Alternatives to the All-cause Mortality Endpoint for Studies of Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia

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INTRODUCTION

At the US Food and Drug Administration's request, the Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium convened an expert working group to provide recommendations to support hospital-acquired bacterial pneumonia (HABP)/ventilator-associated bacterial pneumonia (VABP) drug development based on scientifically rigorous, clinically relevant, and routinely feasible non-inferiority (NI) designs.

The multidisciplinary team included representatives from government, academia, and industry with expertise in antibiotic development. The team previously proposed well-defined, symptom-based endpoints and improved trial design for Acute Bacterial Skin and Skin Structure Infections (ABSSSI) and Community-acquired Bacterial Pneumonia (CABP). This presentation focuses on learnings from analyses of recent HABP/VABP trials.

FNIH Biomarkers Consortium Antibacterial Project Progression

- Formation of the CABP/ ABSSSI FNIH BC Team
- Submission of CABP/ABSSSI Recommendations to FDA docket
- Initiation of CABP /ABSSSI PRO Development
- Formation of the HABP/ VABP FNIH BC Team
- Submission of HABP /VABP Recommendations to FDA docket
- Initiation of HABP/VABP PRO Development

PURPOSE

The efforts of the FNIH Biomarkers Consortium HABP/VABP Project Team were to enrich the science of clinical trials while addressing concerns about the scientific validity, feasibility, and rigor of such studies.

The goal was to identify alternatives to the All-cause Mortality (ACM) endpoint that would improve HABP/VABP study design and feasibility, while maintaining scientific validity.

Objectives of analyses included determining:

- ACM incidence during Study Days 14–28;
- Baseline characteristics associated with higher ACM rates;
- Adverse events/ Serious AEs relevant to a "mortality plus" endpoint: "ACM+": a composite endpoint of ACM plus selected AEs reflecting how a patient feels or functions
- Potential utility of a symptom-based endpoint in HABP;
- Impact of prior antibiotic therapy on outcome;
- Impact of adjunctive systemic antibiotic therapy on outcome.

RESULTS

Range of Point Estimates of Percent All-Cause Mortality at Days 14 and 28

Incidence of all-cause mortality within a Day 14–28 endpoint window.

ACM rates are substantial by Day 14, but consistently higher at Day 28. ACM directionality was consistently v-HABP > VABP >> nv-HABP. The observational Barcelona ICU study had both the highest rates of ACM and a statistically significant difference in ACM for v-HABP > VABP > nv-HABP.

Sponsor (analysis population)	VABP	Ventilated HABP	Non-ventilated HABP
Study Day 14			
Shionogi (AT)	6.3–9.8%	9.5–14.9%	3.1–9.6%
Pfizer (AT)	7.9%	6.5%	6.1%
Theravance (AT)	16.8%	16.3%	13.0%
Barcelona (AT-ICU)	19.8%	24.0%	17.4%
Study Day 28			
Shionogi (AT)	10.2–19.9%	20.8–23.2%	11.0–13.5%
Pfizer (AT)	12.6%	15.2%	9.8%
Theravance (AT)	26.3%	30.2%	18.8%
Barcelona (AT-ICU)	27.0%	39.4%	21.7%

AT: All-treated patient analysis population; ICU: Intensive Care Unit

Cox Regression Analysis of Risk/Prognostic Factors for All-Cause Mortality in VABP Patients, Combined Across Studies (All-Treated Population, Dori-08, -09 and -010)

	VABP	
	Hazard Ratio	95% CI
Treatment group	0.955	0.818, 1.115
Older Age	1.400	1.182, 1.659
Female Gender	1.076	0.904, 1.281
Elevated APACHE II score	0.978	0.640, 1.496
Bacteremia	0.937	0.724, 1.211
Non-fermenting gram-negative pathogen or MRSA	1.085	0.832, 1.416
Impaired oxygenation (PaO_2/FiO_2 <250)	0.993	0.828, 1.191
Prior antibiotic use within 48 hours	1.198	1.006, 1.426
Inadequate Pre-Study Therapy	0.917	0.713, 1.178
Inadequate Initial Therapy	0.818	0.558, 1.199
Study -08	1.359	1.130, 1.635
Study -09	1.028	0.791, 1.336

MRSA: methicillin-resistant *Staphylococcus aureus*; CI: Confidence interval

Baseline characteristics associated with higher rates of all-cause mortality

The most robust analyses were available from the Shionogi doripenem studies. Older age was the most consistent independent predictor of ACM. APACHE II score was also identified in some analyses.

Point Estimates of Rates of ACM versus ACM+ Endpoints (Study Dori-09)

Endpoint	Endpoint Timing	Non-ventilated HABP Study Drug (N=160) %	Non-ventilated HABP Comparator (N=160) %	VABP Study Drug (N=63) %	VABP Comparator (N=61) %
	Day 14				
ACM		9.6	3.1	9.5	14.9
ACM+		14.1	6.3	19.0	19.8
	Day 28				
ACM		13.5	11.0	20.8	23.2
ACM+		19.4	13.5	30.4	26.5

ACM: All-cause mortality; nv: non-ventilated
ACM+: Mortality plus -ACM plus Toxic/Septic Shock Standardized MedDRA Query adverse events
HABP: Hospital-acquired bacterial pneumonia; VABP: Ventilator-associated bacterial pneumonia

Incidence of events that could form the "plus" in a mortality-plus endpoint

A fixed 10% NI margin is acceptable if ACM is ≥15–20%; if lower, a fixed (risk-difference) NI margin of 10% is not supportable, requiring an odds-ratio analysis approach, increasing study sample size. Methods to increase the endpoint event rate could avoid this issue.

Improvement/Resolution of Symptoms by Study Day (Shionogi Database)

	Non-ventilated HABP			
	Doripenem % (n/N)		Piperacillin/Tazobactam % (n/N)	
	Day 5	Day 7	Day 5	Day 7
Improvement in at least 2 symptoms*	71.4% (80/112)	83.8% (78/93)	77.6% (90/116)	82.1% (78/95)
Improvement in 3 symptoms**	69.7% (23/33)	65.5% (19/29)	79.1% (34/43)	89.2% (33/37)

*Denominator is the number of subjects with 2 or 3 symptoms at baseline; subjects who died are included in the denominator
**Denominator is the number of subjects with 3 symptoms at baseline; subjects who died are included in the denominator.

Utility of a symptom-based endpoint in nv-HABP

In the Shionogi database, 71.3–73.1% of nv-HABP patients had two or more pneumonia symptoms at baseline. The table shows improvement/ resolution of pneumonia symptoms.

In the Pfizer database, 78.9% of all patients had two or more baseline pneumonia symptoms: 95.6% for nv-HABP versus 72.1% for v-HABP and 46.8% for VABP. Approximately 75% of the nv-HABP patients had improvement or resolution in one or more symptoms by Day 5.

METHODS

Cox regression analysis of risk/prognostic factors for ACM was performed on Shionogi studies Dori-08, Dori-09, and Dori-10 for specified patient baseline variables as shown in the table (at left). Treatment group was doripenem vs. comparator. Bacteremia was as specified by the sponsor's database. "Inadequate" therapy was defined as discordance between the antimicrobial received and the susceptibility profile of the isolated baseline pathogen(s).

A "mortality-plus" (ACM+) endpoint was constructed by combining study-specific rates of ACM and of severe, infection-related, patient-relevant adverse events from the Medical Dictionary for Regulatory Activities (MedDRA) using the Toxic/Septic Shock Standardized MedDRA Query (SMQ) tool; SMQs are validated database interrogation tools. The Toxic/Septic Shock SMQ interrogates a study database for multiple, clinically important pneumonia complications (e.g., sepsis, septic shock, acute respiratory failure, acute renal failure) that would be important to a patient's "feels and functions" over and above survival.

CONCLUSIONS

Hypothesis	Findings	Interpretations
Published data on v-HABP, VABP, and nv-HABP suggest substantive clinical differences among groups that could impact study design.	At study day 28, mean ACM was v-HABP (27.8%; range: 15.2-39.4), VABP (18.0%;10.7-27.0), and nv-HABP (14.5%;9.8-21.7).	Simple pooling of these groups in a single study raises methodological issues.
A fixed 10% NI margin is acceptable if ACM is ≥15–20%; if lower, a fixed (risk-difference) NI margin of 10% is not supportable, requiring an odds-ratio analysis approach, increasing study sample size. Methods to increase the endpoint event rate could avoid this issue.	Using the Toxic/Septic Shock SMQ tool to define the "plus" events to be added to the ACM event rate resulted in an ACM+ rate 3–10% higher than for ACM alone across treatment groups and studies.	The increased event rate in an ACM+ analysis could avoid an odds ratio analysis approach, facilitates an earlier endpoint (e.g., at 14 days), and enables patient-relevant sensitivity analyses.
Less restrictive enrollment criteria would increase ACM and results' generalizability, while decreasing study sample size (risk-difference metric). Identifying prognostic factors for ACM would inform study design.	Independent predictors of higher ACM rates included older age and higher APACHE II score.	Straightforward alterations to enrollment criteria could modify the rate of ACM.
A clinically meaningful endpoint of symptom improvement is supported by data for CABP.	nv-HABP (but not v-HABP or VABP) patients frequently reported pneumonia symptoms at baseline/ on therapy.	A PRO instrument for nv-HABP could standardize capture of patient-relevant symptoms for a new endpoint.

AFFILIATIONS

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STUDY DATABASES

- Telavancin ATTAIN "Study 0015" and "Study 0019" (HABP and VABP) (Theravance Biopharma)
- Tigecycline "Study 311" " (HABP and VABP) (Pfizer, Inc.)
- Doripenem VABP "Study 3008"; doripenem HABP/ early VABP "Study -09"; and doripenem VABP "Study -10" (Shionogi)
- Prospective, observational ICU study (Institut Clínic del Tórax, Hospital Clínic, Barcelona, Spain)