Official Protocol Title:	An Open-Label, Single-Dose Study to Investigate the Influence of Renal Insufficiency on the Pharmacokinetics of MK-7264
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9.7 Changes in the Conduct of the Trial

The original protocol dated 22-Mar-2017 [16.1.1.1] was amended on 04-May-2017 [16.1.1.2], 16-May-2017 [16.1.1.3], and 09-Jun-2017 [16.1.1.4]. Amendment 1 was generated to add Part 2 to the study to assess the PK of MK-7264 in subjects with ESRD requiring HD. Amendment 2 was generated to: 1) correct an error in the calculation of the total blood volume in Part 2 and to clarify that blood (pre-dialyzer and post-dialyzer) and dialysate samples were to be collected immediately after HD was stopped and 2) that HD would be approximately 4 hours in duration. Amendment 3 was generated to: 1) correct the blood volume drawn during the study in Part 2 to account for 3 samples per time point during HD; 2) to clarify that the last post-dialyzer blood sample and dialysate sample were to be collected immediately before HD was stopped; 3) to clarify that dialysate samples were to be collected pre-dialysis, post-dialysis, and for 1 minute every 30 minutes during HD for MK-7264 analysis; and 4) to modify the nomenclature of PK parameters calculated on plasma MK-7264 concentrations from the pre- and post-dialyzer lines. A protocol clarification letter (PCL) was issued on 06-Jun-2017 that described the changes outlined in Amendment 3. A second PCL was issued on 27-Jul-2017 to clarify the number of dialysis sessions (2) during the 7-day washout period between MK-7264 dosing in Periods 1 and 2 of Part 2. All 3 amendments were finalized after the initial screening date (14-Apr-2017) but prior to dosing of the ESRD subjects in Part 2 (28 and 29-Jul-2017). The 3 amendments outlined changes that were only relevant for Part 2 of the study; these amendments had no impact on Part 1 of the study that had already begun prior to their finalization. The PCLs were finalized prior to the washout period between Periods 1 and 2 of Part 2. There were no other changes in the conduct of the study.

9.8 Statistical Analysis Plan

9.8.1 Statistical and Analytical Plans to Address Study Objectives

Refer to Section 9.8.3.

9.8.2 Determination of Sample Size and Power to Address Study Hypotheses

Refer to the protocol [16.1.1.4].

9.8.3 Statistical/Analytical Methods and Issues

Pharmacokinetics

The plasma PK of MK-7264 administered to subjects with varying degrees of RI was compared to healthy matched control subjects using regression and categorical analysis.

Regression Analysis (Part 1)

Separately, individual values of AUC0-last, AUC0-∞, Cmax, CL/F, and CLr were ln-transformed and evaluated with a linear fixed-effects model containing eGFR as a continuous variable. The subject's mean renal function value derived from 2 serum creatinine

measurements at screening were used for the analysis. Estimates of the slope and intercept, together with corresponding 95% confidence intervals (CI) were obtained. The estimated mean and corresponding 95% CI for each RI group were predicted at the mid-point of the defined eGFR range for each group (45 mL/min/1.73 m^2 for moderate and 22.5 mL/min/1.73 m^2 for severe). Although subjects with mild RI were not enrolled in this study, the PK of MK-7264 were also predicted in this population at the eGFR of 75 mL/min/1.73 m^2 (the midpoint of the eGFR range for mild RI of 60 - 89 mL/min/1.73 m^2). For the healthy population, the estimated mean and corresponding 95% CI were predicted at the median of the observed eGFR values. The predicted means and corresponding 95% CIs were exponentiated to obtain estimates on the original scale. In addition to running the regression analysis using BSA normalized eGFR as the measure of renal function for each subject, the analysis was also run using BSA non-normalized eGFR and CrCL from the Cockcroft-Gault (C-G) equation.

Categorical Analysis (Part 1 and Part 2 Period 1)

Separately, individual values of AUC0-last, AUC0-∞, Cmax, CL/F, and CLr were ln-transformed and evaluated with a linear fixed-effects model containing a categorical effect for population (ESRD Non-HD, severe RI, moderate RI, and healthy matched control, based on BSA normalized eGFR). The REPEATED statement with the GROUP=Population option was used in SAS PROC MIXED to estimate separate variances for each population. The Kenward-Roger adjustment was used to calculate the denominator degrees of freedom for the fixed-effect (DDFM=KR). Ninety-five percent (95%) CI for the least-squares means for each population were constructed on the ln-scale and referenced to the t-distribution. The least-squares means (LSM) and their corresponding 95% CI were exponentiated to yield estimates for the population geometric means (GM) and CI about the GM on the original scale. To compare subjects with RI in each of the renal categories to subjects with normal renal function, a two-sided 90% CI for the true difference in means (renal impairment – normal renal function) was calculated for each PK parameter (AUC0-last, AUC0-∞, Cmax, CLr, and CL/F) using the mean square error from the model and referencing a t-distribution. For each of the RI populations, these confidence limits were exponentiated to obtain the 90% CI for the true GMR renal impairment/normal renal function) for each PK parameter. Figures showing individual PK values with GMs (95% CI) by population, were provided for AUC0-last, AUC0-∞, Cmax, CL/F, and CLr.

ESRD HD vs ESRD Non-HD (Part 2)

To evaluate the extent of MK-7264 removal by HD in Part 2, a linear mixed-effects model with population (ESRD Non-HD, ESRD HD) as a fixed effect was used. An unstructured covariance matrix was used to allow for unequal variances and to model the correlation between the two measurements within each subject via the REPEATED statement in SAS PROC MIXED. The Kenward-Roger adjustment was used to calculate the denominator degrees of freedom for the fixed-effects (DDFM=KR).A ln-transformation was applied to AUC0-last, AUC0-∞, Cmax, and CL/F. For each PK parameter, 95% CIs for the LSMs was constructed on the ln-scale and referenced the t-distribution. The LSMs and corresponding 95% CIs were then exponentiated to obtain population GM and CI about the GM on the

original scale. A two sided 90% CI for the true difference in means (ESRD HD - ESRD Non-HD) was calculated for each PK parameter (AUC0-last, AUC0-∞, Cmax, and CL/F) using the mean square error from the model and referencing a t-distribution. These confidence limits were exponentiated to obtain the 90% CI for the GMR (ESRD HD / ESRD Non-HD) for each PK parameter.

Other Pharmacokinetic Analyses

Subjects with moderate and severe RI and healthy matched control subjects (based on their BSA normalized eGFR) were re-categorized into different renal categories based on their BSA non-normalized eGFR and CrCL. Non-model based summary statistics by population were provided for AUC0-last, AUC0-∞, Cmax, CL/F and CLr.

Non-model-based %CV of the GM were presented for plasma MK-7264 AUC0-12, AUC0-24, AUC0-48, apparent terminal t½, and Vz/F for subjects with moderate and severe RI, ESRD Non-HD, ESRD HD, and healthy matched control subjects. Individual values were also listed for each PK parameter by population and non-model-based descriptive statistics were provided.

Arithmetic mean (AM) concentration-time plots (with and without standard deviation [SD] error bars) of plasma, pre- and post-dialyzer plasma, and dialysate MK-7264 were presented by population on a linear-linear scale plot with an inset semi-log scale plot. The BLQ values were treated as 0 for the calculation of the AM (and SD, as appropriate). At the beginning of the profile, if < 50% of subjects had a quantifiable concentration ≥ LLOQ for a given time point, the AM concentration was presented as 0. At the end of the profile when concentrations from some subjects began to fall BLQ, the AM value was only plotted if ≥ 50% of subjects had quantifiable concentrations ≥ LLOQ and the AM value was ≥ LLOQ. However, all AM values were presented in the concentration tables. A reference line for the LLOQ value was added to the plot, where possible, as well as a footnote indicating the AM concentrations at or after certain time points that were not presented since > 50% of subjects had values < LLOQ or the AM was < LLOQ.

AM (with and without SD error bars) cumulative Ae-time plots of urine MK-7264 were presented by population on a linear-linear scale plot. BLQ urine MK-7264 concentration values were treated as 0 for the calculation of the Ae and respective AM (and SD, as appropriate). AM (with and without SD error bars) rr - time (with time corresponding to the midpoint of the 1-minute dialysate collection) plots of urine MK-7264 were presented on a linear-linear scale plot. BLQ MK-7264 concentration values were treated as 0 for the calculation of the rr and respective AM (and SD, as appropriate).

Safety

Safety and tolerability of MK-7264 was evaluated by clinical assessments, including AEs, vital signs, physical examination, 12-lead ECGs, and standard laboratory safety tests (hematology, chemistry, and urinalysis) which were obtained at pre-specified time points throughout the study. AEs were coded according to Version 20.0 of the Medical Dictionary

for Regulatory Activities (MedDRA®) as modified by Merck. Incidence of the number of subjects with AEs was tabulated by population. AEs related to study drug were also tabulated by population. AEs were listed by subject. Since no meaningful changes in individual laboratory safety values, ECGs, and vital signs were observed, summary statistics were not provided.

9.8.3.1 Handling of Dropouts or Missing Data

There were no subject discontinuations in this study.

Peripheral blood samples could not be collected at 6 time points (0.25, 3, 3.5, 4.5, 5.5, and 36 hours postdose) for 1 subject with ESRD in Part 2, Period 1, and for 1 time point (16 hours postdose) for the same subject in Part 2, Period 2, due to difficult venipuncture. Therefore, the plasma MK-7264 concentrations at these time points were treated as missing.

Urine samples could not be collected in Periods 1 and 2 of Part 2 for the same 5 of 6 subjects with ESRD. Therefore, urine MK-7264 concentrations at each collection interval were treated as missing.

The dialysate samples at 4 hours postdose for 1 subject and at 4.5 hours postdose for 2 subjects were mistakenly discarded. Therefore, the dialysate MK-7264 concentrations at these time points were treated as missing.

9.8.3.2 Multicenter Studies

This study was conducted at 2 clinical sites. Data from both sites were combined for data summarization and analyses. Study site was not included as a factor in the statistical analyses.

9.8.3.3 Multiple Comparisons/Multiplicity

No hypotheses were tested so no multiplicity adjustment was needed for the study.

9.9 Changes in the Planned Analyses

One (1) subject with ESRD had 6 missing peripheral blood samples (Part 2, Period 1) due to difficult venipuncture. This 1 subject was excluded from the primary PK analyses presented in Section 11. Supplementary analysis including all 6 subjects is shown in Section 14.

One (1) dialysate sample was missing for 3 subjects (4-hour for 1 subject; 4.5-hour for 2 subjects) as they were mistakenly not processed and discarded; therefore, the AD and rr values at these time points could not be determined. In addition, a sensitivity analysis was performed and it was determined that the missing sample had minimal impact (≤ 1%) on the extent of removal of MK-7264 by HD; therefore, a decision was made to include all subjects in the analysis.

Five (5) of the 6 ESRD subjects did not produce urine; therefore, PK parameters in Periods 1 and 2 of Part 2 could not be calculated. Although the remaining subject did produce urine, MK-7264 concentrations in urine were not quantifiable.

For Part 1, the protocol classified the categorical analysis as a secondary analysis; however, when Part 2 was added, it was considered as a part of the primary analysis used to assess the primary PK objective in ESRD subjects, and was described as such in the statistical analysis plan.

The protocol stated that dialysate samples would be collected pre- and post-HD, as well as for 1 minute every half hour during HD; however, as dialysate is a product of HD, no pre- or post-HD samples were obtained.

Non-model based summary statistics by population based on BSA normalized eGFR were provided for both primary (AUC0-∞, AUC0-last, Cmax, CL/F, and CLr) and exploratory endpoints (AUC0-12, AUC0-24, AUC0-48, Tmax, Vz/F, apparent terminal t½, Ae0-12, Ae12-24, Ae24-48, Ae0-24, Ae0-48, Fe0-12, Fe12-24, Fe24-48, Fe0-24 and Fe0-48). However, non-model based summary statistics by population based BSA non-normalized eGFR and CrCL using C-G equation were provided only for primary AUC0-∞, AUC0-last, Cmax, CL/F and CLr, as some categories had few or no subjects.

There were no other changes to the planned analyses of the original protocol [16.1.1.4].

10 TRIAL SUBJECTS AND DATA SETS ANALYZED

Individual subject level data listings are provided in [16.2.1, 16.2.4, 16.2.5, 16.2.7, and 16.2.8]. Individual subject case report forms [16.3] are available upon request.

10.1 Subject Disposition

Twenty-four (24) subjects were enrolled into the study; 6 healthy matched control subjects, 6 subjects with moderate renal impairment, 6 subjects with severe renal impairment, and 6 subjects with ESRD requiring HD. All 24 subjects completed the study per protocol [16.1.1.4, 16.2.1, 16.4]. See Table 10-1 below for the study subject disposition details.

All subjects satisfied all inclusion and none of the exclusion criteria, with verification at check-in. Individual subjects' information related to check-in and inclusion/exclusion criteria is presented in [16.2.5.1, 16.4].