Optimizing Operational Efficiencies for Data Collection in HABP/VABP Trials

Executive Summary of Meeting held November 12, 2013

Crystal City Marriott, Arlington, Virginia

CTTI's Antibacterial Drug Development (ABDD) Data Collection Work Stream group held a 1-day conference that included presentations as well as joint and breakout discussions. The meeting was attended by various stakeholders representing academia, the pharmaceutical industry, government agencies, and patient advocates who convened to seek practical solutions to streamline the operational processes and build efficiencies for data collection in hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP) trials. The agenda, presentations, and participant list are available.

The opening remarks summarized the key issues and objectives: namely, reaching agreement and setting expectations on what a more streamlined yet satisfactory data set would look like, and how to address the concern that particular data not gathered during the conduct of a trial may later be requested by regulators or by advisory committees. These priorities were reflected in the session topics as described below.

Session 1 examined the need for appropriate data collection in HABP/VABP trials for efficient development of antibacterial drugs without relaxing standards, to determine the risk/benefit of new drugs. Challenges and consequences of excess data collection in Phase 3 trials were presented and discussed, including increased time and expense, and fatigue on the part of investigators and monitors due to excessively detailed record keeping, which necessitates additional staff training and can result in loss of sites and participants. Further, this type of data collection does not seem to provide direct benefit to patients or increase the chances of detecting an unexpected safety signal. Several potential solutions were presented; in particular, the FDA described recent efforts to streamline antibacterial drug development, and key points on simplifying data collection from the recently released draft guidance for safety data collection were discussed. Suggestions to improve clinical trial feasibility included:

- utilizing a single HABP/VABP trial along with other supportive evidence.
- use of intention-to-treat (ITT) as the primary analysis population (with a positive gram stain as an enrollment criterion, and a sensitivity analysis in the microbiological ITT population).
- allowance of 24 hours of prior antibacterial therapy.
- use of risk difference vs. odds ratio for primary analysis if control mortality rates are low.
- consideration of the use of approved active comparators that are not labeled for HABP/VABP.

The follow-up discussion included:

- FDA regulations governing staff training and site inspections.
- The culture of investigational new drug research as a central challenge, and how the struggle now being experienced in antibacterial studies regarding streamlining data collection has been faced and overcome by other disciplines (such as cardiovascular studies).
- The need for cultural change and consensus regarding the data considered essential for determining the risk/benefit of antibacterial drugs under development. The FDA's recent changes in policy and approach appear to have had a positive effect but are still not widely adopted.

Presentations in Session 2 focused on safety reporting as well as differences and similarities between US and European regulations, from an FDA and an industry perspective, followed by a group discussion. Several strategies to streamline safety data collection for Phase 3 studies were raised, and it was suggested that the relevant FDA review division be consulted prior to any implementation. For safety reporting, use of aggregate analysis and randomized comparisons (as opposed to individual safety reports) was emphasized, as well as the

importance of independent data safety monitoring boards. Regarding apparent differing regulations between the United States and Europe, the EMA is generally in alignment with the FDA, such as not requiring reporting of all noncritical adverse events (AEs). However, differences in regulations related to the timing for reporting serious adverse events (SAEs), requests for aggregate reporting, and determination of causality of serious unexpected adverse reactions were noted. The industry perspective on safety data collection focused on complying with the law and protecting patients. A call was made for better clarity from regulators, and the "minor but important" differences in US and European guidelines about investigator and sponsor responsibilities were noted.

The follow-up discussion included:

- Representatives from the EMA concurred with the interpretation of European regulations regarding safety reporting and agreed that there is enough scope in their current legislation for flexibility to streamline safety reporting. If this needs to be made clearer, perhaps an editorial could be written and published in a journal.
- It was noted that several opportunities could be explored to reduce data collection; regulations and guidances should not be solely relied on to provide answers. A collaborative group comprising different views should be convened to develop a strategy to move a product forward in the face of increasing antibiotic resistance.
- The need for adequate data to conduct a thorough risk/benefit analysis was acknowledged. Perhaps a small but finite risk of missing a signal could be tolerated under certain circumstances, without negatively affecting the overall risk/benefit assessment and faster approval of a new drug. However, the participants had divergent views on the amount of risk that should be accepted.

Session 3 discussed practical, real-world steps to streamline data collection. The use of quality-by-design (QbD) principles was endorsed and summarized as two overarching questions: *What data are critical to determine the risk/benefit of the drug? And what would prevent errors in collecting that data?* Successful streamlining in large cardiovascular outcomes trials was offered as an example for efficient data collection.

The follow-up discussion included:

- The need to collect both local and central lab data, as well as *all* vital signs and medications, for patients in the intensive care unit (ICU) was questioned.
- If there is no safety signal from previous research, then collection could be simplified accordingly. The compound and extent to which it has already been studied will partly determine how data collection can be streamlined. The rareness of a specific AE should be taken into account.
- A proposal to streamline procedures by reducing visits and selectively collecting AEs, concomitant medications, and vital signs received a mixed response; participants felt that it would depend partly on the amount of previous data available, especially for a new molecular entity being studied for HABP/VABP in a single trial.

Three breakout groups met separately to discuss assigned topics (1. AEs, SAEs, and Concomitant Medications; 2. Inclusion and Exclusion Criteria, Medical History, and Baseline Characteristics; and 3. Visits and Assessments, Vital Signs/Physical Exam, Clinical Labs, Exploratory Data) and then presented their small group consensus recommendations to the entire group during the final session.

Group 1: Recommendations for streamlining collection of AEs, SAEs, and concomitant medications included collecting AEs only at certain intervals (with the exception of SAEs, causal, and unexpected AEs, and AEs leading to withdrawal), having data safety monitoring boards review SAEs, and collecting only select concomitant medications.

Group 2: The group felt that inclusion criteria did not offer much room for streamlining, but baseline characteristics and medical history might offer opportunities, especially by focusing on critical parameters of efficacy or safety. Use of relevant yes/no questions rather than free text for medical history was proposed. Regarding inclusion criteria, prior antibiotic use was considered to be the biggest limitation to rapid enrollment, with a proposed solution of no antibiotic use for 24 hours before enrollment (which might be further reduced with improved diagnostics) and using the ITT as the primary population for analysis. Enrollment could be based on a positive gram stain and then follow-up with a culture to confirm a microbiologically confirmed population that could be used for a sensitivity analysis.

Group 3: Recommendations to streamline data from visits and assessments were made by classifying the data into three categories: *critical* (mortality, concurrent antibiotic use, temperature, components of severity of disease scales—e.g., SOFA [sequential organ failure assessment] score, and blood and respiratory cultures), *noncritical* (respiratory rate, pulse, blood pressure, radiography), and *class- or drug-dependent* (laboratory analysis, electrocardiogram). The group agreed that a select set of routinely assessed values associated with the critical list were essential, but other lab values could be considered class- or drug-dependent, and their need for evaluation might be affected by whether a signal existed from preclinical studies or a previous trial. Microbiological assessments would become critical only if a patient was clinically failing. Assessment visits at baseline, Day 3, end of therapy, and a test of cure seemed reasonable time points to the group.

The moderated discussion that followed included the following salient points:

- Caution was raised about paring down data collection too much, in particular for heterogeneous populations, since there is risk of missing differential treatment effects and safety in certain populations, and those differences may confound the stated association between the drug and the outcome. A simple checklist with yes/no questions was suggested for identifying different patient subgroups.
- Identifying a verifiable endpoint such as all-cause mortality might reduce data collection, especially for certain lab values and other variables. However, concern was raised about using the all-cause mortality endpoint in a non-inferiority study and being able to adequately gauge drug effect.
- The impact of return on investment to pharmaceutical companies by streamlining data and reducing cost at the Phase 3 stage for infectious disease programs was debated. Some participants suggested that the savings would not be considerable enough to incentivize the change, since it would be a small proportion of the overall contribution to the total investment. Others felt that since Phase 3 trials have a significantly higher cost than earlier phases of development, companies could be persuaded to adopt the changes.
- Separating trials for HABP and VABP was mentioned. Not all HABP patients will be in the ICU, so the group was challenged to perhaps focus on VABP patients. If a new drug is efficacious for VABP, efficacy in other less severe disease settings may follow.
- Collecting post-marketing safety and efficacy data was recommended as especially data on any safety signals that newly appeared in Phase 3.

The meeting was adjourned after discussing next steps for the group to pursue, which included drawing up recommendations on streamlining data collection. Based on a review of the entire day's discussions, future group efforts would be planned.