Identifying Non-mortality Clinical Endpoints FNIH Approach to CABP and ABSSSI

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Discussion Points

* FNIH Project Overview
* Project Team
* Strategy
* Initial Findings
* Major Take-aways
* Work in Progress
* Conclusions and Next Steps
* Acknowledgements

CABP ABSSSI Project Background

- ★ The goal of this project is to develop reliable and well-defined endpoints for clinical trials of antibacterial drugs for
  - Acute Bacterial Skin and Skin Structure Infections (ABSSSI)
  - Community-Acquired Bacterial Pneumonia (CABP)
- ★ Reliable endpoints for non-inferiority clinical trials in CABP (other than mortality) or ABSSSI have not been established by FDA to be used as a regulatory efficacy endpoint for new antibacterial drugs
- ★ There are significant limitations of the available information to assess quantitatively the effect of antibacterial drug treatment over no treatment or placebo (a requirement for non-inferiority trials) and to identify appropriate endpoints for ABSSSI & CABP
  - Reliance on historical data collected 60 or more years ago

Project Team

- Joseph Toerner, MD, MPH (Co-chair; FDA)*
- George H. Talbot, MD (Co-chair; IDSA)
- Paul G. Ambrose, Pharm D (ICPD)
- Helen Boucher, MD (Tufts University)
- John Bradley, MD (UCSD)
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- Aaron Dane, PhD (AstraZeneca);
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- Mike Dunne, MD (Durata Therapeutics)
- Barry Eisenstein, MD (Cubist)
- Thomas Fleming, PhD (University of Washington)
- Dean Follmann, PhD (NIH/NIAID)
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- Nickolas Kartsonis, MD (Merck)
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- Lily Llorens, PhD (Cerexa)
- Robert Meyer (Merck)
- Sumati Nambiar, MD (FDA-observer)
- Rodger Novak (Nabriva)
- David Oldach (Cempra)
- Elektra Papadopoulos, MD (FDA)*
- John Powers, MD (SAIC in support of NIH/NIAID)
- Philippe Prokocimer, MD (Trius)
- John Rex, MD (AstraZeneca)
- Denise Russo (NIH/NINR)
- Judith A. Siuciak, Ph.D. (FNIH)
- William Stubbings, PhD (Basilea)
- David Wholley (FNIH)

Pediatric Project Team

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* David Friedland, MD (Cerexa)
* Elektra Papadopoulos (FDA)
* Philippe Prokocimer (Trius)
* John Powers (SAIC)
* George H. Talbot, MD (Talbot Advisors)
* William Stubbings (Basilea)

Strategy

- **Phase 1: Retrospective analyses of data from modern-day industry clinical trials to identify relevant outcome measures and other endpoints**
  - **ABSSSI – Pfizer, Durata, Cerexa trials**
  - **CABP – Pfizer, Cerexa, Cubist trials**
- **Phase 2: Qualitative research phase of PRO and ClinRO development involving both literature searches and patient interviews to begin developing well-defined and reliable outcome measures for clinical trials**
  - **RFP for qualitative research phase in ABSSSI published Jan, 2012.**
  - **ABSSSI Outcome Measure studies kickoff meeting - July 27th, 2012**
- **interim summary recommendations for CABP and ABSSSI submitted to the FDA docket for FDA consideration re: final guidances, Aug, 2011**
- **Team met with FDA to discuss recommendations, May, 2012**

Datasets Contributed

ABSSSI

* **Pfizer: a Phase IV hospital-based, randomized clinical trial in ~1200 patients comparing linezolid to vancomycin (~600 patients in each arm) (Weigelt et al., 2005)**
* **Durata Therapeutics: a randomized, double-blind trial in ~900 patients comparing dalbavancin to linezolid therapy. (Jauregui et al., 2005)**
* **Cerexa, Inc.: two, randomized, double-blind, registrational Phase 3 trials of ceftaroline fosamil vs. vancomycin plus aztreonam from 797 patients**

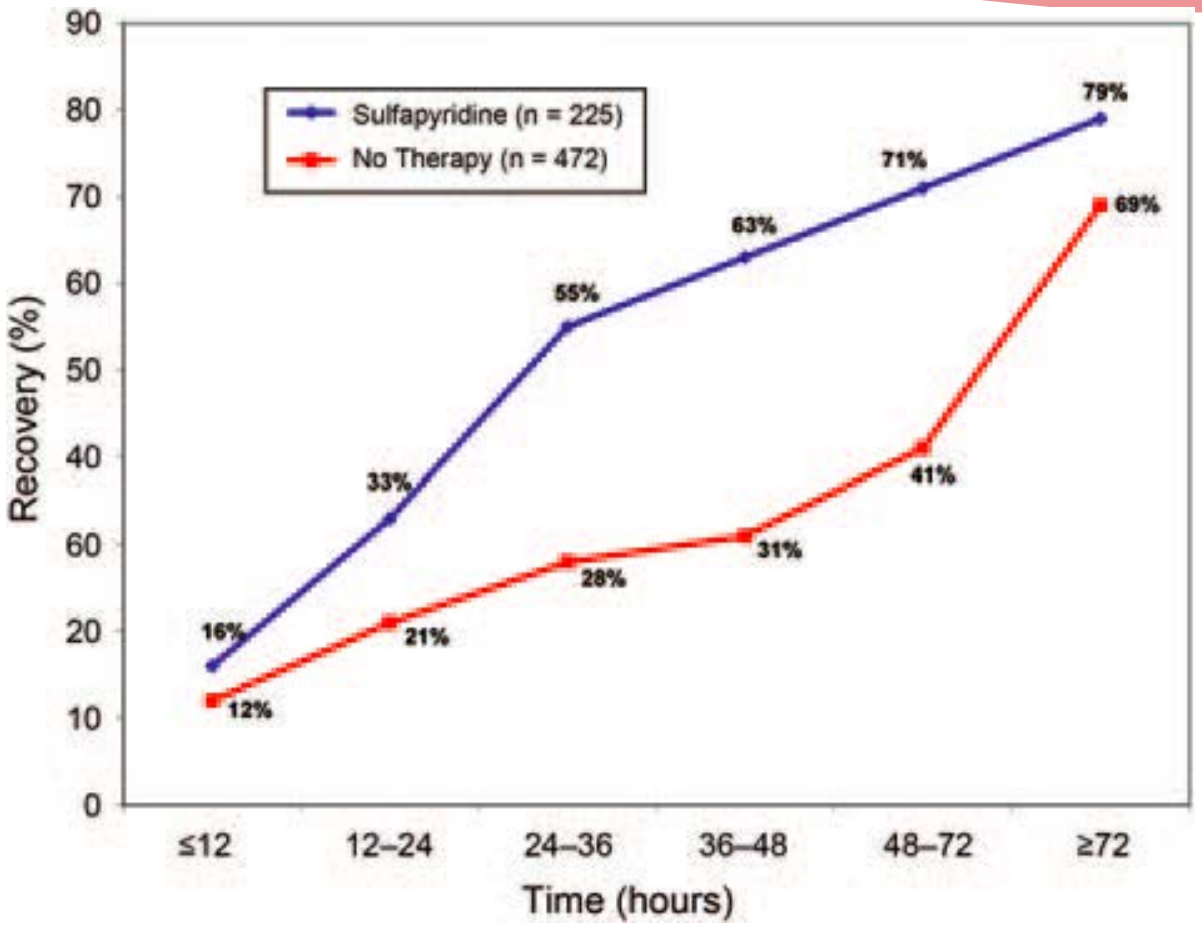
CABP

* **Pfizer: two pivotal randomized Phase III trials of tigecycline vs. levofloxacin in 437 adult hospital patients**
* **Cubist Pharmaceuticals: Data from the ceftriaxone (standard of care) arm two CABP trials in which daptomycin was found inferior to ceftriaxone. The studies include 421 patients**
* **Cerexa, Inc.: two, randomized, double-blind, registrational Phase 3 trials of ceftaroline fosamil vs. ceftriaxone from 308 patients**

Phase 1: Process & Findings

* **Considering FDA's standards for drug approval, the PT**
  - **Evaluated historical evidence for treatment effects;**
  - **Evaluated outcomes in recent clinical trials;**
  - **Outlined research gaps;**
  - **Proposed interim, bridging endpoints; and**
  - **Began developing future research on outcome assessment in ABSSSI and CABP trials**

* **Collectively, pre-antibiotic and early antibiotic era data indicated a significant treatment effect at ~day 3–4 after initiation of therapy**



Singer M. Treatment effect of antibacterial drugs in community acquired bacterial pneumonia. Paper presented at: Anti-Infective Drugs Advisory Committee Meeting, 9 December 2009. Available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm195619.htm.

Phase 1: Process & Findings

* **These data do have limitations:**
  - **They mostly derive from observational or small studies;**
  - **Cross-study comparisons were used to determine treatment effect; and**
  - **The endpoints were not clearly defined, although they were clinically reasonable.**

* **The PT performed retrospective analyses of datasets from modern clinical studies to**
  - **Refine the FDA-proposed outcome measures by evaluating their operational characteristics, changes over time, and responsiveness to change at specific time points and**
  - **identify additional relevant endpoints or biomarkers.**

Phase 1: CABP Recommendations

* Assessment of symptom improvement at ~72h after randomization provides relevant data on how patients feel and function and provides evidence of a strong treatment effect for antibiotics via its link to assessments of symptom improvement in historical studies.
* Four biologically relevant symptoms (cough, pleuritic chest pain, dyspnea, and sputum production, scored on a 4-point scale of Absent, Mild, Moderate, and Severe) are recommended for adults.
* The interim, bridging endpoint measure comprises:
  - A one-point improvement in at least two symptoms,
  - No worsening of any other symptoms, and
  - Assessment made on study Day 4.

Phase 1: CABP Recommendations

* **Absence of fever should not be a component of the primary outcome measure**
  - **in particular because it is not on the causal pathway of the disease**
  - **Requiring fever as an inclusion criterion would exclude important patient populations (e.g., the elderly)**
  - **Frequent temperature measurements cannot be obtained reliably in many clinical trial settings**
* **However, resolution of fever is important in clinical practice. Thus, resolution of fever and achievement of stability in other physiological parameters should be included as sensitivity analyses and/or as part of late assessment endpoints.**

Phase 1: Major Take-aways

- An early response endpoint can anchor a non-inferiority trial design, and provides an interim, pragmatic solution for CABP and ABSSSI registrational trial design
- We now understand how certain trial design assumptions influence response rates -- and thus sample size -- of new P3 trials using the FDA interim endpoints
- Assessment of early response, while useful to clinicians and regulators, is by itself not sufficient to determine what matters most to patients
- A measure of late response is an essential component of trial design and evaluation

Progress on Developing Endpoints for Registrational Clinical Trials of Community-Acquired Bacterial Pneumonia and Acute Bacterial Skin and Skin Structure Infections: Update From the Biomarkers Consortium of the Foundation for the National Institutes of Health

George H. Talbot,[1] John H. Powers,[2] Thomas R. Fleming,[4] Judith A. Siuciak,[3] John Bradley,[5,6] Helen Boucher,[7,8] on behalf of the CABP-ABSSSI Project Team

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A Collaborative Model for Endpoint Development for Acute Bacterial Skin and Skin Structure Infections and Community-Acquired Bacterial Pneumonia

Joseph G. Toerner,[1] Laurie Burke,[1] Scott Komo,[2] and Elektra Papadopoulos[1]

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"The FNIH PT brought together a wide range of experts in infectious diseases, statistical sciences, and clinical trials research from the academic research community, biopharmaceutical companies, and government. A unique perspective of the FNIH PT was the retrospective evaluation of outcome measures in data from various clinical trials of biopharmaceutical sponsors…."

"….Clinical development programs incorporating these outcome measures right now should be reassured that we will accept efficacy endpoints based on improvement in symptoms for CABP and control of lesion spread for ABSSSI, even as further work is being done by the FNIH PT on their next phase of the project……"

Clinical Infectious Diseases 2012;55(8):1122–3

Content Validity Phase
PRO & ClinRO for Clinical Trials

- **Primary Goal: Complete the content validity phase of development for a PRO and a ClinRO for clinical trials of ABSSSI and CABP**
- **Develop PRO & ClinRO in accordance with FDA PRO Guidance**
  - **Literature Review**
  - **Expert Interviews**
  - **Patient Feedback**
- **Follow the FDA qualification process per Qualification DDT Draft Guidance (2010)**

Conclusions and Next Steps

- An early response endpoint can anchor a non-inferiority trial design, and provides an *interim*, *pragmatic* solution for CABP and ABSSSI registrational trial design
- FDA will accept these interim endpoints, which for ABSSSI are being used by multiple companies in P2/P3 trials
- Development of new endpoints a priority
- FDA has asked FNIH to evaluate non-mortality HABP endpoints
  - What endpoint(s) could be used (interim or final)?
  - What are their operating characteristics, based on analysis of existing datasets

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* Equity in Calixa, Cempra, Cerexa, Durata, Mpex, & Nabriva.
* Travel expenses for this meeting provided by IDSA

Back-up Slides

Content Validity Phase

PRO & ClinRO for Clinical Trials: ABSSSI

1. **Literature Review and Gap Analysis***
   - Targeted lit review on signs/ symptoms of ABSSSI
     - Inform development of interview guides- patient and clinician
     - Evidence for draft conceptual framework (if necessary for scoping document)
   - Targeted lit review of existing PROs and ClinROs
     - Description of each measure identified
     - Gap analysis based on qualitative and quantitative requirements in FDA PRO Guidance
   - Deliverables:
     - Strategy Document- search terms, databases, and article inclusion/ exclusion
     - Literature review and gap analysis tabulation and bibliography

Content Validity Phase

PRO & ClinRO for Clinical Trials: ABSSSI

2. **Concept Elicitation and Item Generation**
   - **Clinical Expert Interviews (FNIH to identify about half of the participants)**
     - Up to 10 ABSSSI clinical experts in the US
     - Up to 5 additional experts outside of the US
   - **Develop Patient Interview Materials**
     - Screener, interview guide, medical history form, demographics form
   - **Develop Study Protocol and Submit IRB Application**
     - Protocol, informed consent form, central IRB submission
   - **Site Recruitment, Contracting and Management**
     - 3 specialist research sites in the US
   - **Patient Recruitment**
     - 24 English speaking, 12 Spanish speaking ABSSSI patients in the US
       - Wound infection patients (8 US English, 4 US Spanish)
       - Cellulitis and erysipelas (8 US English, 4 US Spanish)
       - Abscess patients (8 US English, 4 US Spanish)

2. Concept Elicitation and Item Generation (cont)

* Individual Patient Interviews
  - Explore ABSSSI symptoms and experiences
  - Elicit symptom-focused concepts of importance
  - Continue interviews until saturation is reached (assessed after ~10 interviews)
* Qualitative Analysis
  - Thematic analysis
  - Inductive inference- identify topics emerging directly from the data
  - Abductive inference- apply prior knowledge to identify themes (lit review, clinician interviews)
* Develop Draft Items
* Translatability Assessment of Draft Items
* Finalization of Draft PRO and ClinRO Measures- ready for evaluation phase

3. Evaluation of Draft PRO and ClinRO Measures

* Expert Panel Review
  - Up to 8 clinical experts identified by FNIH BC will review PRO and ClinRO
  - Following inclusion of expert feedback, ClinRO-final and ready for quantitative testing
  - PRO updated based on expert feedback in preparation for cognitive debrief

* Cognitive Debrief Interviews
  - Development of interview guide
  - Protocol amendment and IRB submission
  - Telephone interviews with 15 patients (completed in batches to assess necessary changes to the PRO)
  - Qualitative analysis, item tracking matrix, draft PRO suitable for quantitative testing

Content Validity Phase

PRO & ClinRO for Clinical Trials: ABSSSI

4. **Tasks associated with the FDA qualification process**
   - **Letter of Intent to the FDA (following literature review stage of the project)**
     - **Summary of PRO and ClinRO measures**
       - **Proposed context of use**
       - **Overview of available data**
       - **Summary of studies planned to generate data to support qualification**
   - **Meeting with FDA and Scoping Stage Summary Document (SSSD)**
     - **Plans for qualitative work**
     - **Hypothesized conceptual framework based on lit review results**
     - **Hypothetical endpoint model (as requested in DDT guidance)**
   - **Update FDA SSSD (following completion of draft measures)**
   - **FNIH BC and FDA Meeting**