

Biomarkers Consortium Project Aims To Develop Well-Defined Endpoints in Antibacterial Clinical Trials for Bacterial Pneumonia and Skin Infections

Project: *Developing Endpoints for Clinical Trials of Drugs for Treatment of Acute Bacterial Skin and Skin Structure Infections and Community-Acquired Bacterial Pneumonia*

Community-Acquired Bacterial Pneumonia (CABP) is a leading cause of morbidity and mortality. It is estimated that approximately one million episodes of CABP occur annually in adults 65 years of age and older in the United States. Overall mortality remains relatively high, ranging from 5.1% for patients hospitalized or treated in an ambulatory setting to 36.5% for patients treated in an intensive care unit (Fine et al., JAMA, 1996).

Acute Bacterial Skin and Skin Structure Infections (ABSSSI) are common infections that are most often caused by *Staphylococcus aureus*, among other types of bacteria. The recent epidemiological shift to a greater proportion of ABSSSI caused by methicillin-resistant *S. aureus* (MRSA) acquired in the community, approximately 59% in one recent survey (Moran, et al NEJM, 2006), has been a recent cause for concern due to the limited number of orally available antibacterial drugs for treatment of MRSA.

Project Goals: The goal of this project is to develop reliable, well-defined and clinically relevant endpoints for use in clinical trials of antibacterial drugs for CABP and ABSSSI. These endpoints should measure tangible benefits for patients in terms of how they feel, function, and survive. The genesis of the project, which was proposed to the FNIH by the FDA, lies in FDA's conclusion that there are significant limitations in the available information to quantitatively assess the effect of antibacterial drug treatments vs. no treatment or placebo and in comparisons between active agents. These perceived deficiencies and the attendant regulatory uncertainty thereby generated are an impediment to the field of antibacterial drug development for these indications and limit sponsors' ability to perform clinical trials in these areas. The lack of FDA-qualified outcome measures may also impede patient care since clinicians and patients cannot understand the similarities and differences between therapeutic agents when they are not measured in a well-defined, reproducible and clinically relevant manner.

Project Background: A Project Team was constituted in May 2010; a broad array of stakeholders are participating, including FDA, NIAID, IDSA, and industry sponsors. The Project Team has already made significant progress towards the goals of the projects, the results of which will be made public for use by all sponsors as well as others performing clinical trials in these indications.

The Project Team first performed retrospective analyses of datasets from recent clinical studies in ABSSSI and CABP to a) refine/confirm recent FDA-proposed early response outcome measures by determining their performance in a modern clinical trial setting; b) help identify additional endpoints or biomarkers that might be relevant. The Project Team identified several sources of data from existing modern industry clinical trials that have been contributed in-kind to the project. A statistical analysis plan for each data set was prepared, and a variety of primary and sensitivity analyses conducted per the plan. The data generated have clarified the operating characteristics of FDA's proposed endpoints, specifically with regard to the point estimate of the success rate and the impact thereon of changes in assumptions about components of the endpoint and thresholds for defining "success". These data have already facilitated contemporary ABSSSI trial design by allowing for better estimation of clinical trial sample size requirements.

The output of the first phase of the project, as defined above, will result in endpoints for ABSSSI and CABP that FDA will accept in the *interim*, pending completion of the second part of the project. The second part of the project will focus on the development of new drug development tools (DDT) that could be used in future

ABSSSI and CABP trials, both for regulatory submission and for non-regulatory purposes. Any DDT emerging as a result of the FNIH process will be made available publicly and will be submitted to the FDA for qualification.

Public Health Impact: This project will have a significant positive impact on public health by generating the data needed to advance, among the scientific community, clinicians and regulators, the definition of clinical trial endpoints for determining the efficacy of antibacterial treatment of CABP and ABSSSI. The project is designed to modernize our understanding of, and standardize our approach to, these endpoints and their use in clinical trials. Greater clarity in the regulatory requirements for clinical trial conduct and analysis will remove an overhanging uncertainty that, if unresolved, will negatively impact industry investment in this area. Finally, new, validated endpoints could also have potential value for application in the clinical setting at point of care.

Next Steps: The Project Team will submit its recommendations regarding “interim” primary endpoints to FDA to inform their draft guidance for clinical trial endpoints in both areas. The “interim” primary endpoint recommendations will assist in clinical development programs being conducted now, while additional research on new efficacy endpoints conducted as part of this project will support the field and FDA’s evaluation of these endpoints in the future.

Call to Action: Contact Judy Siuciak, Scientific Program Manager, Biomarkers Consortium (jsiuciak@fnih.org) or Paris L. A. Moore, Partnership Development Officer, Biomarkers Consortium, for more information about this project.

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About the Biomarkers Consortium

The Biomarkers Consortium is a public-private biomedical research partnership managed by the Foundation for the National Institutes of Health (FNIH) that endeavors to develop, validate, and/or qualify biological markers (biomarkers) to speed the development of medicines and therapies for detection, prevention, diagnosis and treatment of disease and improve patient care. For additional information about the Biomarkers Consortium, please visit www.biomarkersconsortium.org

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