Developing Drugs for Community-Acquired Bacterial Pneumonia (CABP)

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Anti-Infective Drugs Advisory Committee

November 3, 2011

Developing Clinical Trial Designs for CABP

- Challenges inherent to the disease process
  - Biology of infection
  - Acute disease where therapy needs to be started promptly
  - Effects of prior therapy
  - Diagnostic uncertainty
  - Limitations of the available scientific information
- Progress has been made to date
  - IDSA/FDA co-sponsored workshop on CABP clinical trial design
  - FDA Advisory Committee meetings
  - Draft CABP Guidance document
  - Comments to the docket on the draft CABP guidance document
  - Foundation for the National Institutes of Health

Therapies for CABP

- Continued need for new antibacterial drug therapies for treatment of patients with CABP
  - Antimicrobial resistance
  - Patient tolerance e.g., allergy
  - Drug interactions
  - Adverse event profiles – better tolerated options
- Prudent use of new and existing antibacterial drugs essential to preserve utility

CABP Clinical Trials

- CABP trial designs that are
  - Scientifically sound
  - Ethical
  - Feasible
- Evidenced-based designs for CABP clinical trials
  - Non-inferiority trials
  - Limitations of the available information
- Comments to the docket and other fora regarding draft CABP guidance & CABP clinical trial designs
  - Feasibility and Practicality one of the issues frequently brought up

CABP Clinical Trials - 2

- Feasibility and practicality
- Inherent trade-offs in precision of estimates of efficacy and safety for a drug and practicality/feasibility of clinical trials
- Get to feasible, practical trials while maintaining scientifically sound, ethical, clinical trial designs for assessing the safety and efficacy of antibacterial drugs for CABP

Clinical Trials

- Scientifically sound, feasible, and ethical designs
- Options on later stage clinical development programs for drugs being developed to treat patients with CABP
- Seek your advice on these issues for future trials of antibacterial drugs for CABP
- Issues for further discussion at today's Advisory Committee meeting
  - Endpoints -Non-inferiority margins
  - Prior antibacterial therapy -Enriching for the micro-ITT pop
  - CABP development program

Question 1

DISCUSSION: Please discuss the merits and limitations of an endpoint based upon improvement in at least 2 of the 4 symptoms of cough, amount of sputum production, chest pain, and difficulty breathing (and no worsening or new symptoms) at day 3 to day 5 as the primary endpoint for Community-Acquired Bacterial Pneumonia (CABP) trials. In your discussion, please comment on a noninferiority margin of 10% for each of the intent-to-treat (ITT) analyses and possibly a 10%, 12.5% or 15% noninferiority margin for the pooled microbiological intent-to-treat (micro-ITT), based on historical data showing a treatment effect on clinical responses noted at day 3 to day 5 of therapy.

Question 2

DISCUSSION: Please discuss the merits and limitations of each of the proposed development pathways and trial designs. In your discussion, please comment on the use of improvement or stabilization of clinical signs of pneumonia as a co-primary endpoint versus its use as a secondary endpoint.

Question 3

DISCUSSION: Please discuss:

a. issues with receipt of prior antibacterial therapy
b. methods to enrich the micro-ITT population
c. mechanisms to overcome barriers to trial conduct
d. any advice on performing clinical trials of oral antibacterial drugs (i.e., when an intravenous formulation is not available).

Thank you

Community-Acquired Bacterial Pneumonia: Regulatory Background

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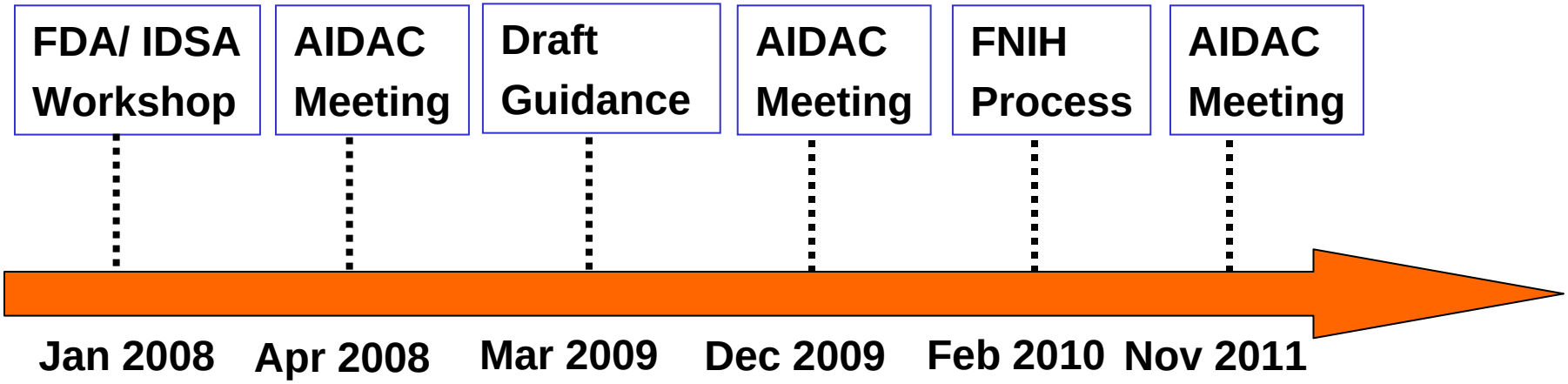
Anti-Infective Drug Advisory Committee Meeting
November 3, 2011

Outline

- Summary of meetings on community-acquired pneumonia (CAP) in 2008
  - FDA/IDSA Workshop, January 2008
  - Anti-Infective Drug Advisory Committee meeting, April 2008
- Summary of March 20, 2009 Draft Community Acquired Bacterial Pneumonia (CABP) Guidance and comments submitted to docket
- Summary of December 9, 2009 Anti-Infective Drug Advisory Committee meeting
- Summary of comments to the docket since June 2009

Timelines


FDA/ IDSA Workshop
AIDAC Meeting
Draft Guidance
AIDAC Meeting
FNIH Process
AIDAC Meeting
Jan 2008
Apr 2008
Mar 2009
Dec 2009
Feb 2010
Nov 2011

Summary of FDA/IDSA Workshop

- Held January 17-18th, 2008
- Trial design and statistical considerations in clinical trials of CAP including discussion of noninferiority trials
- Treatment effect of antibacterials in CAP
- Implications of emerging scientific tools that assist in the diagnosis of the etiology of CAP

Summary of FDA/IDSA Workshop

- Disease Severity
  - Scoring systems (PORT; CURB-65)
- Efficacy Endpoints
  - Mortality for severe pneumonia
    - Objective and most relevant to historical data
    - Low mortality at present time
  - Clinical Response Endpoint
    - Relationship to historical data?
  - PRO for mild pneumonia
- Proceedings published in Clin Infect Dis 2008 (Dec.); vol. 47: Suppl 3

Summary of April 2008 AIDAC Meeting

- Unanimous support for active-control trials
  - Placebo-controlled trials considered unethical even in patients with mild pneumonia
- Support for noninferiority trials
  - No consensus on the primary endpoint when considering the M1, M2, and noninferiority margin
  - Some committee members noted that historical data on treatment effect for mortality could support an clinical response endpoint
  - Other committee members noted that historical data could only support an efficacy endpoint for mortality

Summary of April 2008 AIDAC Meeting

- Agreement that confirmation of bacterial etiology provided a stronger link to the historical data
- Some committee members expressed concerns with use of antibacterials prior to enrollment as it could confound the efficacy findings in a NI trial
- Discussion regarding enrollment in ER/urgent care facilities
  - empiric antibacterials are administered with a presumptive diagnosis of CABP
  - excluding such patients might compromise an ability to enroll patients in a clinical trial

Draft CABP Guidance

- Draft Guidance titled "Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment " was posted for public comment on March 20, 2009
- Comments submitted to the docket (FDA-2009-D-0136) are available at www.regulations.gov and were also appended to the background document for this meeting

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm123686.pdf

Draft CABP Guidance

- Focus on community acquired bacterial pneumonia (CABP) rather than community acquired pneumonia
  - Primary analysis population is those with confirmed bacterial etiology
- Non-inferiority (NI) trials; clinical response endpoint
  - Mortality included in the definition of clinical failure
  - PORT scores as enrollment criterion
  - NI margin of 15% for IV antibacterials; 10% for oral antibacterials
- Superiority trials
  - Patient reported outcomes
  - Time to resolution of signs and symptoms

Draft Guidance: Key Topics

- Several aspects of the draft guidance and related comments submitted to the docket were discussed at the December 2009 AIDAC meeting
- Topics relevant to this meeting
  - Primary endpoint
  - Primary analysis population
  - Use of prior antibacterials

Draft Guidance: Primary Endpoint

- Assessed 5-10 days after EOT
- Clinical Success
  - Patient alive
  - Resolution of disease-specific signs and symptoms
  - No new symptoms/complications attributable to CABP
- Clinical Failure
  - Death within 30 days of starting study drug
  - Lack of resolution of CABP-specific signs and symptoms
  - Progression or development of new symptoms/radiologic findings attributable to CABP at any time after enrollment
  - Development of complications such as empyema/lung abscess
  - Need for rescue therapy with non-study antibacterials

Draft Guidance: Patient Reported Outcomes

- Used in a superiority trial
- Currently no PRO instrument identified as adequate for regulatory purposes for this indication
- If tool is not developed for assessment of the primary endpoint, it may be appropriate to evaluate its use to assess secondary endpoints

Comments: Clinical Response Endpoint

- Reduction in mortality is the most clinically compelling benefit provided by antibacterials in CABP
- Evidence based non-inferiority margins can only be derived for a mortality endpoint
- No evidence based justification exists for use of clinical response endpoint

Comments: Clinical Response Endpoint

- The primary endpoint is a composite endpoint that includes components that are biomarkers
  - Components such as sputum color, body temperature, WBC, and CXR are not direct measures of how a patient functions, feels, or survives
  - Effects on the composite endpoint have not been shown to reliably predict effects on resolution of symptoms or on reduction of risk of complications
  - Reduction in fever is a biomarker and not a relevant clinical outcome

Draft Guidance: Primary Analysis Population

- Microbiological intent to treat (Micro-ITT):
  - Baseline bacterial pathogen known to cause CABP against which the test drug has activity
  - Blood, adequate sputum specimen
  - Other tests such as urinary antigen test
- Use of rapid diagnostic tests for bacterial pathogens need to be discussed before trial initiation
- Rationale:
  - Historical data primarily limited to patients with pneumococcal/lobar pneumonia
  - Few patients with non-pneumococcal disease, acceptable to include in the Micro-ITT population other bacterial etiologies of CABP such as *H. influenzae. S. aureus, M. catarrhalis*

Comments: Primary Analysis Population

- As pathogens are recovered in approximately 30-40% of cases, sample size for a trial with Micro-ITT as the primary population will be large
  - Acceptability of newer diagnostic methods to enrich the Micro-ITT population
- Recommendation to use per protocol analyses for each trial; pooled Micro-ITT be considered co-primary

Draft Guidance: Prior Antibacterial Therapy

- In a NI trial, prior effective antibacterials should be avoided
- Exceptions:
  - Patients who have received therapy and are considered failures if objective criteria for failure are pre-specified and documented
  - If the prior therapy lacks activity against the baseline pathogen
- No concomitant antibacterials for other infections until after the TOC visit
- Rationale:
  - Phase 3 trials comparing daptomycin to ceftriaxone
  - Prior effective antibacterials had a greater impact on the cure rates in the daptomycin arm compared to the ceftriaxone arm

Pertel PE et al. Clin Infect Dis 2008:1142-51

Comments: Prior Antibacterial Therapy

- Exploratory post hoc analysis from a single trial; finding only applied to antibacterials with greater potency and longer half-life
- Single dose of a short-acting antibacterial should be allowed
  - List needs to be defined and should include penicillins, tetracyclines, and trimethoprim-sulfamethoxazole
- Use of concomitant antibacterials that provide coverage for microorganisms not included in the spectrum of the study drug should be allowed

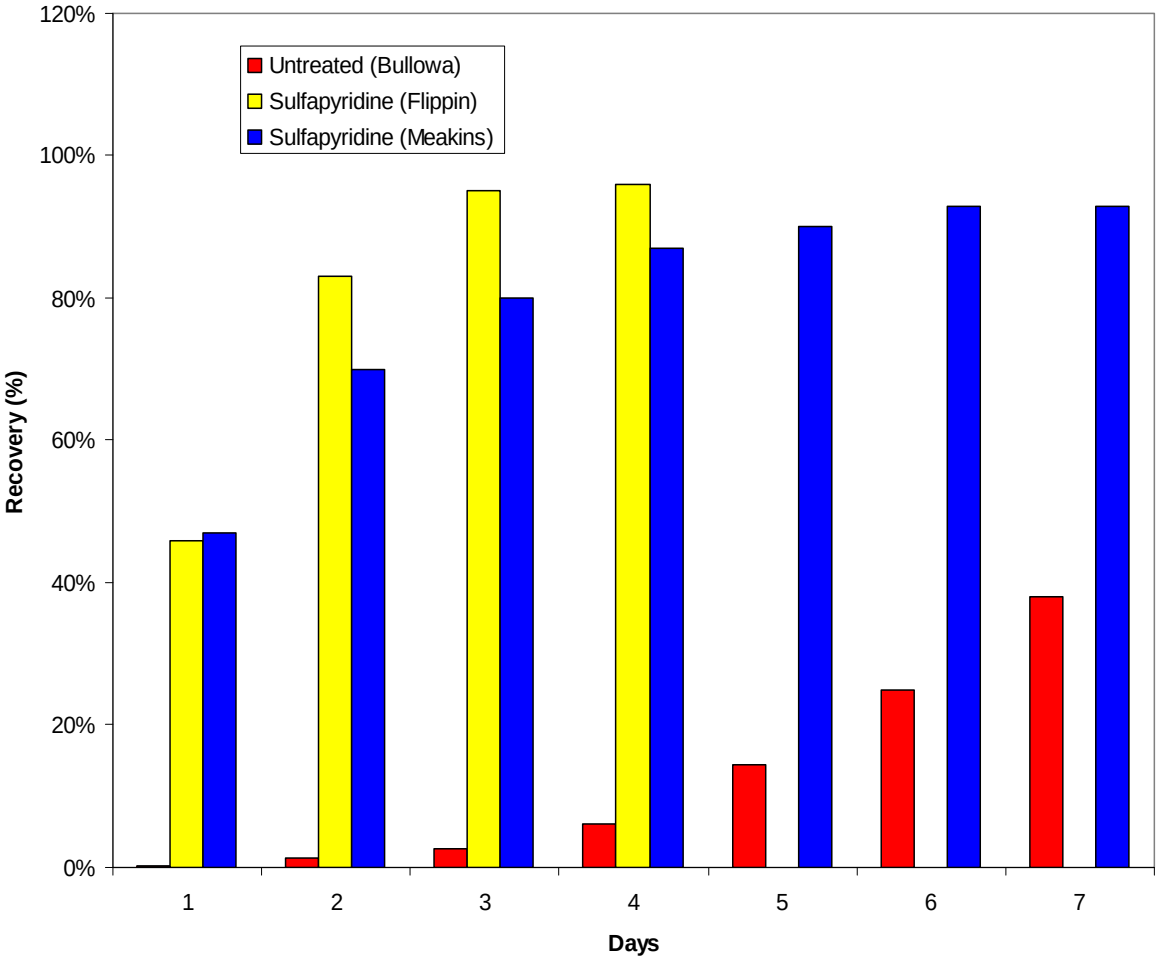
Comments: Prior Antibacterial Therapy

- Patients who received prior effective antibacterials should not be enrolled in a NI trial
  - diminishes the ability of a NI trial to detect a treatment difference between the study drug and active comparator
- Such strict exclusion criteria will make CABP trials difficult, lengthy, or impossible to conduct
- Enrolling patients in the ER setting will increase trial costs and may not be operationally feasible

Summary of December 2009 AIDAC Meeting

- The FDA presented historical data for a large treatment effect for a clinical response endpoint earlier in the course of therapy (days 3-5) for patients with pneumococcal pneumonia (Bullowa 1937, Meakins and Hanson 1939, Flippin, et al.1939)
- Limited data on clinical response in patients with Mycoplasma pneumonia (Smilack et al.1974, Kingston et al.1961)

Antibacterial Treatment Effect on Clinical Recovery of Pneumococcal Pneumonia*



*Adapted from Bullowa (1937); Meakins and Hanson (1939), ; and Flippin, et al. (1939)

Mycoplasma Pneumonia: Outcomes

Kingston, et al., (1961)

Parameter	Treated Mean Duration (days)	Placebo Mean Duration (days)	Treatment Difference (days)
Temperature 100ºF	2.1	8.1	6.0
Fatigue, malaise	2.7	8.5	5.8
Anorexia	2.0	7.0	5.0
Abnormal CXR	9.5	20.0	10.5
Rales	6.9	15.5	8.6
Cough	9.7	22.0	12.3
Bed rest	5.8	9.2	3.4

Summary of December 2009 AIDAC Meeting

- Majority of committee members voted that the historical data presented support the use of a day 3-5 clinical response endpoint (12 Yes, 4 No)
  - Committee members who voted “no” expressed concern regarding lack of information about how the clinical response endpoints were collected

Summary of December 2009 AIDAC Meeting

- All-cause mortality endpoint
  - Committee provided nearly unanimous support (14 Yes, 2 No)
  - Some committee members expressed concerns about the practicability of conducting a trial using all-cause mortality endpoint
- Micro-ITT population as the primary analysis population
  - Most committee members voted yes
  - Concerns were raised that trials may not be feasible to conduct because of large sample sizes

Summary of December 2009 AIDAC Meeting

- Prior antibacterials
  - Most committee members agreed that such patients should be excluded
  - Concerns raised that trials difficult to conduct as patients receive prompt antibacterial therapy for presumed CABP
- Inclusion of atypical pathogens
  - Legionella for trials in “severe” CABP and Mycoplasma and Chlamydia for trials in “mild-to-moderate” CABP
- Use of patient reported outcome measures
  - Inclusion as a primary efficacy measure in superiority trials of mild-moderate outpatient CABP

Additional Docket Comments

- August 2009:
  - Feasibility of a micro-ITT population
  - Atypical pathogens should be included
  - Clarification of endpoints
- January 2010:
  - Use ITT for NI analyses of 2 trials and pool the micro-ITT for an NI analysis
- August 2011: Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium

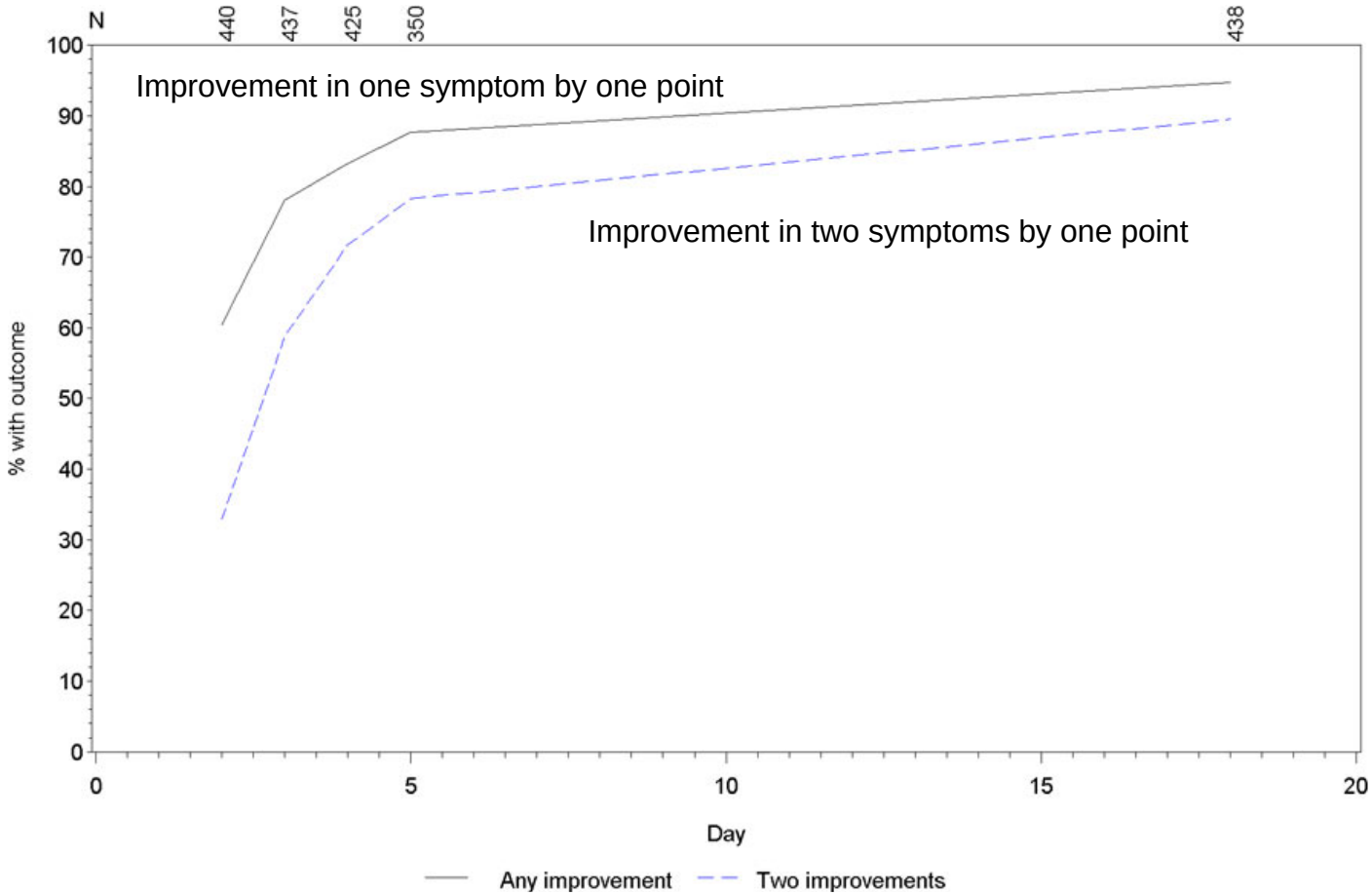
FNIH Process

- Biomarkers Consortium of FNIH is a public-private partnership
  - Approached by FDA after December 2009 AIDAC meeting
  - Endpoint review and potential for new endpoint development for CABP
- Project team comprised of representatives from industry, academia, IDSA, NIH, and FDA; FDA members are non-voting
- First project team meeting to discuss CABP was in June 2010

FNIH Process

- Phase 1: Retrospective data analyses performed to develop a set of interim recommendations
  - Historical data
  - Datasets from previously conducted clinical trials
    - Two Phase 3 CAP trials comparing tigecycline to levofloxacin
    - Ceftriaxone data from the daptomycin CAP trial
    - Analyses performed during FDA review of ceftaroline CABP registrational trials
- Phase 2: Qualitative research phase for possible improvements of endpoint measures and/or development of new measures
  - Research gaps identified in defining all relevant symptoms important to patients and in evaluating the reliability of measurements of patient symptoms
  - Additional research to evaluate validity and reliability of interim recommendations and improve if needed

Symptom Improvement



FNIH submission to Docket FDA 2009-D-0136

Response Rates

Day	One-point improvement in two symptoms	Two-point improvement in one symptom	Two-point improvement in symptom, one-point improvement in another symptom
Day 3	257/437 (59%)	155/437 (35%)	138/437 (32%)
Day 4	305/425 (72%)	209/425 (49%)	193/425 (45%)
Day 5	274/350 (78%)	203/350 (58%)	192/350 (55%)

FNIH Recommendations for an Interim Endpoint

- Symptom Improvement at Study Day 4 (72 h after study initiation)
  - A one-point improvement in at least two symptoms of cough, dyspnea, pleuritic chest pain, sputum production **and**
  - No worsening of any other symptoms
- Symptoms are scored as Absent (or none), Mild, Moderate, Severe

FNIH Recommendations for an Interim Endpoint

- Absence of elevated body temperature and improvement in important measures of physiological clinical stability not included as a part the proposed symptom-based endpoint
- Need for later assessment- end of therapy and at an off-therapy time point

FNIH: Alternative Opinion

- Early endpoints are based on limited historical data; are already part of the TOC endpoint
- Primary outcome measure should be at EOT or beyond
  - Assesses durability of response and is relevant to use of a drug
  - Overall endpoint could include both success at an early time point and at a later time point
  - Need for global harmonization
- Recent analyses show a correlation between drug exposure and traditional clinical and microbiologic endpoints
- Currently available agents approved using traditional TOC endpoints can be used as comparators in future trials

Topics not addressed by FNIH

- Study enrollment criteria
- Receipt of prior effective antibacterials
- Proposed noninferiority margin
- Sample size considerations

Summary

- Summarized discussions held so far
- Identified some key topic areas that still need discussion
  - Primary endpoint
  - Primary analysis population
  - Prior effective antibacterial therapy
- Presented FNIH recommendations for an interim endpoint and the alternative opinion

The Path Forward for CABP Drug Development

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Meeting of the Anti-infective Drugs' Advisory Committee
November 3, 2011

Outline

- Study population
- Comparators
- Prior antibacterial drug use
- Concomitant medications
- Proposed development options
- Issues for discussion

Study Population

- At least two of the following symptoms:
  - Difficulty breathing
  - Cough
  - Production of purulent sputum
  - Chest pain
  - ±chills/rigors/"feverishness", decreased or absent appetite, new limitations in ADLs
- At least two abnormal vital signs:
  - Fever >38ºC or hypothermia <35ºC
  - Hypotension with SBP ≤ 90
  - Tachycardia with HR ≥ 100 bpm
  - Tachypnea with RR ≥ 24 breaths/min
- At least one other clinical sign or lab finding associated with CABP
  - Hypoxemia PaO_2 < 60 mm Hg by ABG or room air pOx < 90%
  - Pulmonary consolidation: dullness on percussion, bronchial breath sounds, egophony
  - Increased WBCs or leukopenia, or elevated bands

Study Population

- Chest radiograph with new infiltrates in lobar or multilobar distribution
  - Include final full radiology reports of pretreatment and subsequent CXRs in CRF
- Purulent sputum by Gram stain
  - <10 squamous epithelial cells and >25 PMNs per low power field
- Enroll subjects with a greater severity of illness
  - Use Pneumonia Patient Outcomes Research Team (PORT) or CURB-65 as approximates of severity scores
  - For IV antibacterial drugs: no subjects with PORT score <2; no more than 25% PORT 2, at least 25% PORT IV-V
  - For po antibacterial drugs: no PORT I, at least 50% PORT III
  - Ties to historical evidence of sensitivity to drug effect such that greatest effect of antibacterial drugs was seen in subjects > 50 y.o. and with bacteremia

Comparators

- Placebo not ethically acceptable
- Active comparator should be an FDA-approved antibacterial drug that is considered standard of care for this indication at the recommended dose and duration
  - e.g. in guidelines published by professional medical societies
  - In approved product labeling

Prior Antibacterial Drug Use

- Avoid because it will reduce the difference between treatment arms; particularly problematic in noninferiority trials
- Except in the case of clinical failure provided objective criteria are prespecified and documented on the CRF
- Or in the presence of resistant organisms, i.e. prior drug was not active
- Impact of prior abx may be greater when using an endpoint assessed at an earlier timepoint such as Day 3-5

Rationale for no prior antibacterial drugs: Clinical Infectious Diseases 2008; 46:1142–51

Effects of Prior Effective Therapy on the Efficacy of Daptomycin and Ceftriaxone for the Treatment of Community-Acquired Pneumonia

Peter E. Pertel,[1] Patricia Bernardo,[1] Charles Fogarty,[3] Peter Matthews,[4] Rebeca Northland,[5] Mark Benvenuto,[1] Grace M. Thorne,[1] Steven A. Luperchio,[1] Robert D. Arbeit,[2] and Jeff Alder[1]

Rationale for no prior antibacterial drugs: Clinical Infectious Diseases 2008; 46:1142–51

Table 6. Clinical cure rates among patients in the pooled clinically evaluable population, by prior effective antibacterial therapy.

	Daptomycin arm		Ceftriaxone arm		
Prior effective therapy	No. of cured patients/total no. of patients	Cure rate, %	No. of cured patients/total no. of patients	Cure rate, %	95% CI[a]
Yes	88/97	90.7	81/92	88.0	−6.1% to 11.5%
No	205/272	75.4	245/279	87.8	−18.8% to −6.0%

[a] For the difference in cure rates.

Comments on Pertel Paper

- Prior effective therapy defined as treatment with abx with greater potency and longer half-lives (e.g. levofloxacin, ceftriaxone, azithromycin, and clarithromycin)
- Biologic plausibility due to susceptibility of *Streptococcus pneumoniae* to active antibacterial drugs with bactericidal activity
- Also, interaction with surfactant bound daptomycin and therefore it was not active in alveolar space
- However, it is a subgroup analysis
- Additional analyses of short vs. long-acting antibacterial drugs may be informative

Effect of prior antibacterial drug use: ceftaroline CABP studies

Table 19: Clinical Cure Rates at TOC by Prior Antibiotic Use; MITTE Population

Study P903-08	Ceftaroline	Ceftriaxone	Difference (95% CI)
Prior Antibiotics	105/137 (76.6)	112/143 (78.3)	-1.7 (-11.5, 8.1)
No Prior Antibiotics	139/154 (90.3)	121/157 (77.1)	13.2 (5.1, 21.4)
Study P903-09	Ceftaroline	Ceftriaxone	Difference (95% CI)
Prior Antibiotics	80/95 (84.2)	91/113 (80.5)	3.7 (-7.0, 14.0)
No Prior Antibiotics	151/189 (79.9)	112/156 (71.8)	8.1 (-0.9, 17.3)

Data Source: FDA reviewer. Nine subjects excluded from Study P903-09 for reasons of data integrity.

Effect of prior antibacterial drug use: ceftaroline CABP studies for Day 3 symptom endpoint

Results from pooled trials derived from the public domain statistical NDA review:

MITTE Population	Ceftaroline	Ceftriaxone	Difference (95% CI)
Day 3 Symptoms			
Prior Antibiotics	189/232 (81.5)	204/256 (79.7)	1.8 (-5.3, 8.8)
No Prior Antibiotics	297/343 (86.6)	252/313 (80.5)	6.1 (0.4, 11.8)

Comments on ceftaroline subanalysis

- Only one dose of short-acting drug allowed
- No clear explanation for finding, as there was for daptomycin
- Prior antibacterial drug use masked differences between ceftaroline and ceftriaxone for clinical response at TOC and for the early endpoint at Day 3
  - Were those subjects more ill?
  - Emphasizes that prior antibacterial use will drive two arms to look similar in noninferiority trials, even when they are not
- In this subgroup analysis that wasn't prespecified, the outcome for subjects with no prior antibacterial drug use showed a numerical trend of better response with ceftaroline, similar to overall efficacy conclusions

Concomitant Antibacterial Therapy

- Avoid use during the trial for other infections, unless it does not have activity against target CABP pathogens
- Subjects who receive such therapy should be excluded from the evaluable population and considered failures in the microITT and ITT analysis populations
- Subjects requiring rescue antibacterial therapy for CABP should be considered treatment failures and should be included in analyses of all populations (ITT, microITT, PP)

Option #1: Two Noninferiority Trials

- 1° endpoint-assessed at Day 3-5
  - Symptom improvement (no worsening of dyspnea, cough, sputum production, chest pain ± exercise tolerance, feverishness, chills/rigors)
  - Assumes 80% success rate in the control group
- Primary analysis populations are ITT for each trial and pooled microITT across trials
  - Key 2º endpoints of stabilization/normalization of vital signs by Day 3-5 and clinical response at end-of-therapy (EOT); consistency with primary will be assessed as well as durability
- NI margin of 10% for ITT; 15% for pooled microITT (assumes 27% micro evaluable)
- N=688 per trial for 80% power, N=860 for 90% power
- Safety database=688 at to-be-marketed dose and duration, in addition to data from Phase 2

Option #2: Two Noninferiority Trials

- Coprimary endpoint-assessed at Day 3-5
  - stabilization/normalization of vital signs and improvement/no worsening of symptoms (dyspnea, cough, sputum production and chest pain)
  - Assumes 80% success rate on symptom and 70% on signs
- Primary analysis populations are ITT in each trial and pooled microITT across trials
  - Key 2º endpoint of clinical response at EOT; consistency with primary endpoint will be assessed and durability
- NI margin of 10% for ITT; 15% for pooled mITT (assumes 27% micro evaluable)
- N=980 per trial for 80% power, N=1180 for 90% power
- Safety database=980 or 1180, plus Phase 3 data

Option #3: One noninferiority trial

- 1° endpoint-assessed at Day 3-5
  - Symptom improvement (no worsening of dyspnea, cough, sputum production, chest pain ± exercise tolerance, feverishness, chills/rigors)
  - Assumes 80% success rate in the control group
- Primary analysis population is microITT (assumes 27% micro evaluable)
  - N=1862 for 80% power, N=2491 for 90% power if NI margin is 10%
  - N=1192 for 80% power, N=1595 for 90% power if NI margin is 12.5%
  - N=828 for 80% power, N=1107 for 90% power if NI margin is 15%
  - Safety database=N/2 if 1:1 randomization plus Phase 2 data
- Supportive information:
  - Successful HABP/VABP trial if drug is broad spectrum or has activity against Gram-positive bacteria
  - Successful ABSSSI trial if drug has activity against Gram-positive bacteria

Issues for discussion

- Endpoints: symptom stabilization/improvement ± assessment of clinical stability based on vital signs
- Noninferiority margin justification based on treatment effect on above at Day 3-5 and acceptability of 10, 12.5, or 15% margin
- Proposed development plans
- Other trial designs
- Receipt of prior antibacterial therapy
- Methods to enrich microITT
- Mechanisms to overcome barriers to trial conduct
- Advice on trials of oral antibacterial drugs

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