

**Food and Drug Administration
Center for Drug Evaluation and Research**

**Final Summary Minutes of the Pharmaceutical Science and Clinical Pharmacology Meeting
May 7, 2019**

Location: FDA White Oak Campus, Building 31 Conference Center, The Great Room (Rm. 1503), Silver Spring, Maryland

Topic: The committee discussed the following topics: (1) approaches to evaluate the effect of renal impairment on drug exposure, and (2) best practice considerations for translating pharmacokinetic (PK) information into dose individualization instructions. Regarding topic 1, many registration trials exclude patients with advanced kidney disease, and product labeling dosing instructions for these patients are commonly derived from our understanding of the change in the PK in individuals with varying degrees of renal function. The most common current approach to determine dosing instructions for patients with varying degrees of renal function begins with a stand-alone renal impairment study, either full design or reduced design. In addition to stand-alone renal impairment studies, drug development programs often use the findings from population PK (POPPK) analyses, which leverage the PK information across all the studies available in a drug development program. An alternative approach to consider is for drug development programs to predict the impact of renal impairment on the PK of the drug, either based on the understanding of the PK of a new molecular entity or using physiologic based PK (PBPK) models, without a stand-alone renal impairment study. Patients with impaired renal function can then be included in later stage clinical trials, with prospective dose adjustment incorporated if deemed necessary based the predictions. The dosing should be confirmed based on analysis of PK samples from the late stage trials (sparse PK, POPPK analysis). Regarding topic 2, dose individualization is typically achieved by applying the concept of ‘exposure-matching’ under the assumption that such a maneuver will result in a benefit-risk similar to that observed in the registration trials. The committee discussed the application of ‘exposure matching,’ including the necessary assumptions and any limitations.

These summary minutes for the May 7, 2019 meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee of the Food and Drug Administration was approved on June 24, 2019.

I certify that I attended the May 7, 2019 meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
JAY R. FAJICULAY, PHARM.D.
*Designated Federal Officer
Pharmaceutical Science and Clinical
Pharmacology Advisory Committee*

/s/
ANDRE TERZIC, MD, PHD
*Chairperson
Pharmaceutical Science and Clinical
Pharmacology Advisory Committee*

**Summary Minutes of the Pharmaceutical Science and Clinical Pharmacology
Advisory Committee Meeting
May 7, 2019**

The Pharmaceutical Science and Clinical Pharmacology (PSCP) Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on May 7, 2019, at the FDA White Oak Campus, Building 31 Conference Center, The Great Room (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA. The meeting was called to order by Andre Terzic, MD, PhD (Chairperson). The conflict of interest statement was read into the record by Jay Fajiculay, PharmD (Designated Federal Officer). There were approximately 175 people in attendance. There was one (1) Open Public Hearing speaker presentation.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda: The committee discussed the following topics: (1) approaches to evaluate the effect of renal impairment on drug exposure, and (2) best practice considerations for translating pharmacokinetic (PK) information into dose individualization instructions. Regarding topic 1, many registration trials exclude patients with advanced kidney disease, and product labeling dosing instructions for these patients are commonly derived from our understanding of the change in the PK in individuals with varying degrees of renal function. The most common current approach to determine dosing instructions for patients with varying degrees of renal function begins with a stand-alone renal impairment study, either full design or reduced design. In addition to stand-alone renal impairment studies, drug development programs often use the findings from population PK (POPPK) analyses, which leverage the PK information across all the studies available in a drug development program. An alternative approach to consider is for drug development programs to predict the impact of renal impairment on the PK of the drug, either based on the understanding of the PK of a new molecular entity or using physiologic based PK (PBPK) models, without a stand-alone renal impairment study. Patients with impaired renal function can then be included in later stage clinical trials, with prospective dose adjustment incorporated if deemed necessary based the predictions. The dosing should be confirmed based on analysis of PK samples from the late stage trials (sparse PK, POPPK analysis). Regarding topic 2, dose individualization is typically achieved by applying the concept of ‘exposure-matching’ under the assumption that such a maneuver will result in a benefit-risk similar to that observed in the registration trials. The committee discussed the application of ‘exposure matching,’ including the necessary assumptions and any limitations.

Attendance:

Pharmaceutical Science and Clinical Pharmacology Advisory Committee Members Present (Voting): Paul M. Beringer, PharmD; Jeffery M. Carrico, PharmD, BCPS; Jerry M. Collins, PhD; Maureen D. Donovan, PhD; Sandra Finestone, PsyD (Consumer Representative); Walter K. Kraft, MD, MS; Tonglei Li, PhD; Kenneth R. Morris; Eric Slud, PhD; Duxin Sun, PhD; Andre Terzic, MD, PhD (Chairperson)

May 7, 2019

Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting

Pharmaceutical Science and Clinical Pharmacology Advisory Committee Members Not Present (Voting): Gregory E. Amidon, PhD; James E. Polli, PhD; Frances J. Richmond, MSc, PhD

Pharmaceutical Science and Clinical Pharmacology Advisory Committee Members Present (Non-Voting): Walid M. Awni, PhD (Industry Representative); Jack A. Cook, PhD (Industry Representative); Srinu Tenjarla, PhD (Industry Representative)

Temporary Members (Voting): Thomas C. Dowling, PharmD, PhD; Patrick H. Nachman, MD; Thomas D. Nolin, PharmD, PhD; Manjunath P. Pai, PharmD; Patricia W. Slattum, PharmD, PhD; Ravi Thadhani, MD, MPH

FDA Participants (Non-Voting): Issam Zineh, PharmD, MPH; Shiew-Mei Huang, PhD; Rajanikanth Madabushi, PhD; Martina Sahre, PhD; Kellie Reynolds, PharmD

Designated Federal Officer (Non-Voting): Jay R. Fajiculay, PharmD

Open Public Hearing Speaker: Ting-Chao Chou (Memorial Sloan-Kettering Cancer Center)

The agenda was as follows:

Call to Order and Introduction of Committee

Andre Terzic, MD, PhD, FAHA
Chairperson, PSCP

Conflict of Interest Statement

Jay Fajiculay, PharmD
Designated Federal Officer, PSCP

FDA OPENING REMARKS

The Impact of Renal Impairment on Patient Drug Response – Assessing the Need for a Consensus Approach

Kellie Reynolds, PharmD
Deputy Director
Division of Clinical Pharmacology IV
Office of Clinical Pharmacology (OCP)
Office of Translational Sciences (OTS), CDER, FDA

FDA PRESENTATIONS

Determination of Dosing Instructions for Patients with Renal Impairment: Current Paradigm

Martina Sahre, PhD
Policy Lead
Guidance and Policy Team, OCP, OTS, CDER, FDA

Translation of Findings to Dosing Recommendations

Rajanikanth Madabushi, PhD
Team Leader
Guidance and Policy Team, OCP, OTS, CDER, FDA

Clarifying Questions to Presenters

BREAK

GUEST SPEAKER PRESENTATION

Industry Perspectives on Approaches to
Evaluate the Effect of Renal Impairment on
Drug Exposure

Richard A. Graham, PhD
International Consortium for Innovation & Quality in
Pharmaceutical Development
Vice President, Head of Clinical Pharmacology
Theravance Biopharma

Clarifying Questions to Presenter

LUNCH

OPEN PUBLIC HEARING

Questions to the Committee/ Committee
Discussion

BREAK

Questions to the Committee/ Committee
Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

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.

Committee Discussion: The committee supported the inclusion of patients with renal impairment in clinical trials to inform dosing for this large population. The committee discussed the complexities of enrolling patients with renal impairment in clinical trials. It was noted that in addition to challenges with enrolling adequate numbers of individuals with more severe levels of renal impairment, there are added safety concerns as well as the potential for confounding efficacy results. Lack of consistency in the use of measures of renal function and a lack of clarity on the regulatory consequences of pursuing a particular enrollment strategy was also discussed.

The committee discussed the advantages and disadvantages of potential solutions for these challenges. It was commented that any method of increasing inclusion of patients with renal impairment in clinical trials should be designed to proactively address the “knowledge deficit” of exposure levels of a drug in patients with the condition. It was further noted that the sponsor should choose an approach that takes into account the totality of evidence for the drug’s safety and efficacy in patients with renal impairment. The committee agreed that no

one solution or trial design is a panacea for this issue and that a tailored, multipronged approach would be needed for each drug development program. Some committee members highlighted the rigor of the data obtained from early stand-alone studies were critical to understanding the effect of renal impairment on drug disposition, safety, and efficacy. Committee members also noted that information from these studies can then be used to help inform appropriate dosing for patients with renal impairment in later-stage trials. Several designs for later-stage trials that could help facilitate the inclusion of patients with renal impairment were also discussed. For example, including patients with renal impairment as a sub-population during phase 2 or 3 trials could limit confounding of efficacy results. In addition, adaptive trial designs take a risk-based approach to including patients with renal impairment, accounting for safety concerns by first enrolling patients with mild or moderate renal impairment and then assessing the exposure levels to determine the likely safety and efficacy outcomes.

The committee also discussed overarching strategies that could improve the outcomes of studies that include patients with renal impairment. Prespecifying adverse events that are associated with renal impairment could also improve data analysis. The committee advocated for the use of eGFR as the measure of renal function. The committee advised using results from clinical studies as opposed to evidence from ‘real-world’ sources, such as electronic health records, at this time. Feedback from regulatory agencies on the sponsor’s proposed approach as well as clear regulatory pathways are also recommended. Please see the transcript for details of the committee’s discussion.

2. **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 a similar exposure-response relationship may not apply.

***Committee Discussion:** The committee acknowledged that the assumption of similar exposure-response relationship for the purpose of exposure-matching is reasonable. However, this assumption remains unverified and should be challenged early on in drug development through the systematic collection of data addressing the impact of, for example, altered physiology in renal disease, patient comorbidities, sex, ethnicity, and protein binding. It was noted that there are clear examples of where differences in exposures as a result of disease manifestations or ethnicity led to dosing recommendations that did not follow the exposure-matching paradigm. It was further noted that certain typical criteria, such as age, may not have the most impact on exposures compared to related criteria, such as frailty. The committee advocated for clear and complete descriptions of the population under study to fully understand the impact of renal impairment on a drug’s safety and efficacy. Please see the transcript for details of the committee’s discussion.*

3. **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.

Committee Discussion: *The committee stated that while there is no ‘all or none approach’ to determining a reference group, there are drawbacks to matching to a group with impaired renal function, including limited sample sizes outside of the normal population and increasing variability with declining renal function. The committee also noted that dosing recommendations do not have to follow the cutoffs for normal, mild, moderate, and severe renal impairment categories, which are primarily used for enrollment purposes. Please see the transcript for details of the committee’s discussion.*

4. **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.

Committee Discussion: *The committee noted that there are insufficient data to determine the validity of one approach over another. However, the committee reiterated that enrollment of patients with renal impairment should cover the spectrum of renal impairment and that the cut-points for enrollment are not necessarily the best cut-points for determining dosing recommendations. For example, to maintain efficacy, it may be necessary to have exposure levels ‘at least’ a certain value; conversely, to prevent adverse events, it may be necessary to have exposure levels ‘no greater than’ a certain value. The committee also noted that there are instances of augmented renal function in certain indications and should be considered when appropriate. Please see the transcript for details of the committee’s discussion.*

The meeting was adjourned at approximately 3:25 p.m.