Supplementary Information

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Food Effects on the Pharmacokinetics of Single Dose and Steady-state Ralinepag, a Novel Oral Prostacyclin Agonist, in Healthy Volunteers

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Statistical Analysis of Pharmacokinetic Effects

The pharmacokinetic (PK) parameters underwent a natural logarithmic transformation and were analyzed using mixed-effect modelling techniques. The model used to compare food effects on day 1 of period 1 included fixed-effect terms for cohort (i.e., fed vs. fasted). The null hypotheses to be tested were that there was no difference in pharmacokinetic (PK) parameters between fed and fasted. Comparisons of interest were to investigate overall food effects on day 1, period 1 after the first administration of a single 60 µg dose of ralinepag extended release (XR).

The model used to compare cohort effects at steady state included fixed-effect terms for cohort (i.e., fed/fasted) and regimen (i.e., dose level), as well as cohort-by-regimen interactions. Participant was fitted as a random effect. The null hypotheses to be tested were that there was no difference between fed and fasted participants. Comparisons of interest included overall and within-dose-level food effects and within-cohort effects.

The adjusted means, including differences for each comparison of interest and the associated 90% confidence intervals (CIs) from each model, were back-transformed to the log scale to obtain adjusted geometric mean ratios and 90% CIs of the ratio. These were presented together with the p-values for each comparison. Individual comparisons were not reported if there were fewer than 3 participants in either group being compared within the cohort or within gender.

The analysis was performed using the SAS Software procedure PROC MIXED, the method was specified as Restricted Maximum Likelihood, and the denominator degrees of freedom for the fixed effects were calculated using the Kenward-Roger method. No adjustment was made for multiple testing.

Statistical Analysis of Tolerability

A participant was defined as tolerating a dose level if they had completed 5 consecutive days of dosing at that level. Participants who de-escalated to a lower tolerated dose were classified as not tolerating the higher dose from which they de-escalated. Participants who were not administered at a dose level higher than their maximum tolerated dose were considered not to have tolerated the higher dose levels for the purposes of the statistical analysis.

The number of participants within each cohort (fed and fasted), stratified by tolerability and dose level, were analyzed using the Cochran-Mantel Haenszel (CMH) test statistic, based on the modified ridit scores, to test for a significant difference between the cohorts across dose levels. A Chi-Square or Fisher’s Exact test was performed at each dose level separately. The null hypothesis was that there was no difference between cohorts in the number of participants who tolerated ralinepag XR. The number and percentage of participants who tolerated and did not tolerate ralinepag XR were presented by cohort and dose level, along with the p-value from the CMH test statistic.

Any differences in the cohort effect across dose levels (i.e., cohort-by-regimen interaction) with respect to tolerability were investigated by examining tolerability within each stratum. Statistical analysis was performed to compare the maximum tolerated dose between the fed and fasted cohorts. A participant was defined as having tolerated their maximum dose if they had completed 5 consecutive days of dosing at their highest dose level. Participants who did not complete 5 days of dosing at a given dose level, or who were never administered at that dose level, were defined as not tolerating that dose level. The maximum tolerated dose was analyzed using Fisher’s Exact.