FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Pharmaceutical Science and Clinical Pharmacology (PSCP) Advisory Committee Meeting
FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503)
10903 New Hampshire Avenue, Silver Spring, Maryland
May 7, 2019

QUESTIONS

Topic 1: Evaluation of the effect of renal impairment on drug exposure

Many registration trials exclude patients with advanced kidney disease. The dosing instructions included in prescription drug labeling for these patients are commonly derived based on our understanding of the change in the investigational drug's pharmacokinetics (PK) in subjects with varying degrees of renal function. The necessary information can be collected in several ways.

The most common current approach to determine dosing instructions for patients with varying degrees of renal function begins with a stand-alone "full design" or "reduced design" renal impairment study. Most often, a full design study (which compares subjects with mild, moderate, and severe renal impairment with subjects with normal renal function) is conducted for drugs with significant renal elimination, and a reduced design study (evaluation of subjects with severe renal impairment against those with normal renal function) is conducted for drugs that do not have significant renal elimination. In addition to conducting stand-alone renal impairment studies, drug development programs often use the findings from population PK (popPK) analysis. PopPK analysis leverages the PK information across all the studies available in a drug development program for which PK samples have been obtained. However, late-stage clinical trials often include limited numbers of patients with renal impairment, so stand-alone renal impairment studies provide most of the information regarding the need for dose adjustment. This current typical paradigm is a retrospective approach to dose individualization that excludes an important patient population from the assessment of efficacy and safety.

We would like to explore alternative paradigms that encourage inclusion of patients with renal impairment in later-stage clinical trials. Such paradigms could predict the impact of renal impairment on the pharmacokinetics of the drug based on available data and modeling, without a stand-alone, full-design renal impairment study. If deemed necessary, doses may be adjusted for patients with impaired renal function. Inclusion of these patients in clinical trials would lead to more generalizable efficacy and safety assessments. Because many late-stage clinical trials include sparse PK sampling for popPK analysis, characterization of the effect of renal impairment on pharmacokinetics would be possible. If patients with severe renal impairment and those with end-stage renal disease on dialysis must be excluded from late-phase trials for safety reasons, a reduced design study and a dialysis study (where applicable) would be the only stand-alone characterization needed for the drug development program.

1. **DISCUSSION:** Please discuss what alternative drug development paradigm(s) would encourage the inclusion of patients with all (or most) degrees of renal impairment in late-stage clinical trials, without the need for a stand-alone renal impairment study, and the advantages and disadvantages of these paradigms as compared to the current paradigm.

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QUESTIONS (cont.)

Topic 2: Translation

For the subgroup of patients with kidney disease, especially those with severely impaired renal function (often excluded from late stage clinical trials), PK data or predictions may be the main source of information for dose individualization. Dose individualization is achieved by invoking the concept of 'exposure-matching' to subjects with normal renal function under the assumption that the 'exposure-matching' will result in a benefit-risk similar to that observed in the registration trials.

During drug development, evaluations of the effect of renal disease tend to focus mostly on the effect on drug clearance and the resulting changes in drug exposure. However, renal disease can affect other organs, alter physiology, and patients with renal disease can present with comorbidities. Both renal disease and the presence of comorbidities could theoretically predispose patients to an increased incidence of adverse events, altered pharmacodynamics, or altered efficacy, thereby altering the exposure-response relationship and/or overall benefit/risk. To date, there is limited information in the literature about the impact of renal disease on drug response. Current practices in drug development often do not allow the assessment of differences in the exposure-response relationship, because patients with advanced kidney disease are either not enrolled or not enrolled in sufficient numbers.

1. **DISCUSSION:** Please discuss if it is reasonable to assume that a drug's exposure-response relationship will usually not be significantly different between patients with impaired renal function and patients included in the registration trials, and the situations where the assumption of similar a exposure-response relationship may not apply.

2. **DISCUSSION:** Often for exposure matching purposes, the normal renal function group serves as the reference group. We propose the reference group be selected based on the understanding of benefit/risk for the drug and be more proximal in terms of renal function (e.g., severe vs. moderate instead of severe vs normal).

   Please discuss the pros and cons of this approach.

3. **DISCUSSION:** There are multiple approaches for establishing an "exposure match" (i.e., matching based on point estimate, confidence interval-based approaches, exposure matching 5th and 95th percentile, etc.).

   Please discuss the criteria for choosing one approach over another.