Bioequivalence Study Report

2×2 crossover bioequivalence assessment (EMA / FDA 80–125 % acceptance window on the 90 % CI of GMR)

Dataset: **ciprofloxacin_be_demo_synthetic.csv**

Job ID: **B3-BE**

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> **Synthetic demonstration data — not real drug data. This report is generated from a synthetic CSV bundled with the FractaLPK platform for evaluation and demonstration purposes. Numerical results do not represent the named compound and must not be cited as such.**

Computational bioequivalence results — informational only. FractaLPK does not issue regulatory advice; bioequivalence interpretation, sponsor commentary, and submission strategy are the responsibility of the user's expert team.
Bioequivalence assessment per EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1, 2010) and FDA Guidance for Industry — Bioequivalence Studies with Pharmacokinetic Endpoints (2021). Two One-Sided Tests (TOST) procedure per Schuirmann, J. Pharmacokinet. Biopharm. 15:657-680 (1987).

Unit basis: concentration: **ng/mL** (default) · time: **h** (default) · dose basis: **mg** (default)

Bioequivalence assessment

Parameter	Role	GMR (T/R)	90 % CI	Within 80–125 %	TOST p	Intra-CV %	n
AUC0-∞ (ng·h/mL)	**PRIMARY**	1.042	[0.9719, 1.118]	✓	3.56e-04	9.59	12
AUC0-last (ng·h/mL)	**SECONDARY**	1.049	[0.9773, 1.125]	✓	4.62e-04	9.62	12
Cmax (ng/mL)	**PRIMARY**	1.076	[1.039, 1.114]	✓	<0.0001	4.77	12

AUC0-∞ is reliable in this dataset (no arm exceeded the 30 % NTP/EXE downgrade threshold); AUC0-∞ is reported as the primary endpoint and AUC0-last as a secondary endpoint.

> **BIOEQUIVALENT — the 90 % CI of the GMR falls inside the 80–125 % acceptance window for the primary endpoint pair (AUC0-∞ + Cmax).**

Scope: 2×2 crossover and parallel-group designs only. Replicate (3-way, 4-way) and reference-scaled BE methods (EMA ABEL, FDA RSABE) for highly variable or narrow-therapeutic-index drugs are not included in this version of the report.

Per-subject NCA estimates

NCA parameters (AUC0-∞, Cmax, Tmax, λz, t½) were derived per subject for the test and reference formulations; their logs were used to compute GMR and the 90 % CI under the bioequivalence model. Flags column: **NTP** = NO_TERMINAL_PHASE (λz not estimable; AUC0-∞ reported as N/A); **HIE** = HIGH_EXTRAPOLATION (%AUCext > 20 %); **EXE** = EXTREME_EXTRAPOLATION (%AUCext > 50 %); **SPI** = SPAN_INSUFFICIENT (regression window < 2 × t½ AND %AUCext > 20 %). TLT (TLAST_TRUNCATED) is a two-arm-only flag for paired AUC0-last comparisons and is not currently emitted by this report (BE keeps AUC0-∞ as the primary endpoint).

Test formulation

Subject	Cmax	Tmax	AUC0-∞	λz	t½	%ext	Flags
1	2.348	2	27.86	0.108	6.416	0.63	—
2	2.353	2	27.7	0.1034	6.702	0.8	—
3	2.701	2	23.25	0.1189	5.828	0.36	—
4	2.562	2	22.77	0.1186	5.843	0.37	—
5	2.357	1	26.88	0.1038	6.675	0.68	—
6	2.457	2	26.87	0.1116	6.212	0.53	—
7	2.362	2	21.75	0.121	5.726	0.38	—
8	2.423	2	28.56	0.1029	6.733	0.82	—
9	2.32	2	23.71	0.1198	5.788	0.35	—
10	2.424	2	22.22	0.1148	6.035	0.39	—
11	2.564	2	25.67	0.1126	6.156	0.48	—
12	2.546	2	22.62	0.1197	5.789	0.37	—

Reference formulation

Subject	Cmax	Tmax	AUC0-∞	λz	t½	%ext	Flags
1	2.165	2	26.24	0.1076	6.443	0.67	—
2	2.143	1	20.07	0.1186	5.843	0.42	—
3	2.281	2	21.84	0.1177	5.89	0.39	—
4	2.229	2	24.53	0.1161	5.972	0.42	—
5	2.293	2	24.57	0.1109	6.248	0.51	—
6	2.38	1	23.34	0.1208	5.74	0.35	—
7	2.314	2	27.16	0.1083	6.397	0.61	—
8	2.363	2	25.36	0.11	6.3	0.54	—
9	2.422	2	22.57	0.1166	5.943	0.38	—
10	2.294	1	24.44	0.1037	6.686	0.71	—
11	2.125	2	24.38	0.1132	6.125	0.47	—
12	2.335	2	22.71	0.1168	5.935	0.38	—

Methodology

Per-subject Cmax and Tmax were taken from the observed concentration-time profile.

AUC0-last was computed by the trapezoidal rule (linear-up / log-down where applicable). AUC0-∞ was computed as AUC0-last + Clast / λz, where λz was estimated by log-linear regression over the terminal phase with the canonical FractaLPK acceptance threshold (adjusted $R^2 \geq 0.90$, ≥ 3 terminal points).

Primary-endpoint policy (FractaLPK canonical, shared by BE and food-effect reports): AUC0-∞ is the primary endpoint when reliable. When at least 30 % of subjects in either arm produce NO_TERMINAL_PHASE or EXTREME_EXTRAPOLATION the population AUC0-∞ chain is no longer trustworthy and the primary endpoint is downgraded to AUC0-last (observed exposure); AUC0-∞ is then reported in parallel as a secondary endpoint. AUC0-last remains available as a secondary endpoint in every report so the same row supports both the primary verdict and the cross-check (FDA Guidance for Industry — BA/BE Studies 2022; PowerTOST documentation 2024).

For the 2×2 crossover design, the bioequivalence statistic is the geometric mean ratio (GMR) of test over reference computed from the within-subject difference of ln(AUC0-∞) and ln(Cmax). The 90 % confidence interval and the TOST p-value are derived assuming a normal distribution of within-subject differences with n−1 degrees of freedom. Intra-subject coefficient of variation is computed as $100 \cdot \sqrt{(\exp(s^2_{within}) - 1)}$ with $s^2_{within} = \text{var}(\ln(\text{test}) - \ln(\text{ref})) / 2$ (Hauschke, Steinijans, Pigeot 2007 §3.2).

Bioequivalence is concluded when the 90 % CI of the GMR falls entirely within the 80.00 %–125.00 % acceptance window for both AUC0-∞ (primary AUC endpoint in this report) and Cmax.

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