ELECTRONIC SUPPLEMENTARY MATERIAL

Randomized, Open-Label, Crossover Studies Evaluating the Effect of Food and Liquid Formulation on the Pharmacokinetics of the Novel Focal Adhesion Kinase (FAK) Inhibitor BI 853520

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1 Methods

1.1 Determination of sample size

Up to 16 patients were planned for entry into each of the food-effect and liquid formulation sub-studies, which would include patients who would potentially discontinue early and would not be included in the analysis. The planned sample size was not based on a power calculation, i.e. to show bio(in)equivalence, but was judged as being sufficient to achieve the aims of these exploratory sub-studies and adequate to provide a minimum of 12 evaluable patients for the analysis, as required by FDA guidance.

The precision of the ratio of geometric means (test/reference) that was expected with a sample size of 12 patients is shown in Table 1. Precision was defined as the ratio of upper to lower CL (confidence interval limit), and is independent of the actual ratio of geometric means. In the first part of the trial (see the article by de Jonge et al. in this issue), the interpatient variability in the geometric coefficient of variation (gCV) for C_{max} varied at the different dose levels. For three assumptions on the intra-individual gCV for $C_{max,}$ an overview of the achievable precision for estimating the ratio of geometric means (test/reference) is shown in Table 1. For illustrative purposes, the expected 90% CIs with 95% coverage probability are displayed for different values of the ratios (test/reference) of geometric means. The expected 90% CIs in the table were derived by CI limit = exp(ln(Θ) ± w), with 'Θ' being the ratio (test/reference) on original scale and 'w' being the distance from the estimate Θ to either CL on the log-scale.

Table 2 shows an overview of the achievable precision for estimating the ratio of geometric means (test/reference) for three assumptions on the intra-individual gCV for $AUC_{0\text{-}oo}$. For illustrative purposes, the expected 90% CIs with 95% coverage probability are displayed for different values of the ratios (test/reference) of geometric means.

1.2 Determination of $T_{1/2}$

The apparent terminal half-life ($t_{1/2(ss)}$) of BI853520 in plasma was calculated from the terminal rate constant using the following equation:

$$t_{1/2(ss)} = \frac{\ln 2}{\lambda_{z(ss)}}$$

The apparent terminal rate constant $\lambda_{z(ss)}$ was estimated from a regression of ln(C) versus time over the terminal log-linear drug disposition portion of the concentration-time profiles. At least three points were used in the calculation of $\lambda_{z(ss)}$.

Table 1. Precision and illustrative two-sided 90% CIs around the ratios of geometric means (test/reference) for different gCVs and ratios (test/reference) for C_{max} in a two-way crossover design trial (n=12)

gCV (%)	Precision upper CL/lower CL	Ratio (%)	90% CI (%)
20	1.49	60	(49–73)
	1.49	80	(66–98)
	1.49	90	(74–110)
	1.49	100	(82–122)
30	1.8	60	(44.7–81)
	1.8	80	(60–107)
	1.8	90	(67–121)
	1.8	100	(75–134)
40	2.16	60	(41–88)
	2.16	80	(54–118)
	2.16	90	(61–132)
	2.16	100	(68–147)

The calculation was performed using R Version 2.10.0[1]

CI, confidence interval; CL, confidence interval limit; gCV, geometric coefficient of variation

Table 2. Precision and illustrative two-sided 90% CIs around the ratios of geometric means (test/reference) for different gCVs for AUC_{0-oo} and ratios (test/reference) in a two-way crossover design trial (n=12)

gCV (%)	Precision upper CL/lower CL	Ratio (%)	90% CI (%)
10	1.22	60	(54–66)
	1.22	80	(72–88)
	1.22	90	(81–99)
	1.22	100	(91–111)
20	1.49	60	(49–73)
	1.49	80	(66–98)
	1.49	90	(74–110)
	1.49	100	(82–122)
40	2.16	60	(41–88)
	2.16	80	(54–118)
	2.16	90	(61–132)
	2.16	100	(68–147)

The calculation was performed using R Version 2.10.0[1]

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References

1. Kupper LL, Hafner KB. How appropriate are popular sample size formulas? Am Stat 1989:43(2);101–5