Dose-Proportionality Report

Power-model assessment (FDA Dose-Response Guidance / Smith et al. 2000 acceptance window)

Dataset: **imatinib_dose_proportionality_demo.csv**

Job ID: **B3-DP**

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Dose levels: **100, 200, 400, 800** (mg)

Dose-range ratio r: **8**

Subjects analysed: **24**

> **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 dose-proportionality assessment — informational only. FractaLPK does not issue regulatory advice; interpretation of linearity and clinical relevance are the responsibility of the user's expert team.
Dose-proportionality assessment via the power model on ln-transformed PK metrics (Gough et al., Drug Inf. J. 29:1039–1048, 1995; Smith et al., Pharm. Res. 17:1278–1283, 2000).

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

Power-model assessment

Parameter (role)	β (slope)	90 % CI of β	Smith window	Verdict	R^2	n
AUC0-last — PRIMARY	0.9953	[0.8918, 1.099]	[0.8927, 1.107]	Inconclusive	0.9253	24
Cmax — PRIMARY	0.968	[0.8902, 1.046]	[0.8927, 1.107]	Inconclusive	0.954	24
AUC0-∞ — SECONDARY	0.9847	[0.8703, 1.099]	[0.8927, 1.107]	Inconclusive	0.9086	24

Smith window = [1 + ln(0.80)/ln(r), 1 + ln(1.25)/ln(r)] with r = max(Dose) / min(Dose) = 8. Dose-proportional → 90 % CI of β inside window; not proportional → CI fully outside; otherwise inconclusive (Smith et al., Pharm. Res. 17:1278-1283, 2000).

Per-dose-level summary

AUC0-last (PRIMARY)

Dose	n	Geom. mean	GCV %	DN (geom.)
100	6	5273	17.5	52.73
200	6	1.145e+04	24	57.25
400	6	2.409e+04	17.1	60.22
800	6	4.103e+04	31.8	51.29

Cmax (PRIMARY)

Dose	n	Geom. mean	GCV %	DN (geom.)
100	6	203.5	12.8	2.035
200	6	387.1	23.3	1.935
400	6	842.2	13.2	2.105
800	6	1470	18.7	1.837

AUC0-∞ (SECONDARY)

Dose	n	Geom. mean	GCV %	DN (geom.)
100	6	5691	19.8	56.91
200	6	1.258e+04	26.5	62.89
400	6	2.643e+04	19.7	66.09
800	6	4.323e+04	33.6	54.03

Per-subject NCA estimates

Per-subject PK parameters fed into the power-model regression. **span λz** reports the absolute terminal regression window in t-column units with its ratio to t½ in parentheses (SPI fires when ratio < 2 AND %AUCext > 20 %). 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 and never fires in single-arm dose-proportionality designs.

Subject	Dose	Cmax	Tmax	AUC0-last	AUC0-∞	λz	t½	%ext	span λz	Flags
1	100	223.6	4	6110	6586	0.03767	18.4	7.23	48.0 (2.61×)	—
2	100	173.3	6	3990	4151	0.04638	14.95	3.88	48.0 (3.21×)	—
3	100	177.5	6	4657	4923	0.04136	16.76	5.39	64.0 (3.82×)	—
4	100	198.7	6	5631	6361	0.03	23.1	11.5	48.0 (2.08×)	—
5	100	220.9	4	5330	5728	0.03728	18.59	6.94	48.0 (2.58×)	—
6	100	235	6	6308	6928	0.03309	20.95	8.95	48.0 (2.29×)	—
7	200	342.2	4	9251	9758	0.04258	16.28	5.19	48.0 (2.95×)	—
8	200	610.4	6	1.801e+04	2.049e+04	0.02956	23.45	12.1	48.0 (2.05×)	—
9	200	349	4	1.145e+04	1.272e+04	0.03255	21.29	9.95	64.0 (3.01×)	—
10	200	352.7	4	1.051e+04	1.15e+04	0.03479	19.92	8.55	48.0 (2.41×)	—
11	200	334.1	8	9892	1.064e+04	0.03778	18.35	7	48.0 (2.62×)	—
12	200	391.4	4	1.135e+04	1.273e+04	0.03114	22.26	10.9	48.0 (2.16×)	—
13	400	843.2	4	2.254e+04	2.441e+04	0.0361	19.2	7.67	48.0 (2.50×)	—
14	400	689.4	4	2.034e+04	2.198e+04	0.03766	18.41	7.48	48.0 (2.61×)	—
15	400	891.2	4	2.216e+04	2.371e+04	0.03817	18.16	6.54	48.0 (2.64×)	—
16	400	770.1	6	2.251e+04	2.445e+04	0.03654	18.97	7.96	48.0 (2.53×)	—
17	400	1006	6	3.263e+04	3.749e+04	0.02979	23.27	13	48.0 (2.06×)	—
18	400	888.9	4	2.617e+04	2.925e+04	0.03122	22.2	10.5	48.0 (2.16×)	—
19	800	1752	6	5.263e+04	5.535e+04	0.04389	15.79	4.91	48.0 (3.04×)	—
20	800	1194	8	3.368e+04	3.506e+04	0.04739	14.63	3.94	48.0 (3.28×)	—
21	800	1635	6	5.438e+04	5.895e+04	0.0367	18.89	7.75	48.0 (2.54×)	—
22	800	1801	4	5.382e+04	5.711e+04	0.04129	16.79	5.76	48.0 (2.86×)	—
23	800	1355	6	2.614e+04	2.653e+04	0.05878	11.79	1.46	48.0 (4.07×)	—
24	800	1208	8	3.519e+04	3.764e+04	0.03922	17.67	6.51	48.0 (2.72×)	—

Methodology

Per-subject NCA: Cmax and Tmax from the observed concentration-time profile. AUC0-last by trapezoidal rule (linear-up / log-down where applicable). AUC0-∞ = AUC0-last + Clast / λz with the same λz acceptance criteria used in the FractaLPK food-effect and bioequivalence suites (adjusted $R^2 \geq 0.90$, ≥ 3 terminal points; SPAN_INSUFFICIENT fires only when the terminal-phase regression window covers < 2 × t½ AND %AUCext > 20 % — below 20 % the AUC0-∞ is reliable by construction; reinforced %AUCext > 50 % with < 4 terminal points → NO_TERMINAL_PHASE).

Dose-proportionality exception (documented, by design, not by inconsistency): the power model is fitted across dose levels and is particularly sensitive to terminal-extrapolation noise propagating through the regression. AUC0-last (observed exposure) is therefore used as the FIXED primary endpoint, consistent with the observed-exposure basis of the Smith power-model approach. This differs from the BE/food-effect default (AUC0-∞ primary when reliable, dynamic downgrade to AUC0-last when ≥30 % of subjects in either arm produce NO_TERMINAL_PHASE or EXTREME_EXTRAPOLATION) by design, not by inconsistency.

Power-model regression: $\ln(PK) = \ln(a) + \beta \cdot \ln(Dose) + \varepsilon$, fitted by ordinary least squares on each subject's individual (Dose, PK) pair. AUC0-last is the primary endpoint because it does not depend on terminal-slope extrapolation; AUC0-∞ is reported as a secondary endpoint using only subjects whose AUC0-∞ is reliable per the NCA quality flags.

Smith acceptance window (Smith et al., Pharm. Res. 17:1278-1283, 2000): the 90 % confidence interval of β is compared to the dose-range-dependent window $[1 + \ln(0.80)/\ln(r), 1 + \ln(1.25)/\ln(r)]$ where r = max(Dose) / min(Dose). Dose-proportionality is concluded when the CI is contained inside the window; lack of proportionality when the CI lies entirely outside; otherwise the study is inconclusive on dose-proportionality.

Dose-normalised geometric means (DN-PK = PK / Dose) are tabulated per dose level as descriptive overlays; under strict proportionality the DN-PK is constant across dose levels.

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