zanidatamab regimen has the potential to offer flexible treatment options compatible with background CT with comparable therapeutic benefit

References: 1. Weisser NE, et al. *Nat Commun*. 2023;14(1):1394. **2.** Ziihera® (zanidatamab-hrii) for injection, for intravenous use. Package insert. Jazz Pharmaceuticals, Inc.; 2025. Accessed 17 June 2026. https://pp.jazzpharma.com/pi/ziihera.en.USPI.pdf. **3.** Jazz Pharmaceuticals, Inc. Jazz Pharmaceuticals receives European Commission marketing authorization for Ziihera® (zanidatamab) for the treatment of advanced HER2-positive biliary tract cancer. 1 July 2025. Accessed 18 June 2026. https://investor.jazzpharma.com/node/21951/pdf. **4.** Harding JJ, et al. *Lancet Oncol*. 2023;24(7):772-82. **5.** Shitara K, et al. *N Engl J Med*. 2026;394(20):2002-14. **6.** ClinicalTrials.gov. Accessed May 13, 2026. https://clinicaltrials.gov/study/NCT05152147. **7.** ClinicalTrials.gov. Accessed May 13, 2026. https://clinicaltrials.gov/study/NCT04466891. **8.** ClinicalTrials.gov. Accessed May 13, 2026. https://clinicaltrials.gov/study/NCT02892123.

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Corresponding author: Filip Van Herpe, MD; filip.vanherpe@uzleuven.be

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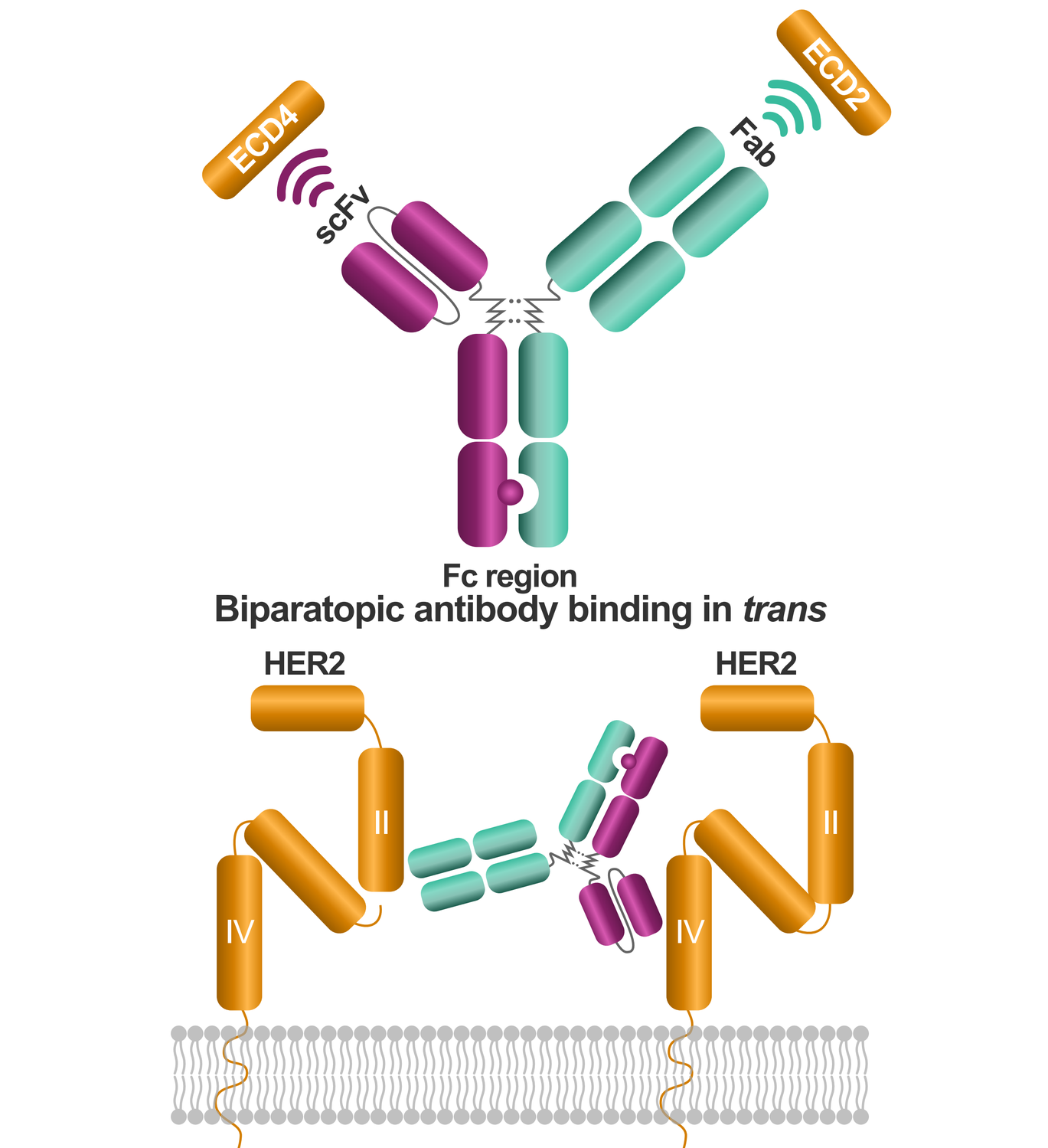
Introduction

- Zanidatamab binds extracellular domains 2 and 4 of HER2 in a *trans* configuration, facilitating the formation of distinct HER2 clusters on the cell surface. Its mechanisms of action include:
  - Increasing HER2 internalisation
  - Reducing phosphorylation of EGFR, HER2, and HER3, thereby inhibiting downstream signalling pathways
  - Inducing immune-mediated effects, including complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity and phagocytosis[1]
- Zanidatamab is a HER2-directed bispecific antibody that received accelerated approval in the US and conditional approvals in China and the EU for adults with previously treated, unresectable or metastatic HER2+ (immunohistochemistry [IHC] 3+) biliary tract cancer (BTC), based on the global pivotal phase 2 HERIZON-BTC-01 trial[2-4]
- In the global phase 3 HERIZON-GEA-01 trial:
  - Zanidatamab + CT ± tislelizumab significantly improved progression-free survival compared with trastuzumab + CT in patients with untreated HER2+ mGEA. In the tislelizumab-containing arm, a statistically significant overall survival (OS) benefit was observed, with a median OS >2 years
  - Diarrhoea was the most common treatment-related adverse event[5]
- Two different weight-based dosing regimens were used, with a 20 mg/kg Q2W regimen in HERIZON-BTC-01 while a simplified 1800 mg (<70 kg)/2400 mg (≥70 kg) Q3W regimen was used in HERIZON-GEA-01
- This analysis included zanidatamab exposure data across 3 studies to generate a population pharmacokinetic (PopPK) model, which was used to demonstrate PK comparability between the Q3W (1800 mg [<70 kg]/2400 mg [≥70 kg]) and Q2W (1200 mg [<70 kg]/1600 mg [≥70 kg]) dosing regimens

Figure 1. Zanidatamab structure and binding



ECD, extracellular domain; Fab, fragment antigen-binding; Fc, fragment crystallizable; HER2, human epidermal growth factor receptor 2; scFv, single-chain variable fragment.

Methods

- Serum zanidatamab concentrations from HERIZON-GEA-01, HERIZON-BTC-01, and the first-in-human phase 1 study were pooled for PopPK analysis
- HERIZON-GEA-01 is a global, randomised, open-label, phase 3 trial in previously untreated patients with HER2+ mGEA[5,6]
- HERIZON-BTC-01 was an open-label, single-arm, phase 2b trial in patients with previously treated, unresectable or metastatic HER2+ BTC[7]
- The phase 1 study included patients with HER2-expressing or *HER2/ERBB2*-amplified solid tumours[8]

Table 1. Zanidatamab studies included in the PopPK model

PopPK analysis (N = 808)	
Study	**Zanidatamab IV dosing**
HERIZON-GEA-01 (NCT05152147)[6] (n = 575)	1800 mg (<70 kg)/2400 mg (≥70 kg) Q3W combined with CT or CT and tislelizumab
HERIZON-BTC-01 (NCT04466891)[7] (n = 86)	20 mg/kg Q2W
Phase 1 (NCT02892123)[8] (n = 147)	5, 10, 15 mg/kg QW 10, 20, 25, 30 mg/kg Q2W 30 mg/kg Q3W

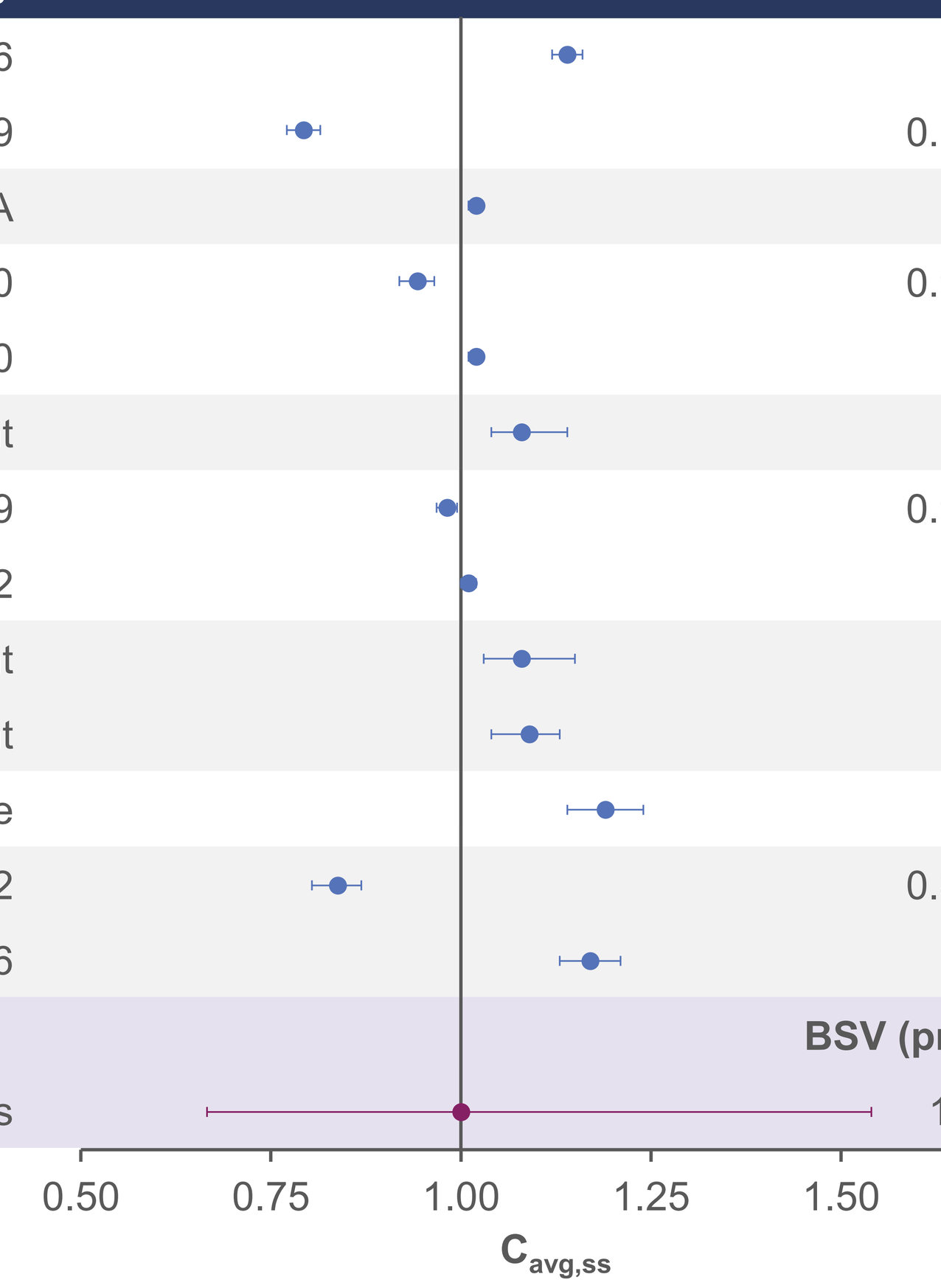
CT, chemotherapy; IV, intravenous; PopPK, population pharmacokinetics; QW, every week; Q2W, every 2 weeks; Q3W, every 3 weeks.

Results

PopPK

Figure 2. Effects of covariates on zanidatamab average concentrations ($C_{avg,ss}$)

Covariates	Range of study	Median (95% CI)
Albumin (g/L)	46	1.14 (1.12–1.16)
	29	0.793 (0.771–0.815)
Cancer type	Non-GEA	1.02 (1.01–1.02)
LDH (U/L)	830	0.943 (0.919–0.965)
	130	1.02 (1.01–1.02)
Hepatic function	Mild impairment	1.08 (1.04–1.14)
Number of cancer lesions	9	0.982 (0.968–0.995)
	2	1.01 (1.00–1.02)
Renal function	Moderate impairment	1.08 (1.03–1.15)
	Mild impairment	1.09 (1.04–1.13)
Sex	Female	1.19 (1.14–1.24)
Body weight (kg)	92	0.838 (0.804–0.869)
	46	1.17 (1.13–1.21)
		BSV (prediction interval)
BSV	90% of reference patients	1.00 (0.666–1.54)

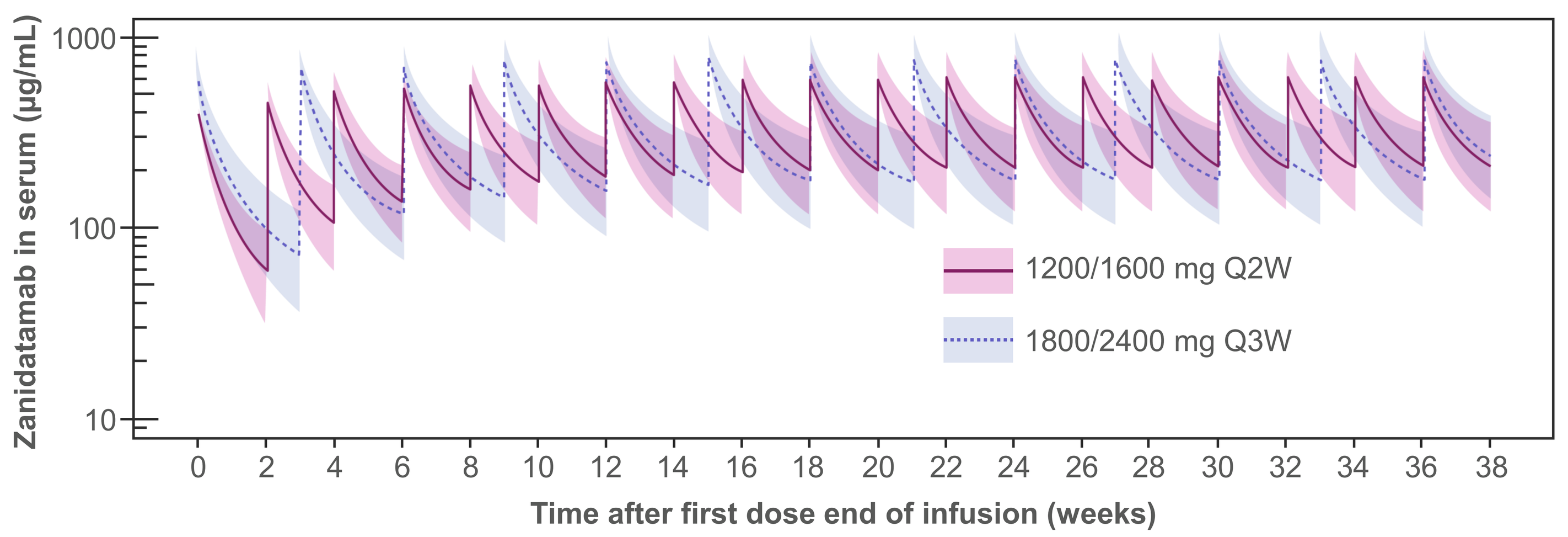


The reference patient is a 64-kg male with GEA, normal renal and hepatic function, a serum albumin of 39 g/L, 4 cancer lesions, and an LDH of 218 U/L; for continuous covariates, lower and higher values in the forest plot represent the 5th and 95th percentiles, respectively, of the covariate distribution at baseline across patients in the analysis dataset.
Analysis includes HERIZON-GEA-01 (HER2+ mGEA), HERIZON-BTC-01 (HER2+ BTC), and the first-in-human phase 1 study (HER2-expressing or HER2-amplified solid tumors).
Clinically meaningful: 95% CI was within 80.0% to 125.0% relative to the reference.
BSV, between-subject variability; BTC, biliary tract cancer; $C_{avg,ss}$, average concentration at steady state; HER2, human epidermal growth factor receptor 2; LDH, lactate dehydrogenase; mGEA, metastatic gastro-oesophageal adenocarcinoma.

- Zanidatamab PK was well characterized by a 2-compartment model with parallel linear and nonlinear elimination processes
  - Estimated clearance (CL) was 0.274 L/day for a typical patient, and PK parameters were consistent with those reported for immunoglobulin G–based monoclonal antibodies
  - Body weight had the most relevant effect on zanidatamab exposure and was positively correlated with CL
  - Zanidatamab PK was not impacted by mild or moderate renal or hepatic impairment, age (range: 22–87 years), sex, race (Asian, White, or other), or HER2 status (IHC 2+/in situ hybridisation+ or IHC 3+), indicating that dose adjustments are not necessary in any of these groups
  - In addition to the covariates analysis shown in the forest plot, treatment-emergent ADAs had no significant impact on zanidatamab PK (data not shown)

PK comparability between weight-based 1200/1600 mg Q2W and 1800/2400 mg Q3W dose regimens

Figure 3. Predicted concentration-time profile of zanidatamab following Q2W and Q3W dose regimens



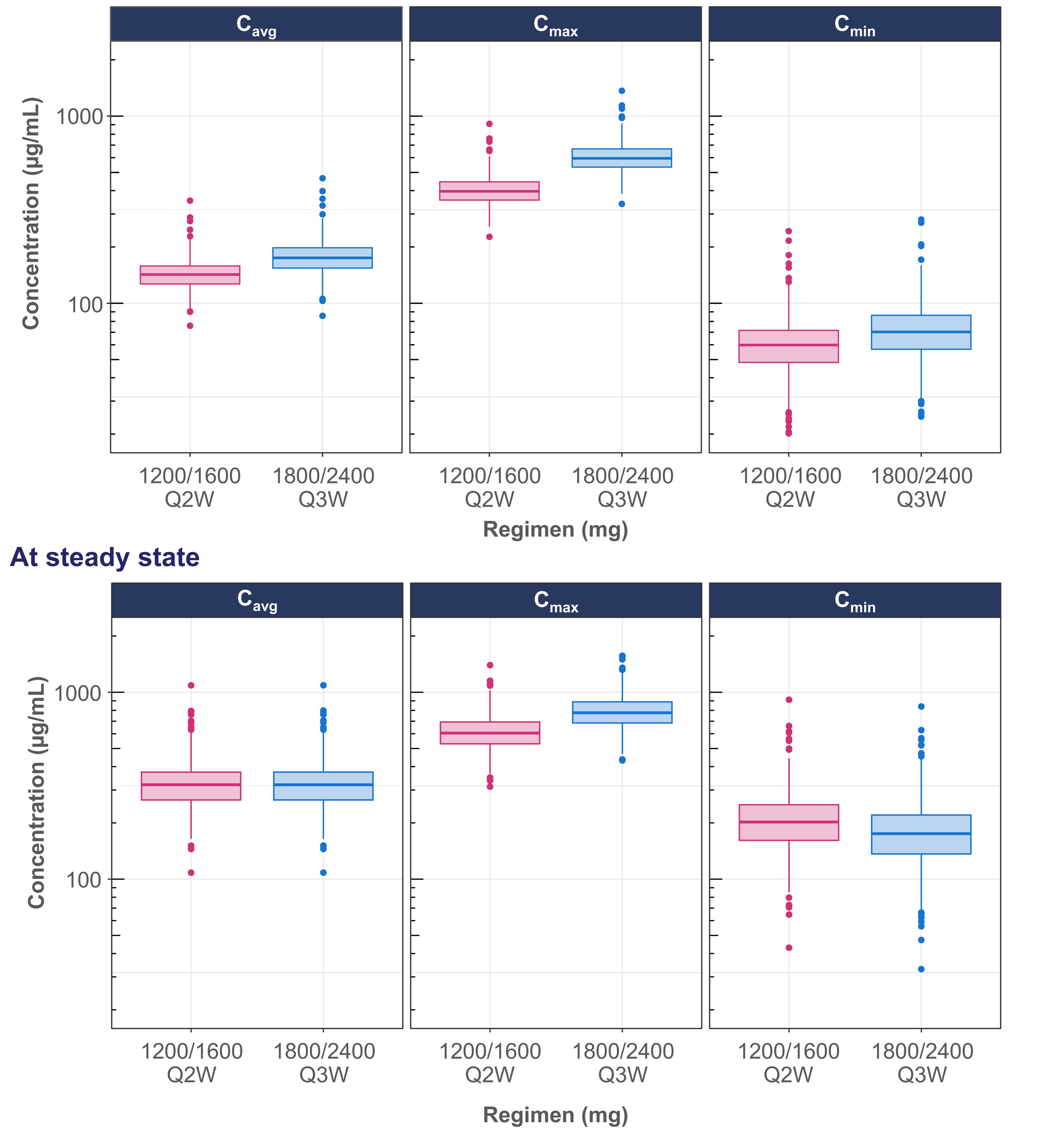
Lines and shaded areas are median and 90% prediction intervals of the simulations, respectively.
Q2W, every 2 weeks; Q3W, every 3 weeks.

Table 2. Predicted zanidatamab exposure after first dose and at steady state following Q2W and Q3W dose regimens

	1200/1600 mg Q2W		1800/2400 mg Q3W	
	First dose	**Steady state**	**First dose**	**Steady state**
C_{avg}, µg/mL				
Median (IQR)	142 (127–158)	320 (265–374)	175 (154–198)	320 (265–374)
10th, 90th percentiles	114, 176	234, 436	138, 221	234, 437
Geo mean (geo %CV)	142 (17.7)	319 (27.4)	175 (19.6)	319 (27.4)
C_{max}, µg/mL				
Median (IQR)	396 (356–445)	605 (530–693)	595 (534–668)	777 (685–888)
10th, 90th percentiles	320, 493	472, 774	480, 740	618, 991
Geo mean (geo %CV)	398 (17.4)	609 (21.1)	597 (17.4)	783 (19.9)
C_{min}, µg/mL				
Median (IQR)	59.8 (47.7–71.3)	202 (161–250)	70.1 (56.4–86.1)	175 (136–220)
10th, 90th percentiles	37.1, 86.1	136, 304	44.2, 102	112, 271
Geo mean (geo %CV)	57.4 (38.8)	203 (36.2)	68.3 (38.7)	176 (39.3)

C_{avg}, average concentration; C_{max}, maximum concentration; C_{min}, minimum concentration; CV, coefficient of variation; geo, geometric; IQR, interquartile range; Q2W, every 2 weeks; Q3W, every 3 weeks.

Figure 4. Predicted PK parameters following Q2W and Q3W dose regimens after first dose and steady state



The shaded box represents the interquartile range, with the line indicating the median. Whiskers extend from the minimum to the maximum.
C_{avg}, average concentration; C_{max}, maximum concentration; C_{min}, minimum concentration; IV, intravenous; PK, pharmacokinetic; Q2W, every 2 weeks; Q3W, every 3 weeks.

- Predicted PK parameters (minimum concentration [C_{min}], maximum concentration [C_{max}], and average concentration [C_{avg}]) after the first dose and at steady state were comparable between the Q2W (1200 mg [<70 kg]/1600 mg [≥70 kg]) and Q3W (1800 mg [<70 kg]/2400 mg [≥70 kg]) dose regimens