# NDA Requirements: Surveillance, Clinical Trial Data, Breakpoints

Kevin M. Krause

Director – Microbiology

Achaogen, Inc.

Presented at the *ASM/ESCMID Conference on Drug Development to Meet the Challenge of Antimicrobial Resistance* September 6–8, 2017, Boston, MA, USA

# Disclosures and Disclaimer

- Kevin Krause is an employee of and shareholder in Achaogen, Inc.
- The views and opinions expressed in this presentation are those of the author and do not necessarily reflect the official policy or positions of Achaogen

# Microbiology for Clinical Development – Requirements and Potential Pitfalls

- Surveillance Programs
  - Best practices for design
  - Using and interpreting the data
- Clinical Trial Data
  - Requirements for regulatory submission
- Breakpoints
  - Approaches to setting tentative and final interpretive criteria

# Surveillance

# Global Surveillance: An Important Investment

- Defines the spectrum of activity for a molecule
- Establish potency against recent clinical isolates
- Determine susceptibility rates against relevant comparators
  - Focus on comparators used to treat the species studies or in the expected clinical indication(s)
- Identifies rates and trends in resistance
  - Robust sampling needed to capture rare resistance types
- Provides the opportunity to build challenge sets of isolates for AST companies and isolates for other non-clinical studies

# Global Surveillance: Consider Starting Early

- Traditionally, surveillance begins before or during Phase 2
- As a result of accelerated development pathways and/or molecules qualifying for 505(b)(2), starting surveillance pre-Phase 1
  - May be necessary to ensure sufficient data for filing
  - May also result in increased financial risk as requires a large investment before proof of concept

# Global Surveillance: Designing a Comprehensive Study

- FDA guidance recommends evaluating activity of the parent molecule, important metabolites and relevant comparators against at least 500 fresh clinical isolates of each potential pathogen in the intended indication(s)
  - Isolates with global geographic diversity are required
  - Must include molecularly characterized resistance mechanisms of relevance
- Recommend completing at least 3 consecutive years global surveillance for NDA/MAA
  - Provides longitudinal analysis of resistance trends
  - Provides ability to identify local and/or clonal outbreaks of resistant isolates

# Potential Pitfall #1 - Final Surveillance Data Sets are Insufficient

- Possible risk to regulatory approval
  - Gain alignment on design with the FDA/EMA as early as possible
  - Consider opportunities to supplement prospective surveillance with institution specific studies
- Missed opportunity for desired label language
  - Important to provide sufficient numbers of isolates for List 2 pathogens
  - Molecular typing of resistance markers is expected to enable label claims
  - Collaborate with surveillance providers on study design

# Potential Pitfall #2 - Discordance Between Clinical and Surveillance Data

- Consider local epidemiology data from surveillance when selecting sites and countries for clinical trials
  - Recommend not opening sites in a region of the world where surveillance data has not been collected
- Compare data from clinical trial data sites to global surveillance
  - Confirm that trial site selection didn't introduce bias
  - If differences are noted, can they be explained by a local outbreak of a rare resistance type or some other sampling issue?

# Clinical Trial Data

# Clinical Study Setup – Working with a Central Lab

- Typically a central lab is used to conduct testing on all pathogens isolated from patients enrolled in clinical trials
  - Species identification
  - MIC data using pre-made frozen or dry-form MIC panels with relevant comparators
  - Kirby-Bauer disk susceptibility data research use only (RUO) disks
  - Molecular characterization
- Sponsor provides tentative breakpoints for investigational agent and defines which breakpoints to apply to comparator

# Clinical Study Setup - Breakpoints for Data Analysis During Trial

- Used to define primary analysis population exclusions for resistant isolate subsets
  - Prospectively define resistance category definitions in the clinical protocol
- Analyze data sets using the appropriate breakpoints for the submission
  - Use MIC trays that include drug dilution ranges able to capture all breakpoints
- Examples
  - For U.S. filings, CLSI breakpoints are typically used when available
    - FDA breakpoints are used when CLSI breakpoints not available
    - EUCAST breakpoints can be used if FDA/CLSI breakpoints aren't available
  - For E.U. filings, EUCAST breakpoints should be used

# Study Setup – Clinical Microbiology and Patient Samples

- Definition of a valid clinical sample
  - Regulatory guidance available but needs to be informed by standard clinical practices
  - Examples
    - Urine sample: $\geq 10^5$ CFU/mL at baseline from midstream clean catch or suprapubic aspiration with no more than 2 uropathogens present
    - Respiratory sample: sputum with >25 WBC and <10 squamous cells
- Establishment of species labeled pathogens and contaminants
  - Would the isolate typically be treated in clinical practice?
  - Do two isolates of the same species represent distinct isolates or a single isolate with a resistant subpopulation?

# Potential Pitfall #3 - Logistics of Sample Transport and Testing

- Capabilities of local labs vs. regional labs
  - Weigh risks of shipping to a regional lab for local ID and AST vs. errors from low quality local labs
- Transit time of sample from patient to culture must be monitored if using a regional lab
  - Proper shipping containers for local temperatures or airplane cargo hold conditions
  - Example – Urine preservative tubes can be used if shipping urine samples long distance, but might be inconsistent with local practice and can't be frozen

# Ongoing Clinical Study - Monitoring of Microbiology Data

- Discordance between local and central ID must be reconciled
  - Pre-define rules for when to retest at central lab, when to test the backup isolate and how to correct local data entry errors
- Tentative breakpoints and resistance development must be monitored
  - Used to define analysis populations
  - Pre-define “resistance development” as well as unusual MICs
    - Set expert rules to automatically flag and retest these isolates
  - Different FDA and EUCAST breakpoints can impact data interpretation for comparator agents
- Prospectively define decision making algorithms for pathogen adjudication
  - Document decisions for each isolate in a manner that will satisfy auditors
- QC should be run each day susceptibility testing is conducted during a trial and all results retested if QC is out of range

# Potential Pitfall #4 - Low Evaluability Rate Leads to Underpowered Study

- Use historical trial data to estimate evaluability rates
- Conduct weekly blinded monitoring of culture positivity rates
  - Look for site level trends and opportunities for retraining
  - Consider closing sites that have very low evaluability rates

# Approaches to Molecular Characterization are Evolving

- PCR for key, defined resistance elements
  - PVL in MRSA, VanA vs VanB VRE
- Multiplex PCR tests for larger scale testing
  - Off the shelf tests for specific resistance clusters (beta-lactamase families)
  - Provides an analysis of what you were looking for, but not what else was present (or absent)
  - Doesn't allow for identifying point mutations in resistance elements
- WGS addresses above challenges and is becoming standard practice

# Potential Pitfall #5 - Use of Sequencing Data in Regulatory Filings

- Data interpretation methods are still in development
- Data presentation can be challenging due to sheer volume of data
- How can the data be curated to ensure integrity for future use?
- The data is valuable for research purposes, but country specific privacy laws might not allow use of the data for other purposes – check patient consent forms!

# Breakpoints

# What are Breakpoints?

- Breakpoints assist in the selection of antibacterial options that are appropriate for treatment of clinical infections
- MIC breakpoints are derived after consideration of:
  - Clinical and microbiological outcomes by baseline MIC from Phase 3 studies
  - Probability of PK/PD target attainment (PTA)
  - In vivo efficacy data
  - MIC distributions from surveillance
- Breakpoints are assigned per pathogen/pathogen group NOT per indication
- Disk breakpoints are derived from MIC breakpoints with the goal of minimizing interpretation error rates

# How are Breakpoints Used?

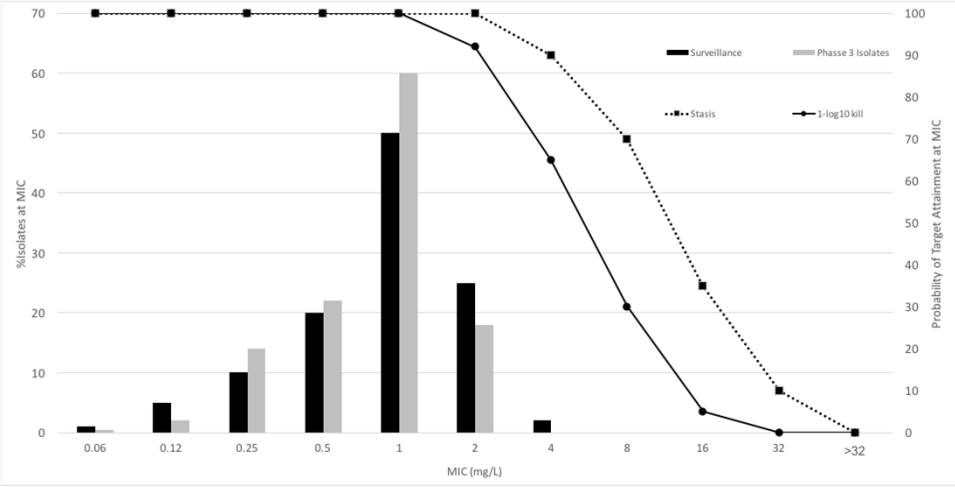
- Breakpoints are interpreted as Susceptible (S), Intermediate (I), Resistant (R) or Non-susceptible (NS)
- S, I and NS/R are reported on a typical hospital antibiogram
  - MIC values are rarely if ever reported
  - Interpretation says nothing about relative potency – only whether or not a drug has a reasonable chance of being effective against a given isolate
- Provisional breakpoints are set based on PK/PD prior to Phase 3
  - Used to exclude patients from primary analysis populations in non-inferiority studies
  - Allows for monitoring of potential “resistance” development during clinical program
  - Used by automated AST companies to set MIC range for test development

# The FDA and EUCAST Provide Guidance on Data Needed for Establishing Breakpoints

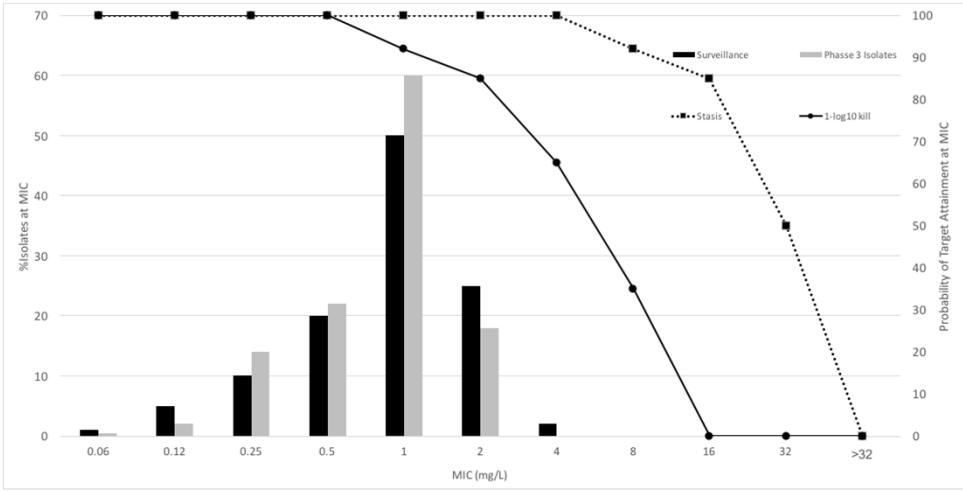
- Clinical and Microbiological outcomes by MIC
  - Ideally provides evidence of efficacy at MICs up to and including the breakpoint
  - However, MICs approaching the breakpoint are rare in most clinical studies
- PTA data is used to supplement the clinical data
  - Uses a statistical approach to predict the likelihood that a given dose could provide sufficient drug exposure to treat a pathogen at a given MIC
  - Data can be used to argue for a higher breakpoint in cases of limited clinical data
- In vivo efficacy studies with human simulated exposures
- The distribution of MICs found in U.S. surveillance
- EUCAST also applies the Epidemiological Cutoff Factor or ECOF
  - The MIC population associated with wild type isolates vs. those with underlying class resistance

# Using PK/PD as Part of a Breakpoint Justification

***Hypothetical Scenario with positive clinical/microbiology outcomes at an MIC of 2 mg/L***




- >90% probability of stasis target attainment at highest surveillance MIC of 4 mg/L
- Phase 3 data supports a breakpoint of 2 mg/L
- Consider using target attainment information to justify a breakpoint of 4 mg/L




- >90% probability of stasis target attainment at MICs up to 16 mg/L
- Phase 3 data supports a breakpoint of 2 mg/L
- Breakpoint of 16 mg/L leaves too much room for MIC creep within susceptible population
- Propose a breakpoint of 4 mg/L

# Potential Pitfall #6 - Tentative Breakpoints are Too High

- Patients may not be properly excluded from primary analysis populations
- Automated AST manufacturers may not be able to accommodate drastic changes between tentative and final breakpoints
  - Could result in redoing a significant portion of AST development
  - Results in significant delays to AST availability
  - Increases cost of AST development significantly
- Use a combination of PK/PD and MIC distributions from surveillance to set realistic tentative breakpoints

# Final Breakpoints Appear in the Microbiology Section (12.4) of the Drug PI

**Table 7: Susceptibility Test Interpretive Criteria for Ceftolozane/Tazobactam**

| Pathogen | Minimum Inhibitory Concentrations (mcg/mL) | | | Disk Diffusion Zone Diameter (mm) | | |
|---|---|---|---|---|---|---|
| | S | I | R | S | I | R |
| Enterobacteriaceae | ≤2/4 | 4/4 | ≥8/4 | ≥21 | 18-20 | ≤17 |
| *Pseudomonas aeruginosa* | ≤4/4 | 8/4 | ≥16/4 | ≥21 | 17-20 | ≤16 |
| *Streptococcus anginosus* *Streptococcus constellatus* and *Streptococcus salivarius* | ≤8/4 | 16/4 | ≥32/4 | --- | --- | --- |
| *Bacteroides fragilis* | ≤8/4 | 16/4 | ≥32/4 | --- | --- | --- |

S = susceptible, I = intermediate, R = resistant

**Table 8. Susceptibility Interpretive Criteria for Ceftazidime/Avibactam**

| *Pathogen* | *Minimum Inhibitory Concentration (mg/L)* | | *Disk Diffusion Zone Diameter (mm)* | |
|---|---|---|---|---|
| | *S* | *R* | *S* | *R* |
| Enterobacteriaceae | ≤ 8/4 | ≥ 16/4 | ≥ 21 | ≤ 20 |
| *Pseudomonas aeruginosa* | ≤ 8/4 | ≥ 16/4 | ≥ 21 | ≤ 20 |

Table 9: Susceptibility Test Interpretive Criteria for Telavancin

| Pathogen | Minimum Inhibitory Concentration (mcg/mL) | | |
|---|---|---|---|
| | S | I | R |
| *Staphylococcus aureus* (including methicillin-resistant isolates) | ≤ 0.12 | -- | -- |
| *Streptococcus pyogenes* *Streptococcus agalactiae* | ≤ 0.12 | -- | -- |
| *Streptococcus anginosus group* | ≤ 0.06 | | |
| *Enterococcus faecalis* (vancomycin-susceptible isolates only) | ≤ 0.25 | -- | -- |

**TABLE 2 SUSCEPTIBILITY INTERPRETIVE CRITERIA FOR PIPERACILLIN/TAZOBACTAM**

| | Susceptibility Test Result Interpretive Criteria | | | | | |
|---|---|---|---|---|---|---|
| | Minimal Inhibitory Concentration (MIC in µg/mL) | | | Disk Diffusion (Zone Diameter in mm) | | |
| Pathogen | S | I | R | S | I | R |
| *Enterobacteriaceae* and *Acinetobacter baumanii* | ≤ 16 | 32 - 64 | ≥ 128 | ≥ 21 | 18 - 20 | ≤ 17 |
| *Haemophilus influenzae*[a] | ≤ 1 | - | ≥ 2 | ≥ 21 | - | - |
| *Pseudomonas aeruginosa* | ≤ 64 | - | ≥ 128 | ≥ 18 | - | ≤ 17 |
| *Staphylococcus aureus* | ≤ 8 | - | ≥ 16 | ≥ 18 | - | ≤ 17 |
| *Bacteroides fragilis* group | ≤ 32 | 64 | ≥ 128 | - | - | - |

[a] These interpretive criteria for *Haemophilus influenzae* are applicable only to tests performed

ACHAOGEN

# Resources

- FDA - *Microbiology Data for Systemic Antibacterial Drugs — Development, Analysis, and Presentation Guidance for Industry*
- EMA - *Guideline on the Evaluation of Medicinal Products indicated for Treatment of Bacterial Infections*
- EMA - *Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products*