



May 26, 2016

Janssen Research & Development, LLC  
Attention: Purve Patel, RPh  
Director, Global Regulatory Affairs  
920 Highway 202, South  
Raritan, NJ 088969

Dear Ms. Patel:

Please refer to the submission by Janssen Pharmaceuticals and Novartis Pharmaceuticals intended to support the use of MCP-Mod<sup>1,2</sup> as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty. We have completed our review of your submission and have determined it is fit-for-purpose in the context outlined in this letter.

#### Goal and Intended Applications

Although dose selection is a critical component in drug development, inadequate design and analysis of dose finding studies continues to plague many development programs. The consequences of inadequate dose exploration include limited understanding of the dose-response relationship, failed Phase III trials, and post-marketing dose adjustments. To address the need for better informed dose selection, Janssen and Novartis have submitted a proposal for the use of MCP-Mod. The goal of MCP-Mod is to serve as a principled strategy to explore and identify adequate doses for drug development. The submission suggests that the methodology is best used in trials with the following characteristics:

- a univariate response variable
- a minimum of four distinct doses, including placebo
- doses measured on any continuous, quantitative scale
- exploratory dose finding studies intended to support dose selection in a confirmatory setting

#### FDA Assessment

Traditionally, the analysis of dose-response studies has been divided into two primary strategies: multiple comparison procedures and model-based approaches. When applied separately, each strategy has shortcomings that may impact the decision-making process. The current application combines principles of multiple comparisons with modeling techniques under a single approach referred to as MCP-Mod.

The MCP-Mod procedure consists of a design stage and an analysis stage. In the former stage, a set of plausible candidate models are selected based on the known pharmacology of the drug and any relevant previous experience with similar compounds. The subsequent analysis stage

includes the MCP and Mod steps. The MCP step aims to assess the dose-response signal using multiple comparison methods and to select the “best” model(s). The Mod step then entails fitting the selected model(s) to the data and estimating the target dose(s).

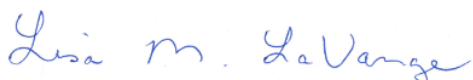
The applicant additionally submitted examples of the methodology and described the use of MCP-Mod for both general parametric models and response adaptive dose finding studies. The goal of the examples and extensions was to demonstrate the generality of the procedure. A list of literature articles and studies from Novartis and Janssen further highlighted the applicability of the procedure. The submission also included results from two simulation studies. The purpose of these studies was to compare MCP-Mod to other established methods for testing a positive dose-response relationship and to assess the dose selection performance. Of note, the submission included a discussion of a publicly available software package to implement MCP-Mod; however, an evaluation and opinion of the software package is beyond the scope of this assessment.

A multidisciplinary team with representation from the Office of Biostatistics and the Office of Clinical Pharmacology in the Office of Translational Sciences, Center for Drug Evaluation and Research has reviewed the submission. The team has reviewed all aspects of the submission with particular focus on the simulation studies provided. The team finds that the methodology is scientifically sound. MCP-Mod is advantageous in that it considers model uncertainty and is efficient in the use of the available data compared to traditional pairwise comparisons. MCP-Mod performs favorably when compared to other methods in simulation studies; however, we note that findings from simulation studies are driven by the models considered and their parameters.

### General Comments

The importance of adequately understanding the dose-response relationship is well-recognized in drug development. Dose finding studies, however, are often designed with a small number of doses and a narrow dose range using suboptimal analysis techniques. The MCP-Mod approach seeks to motivate better design and analysis of dose-ranging studies. We support the use of MCP Mod; however, our support does not preclude the availability and use of other statistical methods for dose selection. In addition, we encourage further development of MCP-Mod with possible consideration of multivariate responses for safety and efficacy and exposure-response modeling.

Sincerely,



Lisa LaVange, PhD | Director, Office of Biostatistics  
Office of Translational Sciences | Center for Drug Evaluation and Research



Issam Zineh, PharmD, MPH | Director, Office of Clinical Pharmacology  
Office of Translational Sciences | Center for Drug Evaluation and Research

#### Attachments Discipline Reviews: Biostatistics and Pharmacometrics

<sup>1</sup> Bretz, F., Pinheiro, J., and Branson, M. (2005). Combining multiple comparisons and modeling techniques in dose-response studies. *Biometrics* 61, 738-748.

<sup>2</sup> Pinheiro, J. Bornkamp, B., and Bretz, F. (2006b). Design and analysis of dose finding studies combining multiple comparisons and modeling procedures. *Journal of Biopharmaceutical Statistics* 16, 639-656.