Antibacterial Drug Development Program Update

Summary of Working Group Webinar held 29, August 2013

Clinical Trials Transformation Initiative

Meeting background

The Clinical Trials Transformation Initiative's (CTTI) Antibacterial Drug Development (ABDD) Working Group held a half-day webinar that included presentations and a moderated discussion. The webinar was attended by a diverse group of stakeholders representing hospitals, academia, the pharmaceutical industry, government agencies, and patient advocates. These representatives convened for an update on the progress of the program and to discuss aspects of the hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP) pilot study work stream, particularly the choice of primary efficacy endpoint to progress their recommendations.

A summary of the webinar is provided below. Brief recaps of the presentations and a synopsis of the general discussion that followed are provided. The agenda, presentations, and participant list are available.

Welcoming remarks

Participants were welcomed by *Pamela Tenaerts, MD, MBA, Executive Director of CTTI,* and thanked for their time and efforts. After discussing the 1-year timetable for developing the HABP/VABP pilot study, she stressed that the goal is to streamline ABDD trials by simplifying the protocol, using state-of-the art thinking to move forward, determining endpoints for the pilot study, setting up a network of potential study sites, and creating a patient-focus group. These efforts will be detailed in her presentation of the work streams currently in place at CTTI.

Rachel Sherman, MD, MPH, Co-Chair of CTTI; Associate Director of Medical Policy, Center for Drug Evaluation and Research (CDER); and Director of the Office of Medical Policy, CDER, US Food and Drug Administration (FDA), echoed Dr. Tenaert's introductory remarks and stressed that the goal was to coordinate and further advance efforts on the work streams.

CTTI Antibacterial Drug Development Program Update. *Pamela Tenaerts, MD, MBA, Executive Director of CTTI*

Pamela Tenaerts reviewed the CTTI's four current work streams—HABP/VABP Pilot Study, Infectious Disease (ID) Site Networks, HABP/VABP Patient Focus Group, and Data Collection Simplification—and their objectives, deliverables, and anticipated impact.

For the HABP/VABP Pilot Study, this current webinar meeting is a follow-up to a face-to-face meeting held in April 2013 where quality-by-design principles were used to identify barriers and seek solutions for successful conduct of HABP/VABP studies.

The ID Site Networks work stream has the goal of building a network of potential study sites worldwide. The project team, led by Vance Fowler and Heather Cross, has approached nearly 100 sites (U.S., Canada, Spain, Thailand, Croatia, Peru, Argentina, Australia, Greece, Brazil, Colombia); 47 sites have responded. Interesting data are being gathered on HABP/VABP frequency, organisms, and standard of care.

The HABP/VABP Patient Focus Group seeks to assess patients' risk tolerance and willingness to be treated with drugs approved through nontraditional trials and to participate in those trials. The project team has developed a project plan as a result of discussions with stakeholders, and the institutional review board process is underway.

The objective of the final work stream is to simplify data collection in HABP/VABP trials by looking closely at case report forms (CRFs) and eliminating the gathering of nonessential data.

Dr. Tenaerts also pointed out that the data contained within the ClinicalTrials.gov database form one of the largest clinical trials registries, and CTTI has transformed this into a searchable relational dataset. The 2010 database is being explored for trends in trials for lower respiratory tract infection.

FNIH Update for CTTI. *George Talbot, MD, Co-Chair, HABP/VABP Working Group, and Acute Bacterial Skin and Skin Structure Infection/Community Acquired Bacterial Pneumonia (ABSSSI/CABP) Project Team, Biomarkers Consortium, Foundation for the National Institutes of Health (FNIH)*

George Talbot discussed the efforts of the HABP/VABP Working Group, which was formed in response to an FDA request to provide recommendations for clinically relevant and scientifically rigorous HABP/VABP drug studies focusing on a non-inferiority design and emphasizing feasibility while retaining reliability, validity, and meaningfulness for patients, caregivers, and clinicians.

The group's processes include evaluating the medical literature, discussing feasibility constraints, and examining data from multiple (six or more) modern-day clinical trials donated in kind to determine the possibility of identifying non-mortality endpoints for use as the primary endpoint or as part of a composite primary endpoint ("mortality-plus"). Dr. Talbot also presented the group's interim considerations that have been submitted to the FDA docket—chief of which is that the group participants feel comfortable with all-cause mortality (ACM) as an endpoint, especially for VABP, if trial feasibility could be addressed by changing parameters of study design. Timing of ACM assessment is a key question. Other questions that have arisen include whether HABP and VABP should be considered as different diseases or combined, whether less restrictive exclusion criteria would facilitate enrollment and improve generalizability, and whether changes to trial design such as using intention-to-treat (ITT) analysis and measuring oxygenation as an endpoint would be useful and improve feasibility. Symptom improvement might be a good endpoint for HABP trials that could help with feasibility and relevance to patients.

After the working group finishes a preliminary exploration of data from a subset of the HABP/VABP trials, it will comprehensively analyze data from all the trials. The group will make evidence-based recommendations that should be complementary to CTTI efforts.

Remarks from the Office of Antimicrobial Products. *Edward Cox, Director, Office of Antimicrobial Products, FDA/CDER*

Ed Cox made some general comments, first reiterating that the shared goal of the various ongoing workshops and advisory committee meetings is trial design that is feasible and scientifically sound so that antibacterial drugs can be developed. He discussed new ideas in HABP/VABP clinical trials.

He emphasized the value of stepping back and thinking about ways to improve efficiency and quality of HABP/VABP clinical trials and noted a few potential options including making better use of the data being collected and improving the consent process. While there have been a number of advances over the last few years, and as a result, trial designs are much more feasible, there are still opportunities to further improve quality and feasibility. He prefaced the presentation to follow from Daniel Rubin by adding that analyzing data from previously conducted trials to test new ideas provides a reality check for alternatives and allows us to see what these trade-offs entail.

HABP/VABP Patient Outcomes From Previously Conducted Trials. *Daniel Rubin, PhD, Mathematical Statistician, Office of Biostatistics, FDA/CDER*

Daniel Rubin presented results of a retrospective data analysis conducted by the FDA on HABP/VABP trials. He discussed progress in HABP/VABP trial designs, the desired properties of the primary endpoint,

and the rationale and methods of his analysis. By looking at symptoms in non-ventilated HABP subjects and signs and symptoms in subjects with VABP and ventilated HABP, and comparing results with community-acquired bacterial pneumonia (CABP) datasets, his analysis showed that:

- An endpoint based on early symptoms may not be exchangeable between CABP and non-ventilated HABP.
- A composite endpoint of mortality and major nonfatal events could be considered but would need further refinement.
- Endpoint selection can have a counterintuitive impact on sample sizes in a non-inferiority trial using the risk difference scale, because moving away from the ACM endpoint in many cases increases the required sample size.

Moderated Discussion. *Moderator: Robert Califf, MD, Co-Chair of CTTI and Vice Chancellor of Clinical and Translational Research, Duke University Medical Center*

The following questions were presented as a guide for discussion:

1. For developing a protocol for the pilot study, should all-cause mortality be used to develop a study design due to the current uncertainty surrounding clinical response endpoints?
2. What method(s) will be used to establish historical evidence of sensitivity to drug effect (HESDE) from modern clinical trial data?
3. Should recommendations also include any exploratory data collection on biomarkers with the purpose of collecting data that may aid in future development?

The moderated discussion included the following:

- On the FNIH's approach to examination of datasets: Given the *pro bono* nature of the effort in terms of contribution and time, it was decided to explore data from one or more of the available trials first to get a feel for the prevalence of, for example, baseline symptoms and mortality. A statistical analysis plan is being created to guide the approach to this phase of the project, as well as the subsequent phase in which all available trials will be analyzed. The FNIH Working Group includes many statisticians with expertise in antibacterial clinical trial design and analysis. This approach avoids rework/excess work and allows for better understanding upfront and then proceeding in an informed fashion. The goal is to settle on hypotheses that have robust datasets for analysis.
- Regarding the ACM endpoint, the FNIH will examine timing of its assessment; perhaps it would be better to look earlier than Day 28? The mortality rate would drop, but data collection and analysis would be reduced. Also, it was noted that the mortality-plus events cited in Daniel Rubin's presentation are based on how patients feel and function; ignoring patients with empyema, re-intubation, etc., might not give a full picture of the impact of these diseases; oxygenation is a great measure of function and, while sensitive to treatment effect, should not be ruled out.
- Considerable discussion took place regarding the idea of a mortality-plus endpoint that would include such events as acute respiratory distress syndrome (ARDS) or acute renal failure requiring dialysis. It was noted that rare infectious complications can be present at the time of enrollment and do not necessarily reflect response to antibiotic treatment but complicate treatment if not recognized. Perhaps organ failure (such as acute renal failure) would be a better component than infectious complications. Both antibiotic effect and antibiotic toxicity would need to be looked at. The "plus" components of such a composite would need to be refined, and care must be taken moving forward with composite endpoints to avoid weakening by addition of components and decreasing interpretability. Oxygenation as a surrogate endpoint in non-

ventilated patients generally correlates with clinical outcomes, but caution was advised in ventilated patients as oxygenation can be manipulated in this case. Need to exclude conditions present at baseline.

- Fundamental principles should guide endpoint selection: the endpoint should have a direct measure of "functions, feels, survives" and be well-defined and reliable; also, there should be simplicity in measurement to avoid missing data. For a non-inferiority analysis perspective, an active comparator must have a major, well-defined benefit on the specific endpoint being used. ACM as an endpoint has great strength in all these areas and is a workable approach, but can it be improved? A range of 15%-20% for mortality would be the optimal approach to make studies as feasible as possible.
- Endpoints should be validated by looking at the relation between drug exposure and response, and at pharmacokinetic profiles; the FDA is exploring such analyses. The fundamental issue with clinical response is whether the components are reliable, quantifiable, and well-defined.
- The mortality margin was discussed; instead of a 10% mortality margin, perhaps a 15%-20% margin should be considered. Sample size could then be reduced.
- From a patient perspective, it is important to check whether the patient feels improvement; can a patient-reported outcome (PRO) be incorporated in a meaningful way? The FNIH is considering whether making inclusion/exclusion criteria less restrictive would facilitate enrollment and improve generalizability, and CTTI might consider this for the draft protocol. A PRO is important to FNIH and being developed for CABP. Perhaps a general pneumonia PRO could be developed and included.
- The ACM endpoint appears feasible and straightforward, but alternative endpoints should still be explored. Clinical trials will be conducted in the United States and overseas, and the work that CTTI is doing should take a global development focus into account and look at additional endpoints to increase relevance for sponsors and non-US regulatory authorities. In the interest of time, the FNIH feels ACM is the appropriate primary endpoint for the CTTI "interim study design," and the mortality-plus endpoint would be premature as the primary endpoint for the pilot study.
- The use of an odds ratio scale was also raised, based on the fact that historical data did not support a large antibacterial treatment effect on mortality on the absolute scale for younger, non-bacteremic subjects with lower underlying risk of death. However, a large antibacterial treatment effect on mortality on the absolute scale could be supported for subjects with greater severity of illness. One option for conducting a non-inferiority trial using the risk difference could be to handle this issue through inclusion criteria rather than the scale of the primary efficacy analysis, and enroll subjects considered to be at high risk of death in the absence of effective antibacterial therapy. If the mortality rate in the control arm is markedly different from past experiences, this could be considered as a "review issue."
- Concern was raised that the overall event rate would be lower than expected; the FDA acknowledged that a blinded pooled interim analysis to enable knowing whether the expected event rate is being approximated could be considered.
- There was discussion that mortality is a confounded endpoint for HABP/VABP trials in the setting of active antibiotic therapy. The concern is that mortality is in large part driven by underlying diseases, since most of the attributable mortality due to infection is prevented in these trials. It was pointed out that the key for a non-inferiority trial is to be sure that the comparator is more effective than placebo, and a previous FDA analysis demonstrates that a lower bound estimate of 30% reduction in mortality with effective antibiotics is acceptable. Therefore, the confounding does not invalidate the endpoint. Further, the mortality endpoint combined with a -10% NI margin ensures that non-inferior therapy will be superior in efficacy to placebo. With this reasoning, the participants felt that in general the mortality endpoint is valid. However, it was also

pointed out that the confounding does decrease the assay sensitivity of the endpoint to distinguish subtler differences in efficacy between two drugs.

- The second question on the agenda (re. historical evidence of sensitivity to drug effect [HESDE]) was discussed in the context of clinical response: a question was posed on validating clinical response endpoints using modern trial data, and to show a definable treatment effect size, compared to ineffective or no therapy for a specific clinical response endpoint. Clinical response is a subjective endpoint and can be very different from clinician to clinician. Symptoms that clinicians should look for should be specified and clearly defined in order to know what is being measured and to decrease variability in the measurement. The key is to not discard what has been done in previous trials, but just try to define it better, and to be careful when comparing patient groups that are not like each other; in this way, the clinical response endpoint could be made more objective.
- Can HESDE really be gained from a sponsor-conducted randomized controlled trial? Look at effective vs. ineffective therapy for a clinical response endpoint to justify HESDE. It was pointed out that a clinical response endpoint includes mortality as an important component, especially in HABP; the FNIH is trying to make marginal clinical events more quantifiable and easier to monitor.
- Recommendations from the CTTI working group regarding the design of the HABP/VABP pilot study could possibly include using ACM as the primary efficacy endpoint and having a secondary mortality-plus endpoint with "plus" items such as ARDS or respiratory insufficiency, or going with a hierarchy in which sponsors could start with mortality and have the option of then proposing a clinical response endpoint; the details of the design would depend on the specific drug/program and could be determined during discussion with the FDA.
- The FDA reiterated that sponsors are free to come to the FDA during the process and propose something different from FNIH and/or CTTI recommendations; also, these work group discussions and conclusions do not constrain a sponsor.
- Eligibility criteria for the pilot study could be made more inclusive, and the ITT population could be used as the analysis population. Trial personnel should not be overburdened with data collection that may not be informative. Irrespective of the endpoint chosen, the aim is to gain a broader sense about a drug's efficacy and biological activity. Enlightening sponsors regarding how to balance fulfilling study objectives while streamlining data collection in the protocol is a project goal.

In closing, participants affirmed that tremendous progress had been made. The streams of work could be a guide for designing trials. CTTI has the feedback it needs to design the HABP/VABP protocol, and it was suggested that the best way to cut costs would be to stop collecting unessential data, and the protocol should reflect this, using quality-by-design principles. With the hope expressed for continued progress, the meeting was adjourned.