Drug X-1
P3 Clinical Program

"All models are wrong...

some are useful."

George E. P. Box

Big picture

- X-1 looks useful! But, how do we study it?
- Three approaches are outlined
  - Scenarios A-C: Attempt to build a program based on trials that are (just) large enough to support non-inferiority-based hypothesis testing
  - Scenarios D-E: Really can't get to sufficient N for hypothesis testing.
    - What about the Animal Rule?
    - What about External Controls?
  - Scenario F: Audience participation! What else?

Constraints

- Proposals must be credible, non-BFMI solutions
  - BFMI (Brute Force, Massive Ignorance): e.g., enroll 10k
- Perfect diagnostics do not / will not exist: e.g., we can't have
  - Instant susceptibility of all pathogens in sputum
  - Instant knowledge that only *P. aeruginosa* is present
- Superiority via study of just MDR *P. aeruginosa* is not possible
  - Much too rare: Would require a well-timed outbreak
- Funding is (only) enough for ~1000 enrolled in P3
  - And it's not just funding … if we need to enroll 5000, then other drugs may struggle to proceed in parallel
- Add-on therapy approach is too risky
  - Hard to envision SOC + X-1 showing superiority to SOC + placebo
- In short, # of required miracles is kept at < 1
  - Would never reject luck, but won't plan on it

	Studied Diseases	Total N enrolled	N with pathogen	Issues and Questions
A	NP, cIAI in the RCT (N shown at right is for the RCT)	915	175	1. This Scenario is shown at length: most of the details for the other scenarios are found here. 2. Wide confidence intervals (CIs) 3. Parity of results with comparator 4. Confounding issues are limited to the concomitant amikacin in the HABP-VABP group 5. Overall, the simplest possible story — but still challenging!
B	NP, cIAI, and cUTI in OL LTO study	915	175	1. Very wide CIs 2. Trend towards worse results with X-1
C		915	104	1. Pathogen recovery rate lower than expected 2. Parity of results with comparator 3. But, very wide CIs (similar to CIs of Scenario B)
D	One infection (NP?) in the RCT	726	36	1. Very rare pathogen 2. Very small N for pathogen of interest despite substantial clinical program. 3. Tripling of the program size only gets you back to Scenario C in terms of N with target pathogen. 4. Can the Animal Rule or External Controls be used?
E	NP, cIAI, and cUTI in an OL LTO study?	726	36	1. Very rare pathogen 2. Very small N for pathogen of interest despite substantial clinical program 3. Tripling of the program size only gets you back to Scenario C in terms of N with target pathogen. 4. Animal models compliant with the Animal Rule are not possible. 5. Can you rely on clinical data alone (with External Controls)?
F	??	??	??	1. Audience choice!

Sponsor analysis (1 of 3)

- What do we have/need for the safety db?
  - Phase 1: 120 HVs (40 received full dose x 14 d)
  - Phase 2: 10 subjects (all full dose x 14d)
- That's 50 at full dose & duration:
  - Pre-clinical signals are easily monitored
  - P3: Seek ~200 more on full dose/duration
  - Pretty clean preclinical package … getting close to 300 would be a good start (rule of 3)

Sponsor analysis (2 of 3)

- Culture-positive rates need to be 15% or more
  - At 80% response, 85% power, 1:1 randomize…
    - 15% margin, 15% culture-positive: 2n = 1702
    - 15% margin, 20% culture-positive: 2n = 1276
    - 20% margin, 15% culture-positive: 2n = 958
  - (Imaginary) screening device exists
    - Lateral-flow immunochromatographic device
    - Low tech, simple training, 20-minutes to develop
    - Gets to 25% culture-positive in NP, 16.5% in cIAI
    - NOT cleared, not definitive: still must be culture-positive for microITT popultion

Sponsor analysis (3 of 3)

- Concomitant antibiotics are a problem
  - Important to study in NP
  - Guidelines often lead to 2 drugs (next slide)
  - Important to get data using X-1 as monotherapy
- Valuable to see data in more than one setting
- Decision: Two clinical trials, 3 indications
  - RCT with separate sub-arms for NP and cIAI
    - Can (just barely) eek out a non-inferiority design
  - Open-Label in Limited Treatment Options (OL LTO)
    - All-comers, NP, cIAI, cUTI

2016 IDSA Guidelines
Mono or combo for P. aeruginosa?

- **EMPIRIC:** We suggest prescribing one antibiotic active against *P. aeruginosa* for the empiric treatment of suspected VAP in patients without risk factors for antimicrobial resistance who are being treated in ICUs where ≤10% of gram-negative isolates are resistant to the agent being considered for monotherapy *(weak recommendation, low-quality evidence)*.

- **KNOWN (A):** For patients with HAP/VAP due to P. aeruginosa who are not in septic shock or at a high risk for death, and for whom the results of antibiotic susceptibility testing are known, we recommend monotherapy using an antibiotic to which the isolate is susceptible rather than combination therapy *(strong recommendation, low-quality evidence)*.

- **KNOWN (B):** For patients with HAP/VAP due to P. aeruginosa who remain in septic shock or at a high risk for death when the results of antibiotic susceptibility testing are known, we suggest combination therapy using 2 antibiotics to which the isolate is susceptible rather than monotherapy *(weak recommendation, very low-quality evidence)*.

Kalil, A. C., M. L. Metersky, et al. (2016). "Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society." Clin Infect Dis.

Scenario A (RCT, Background)

- About ertapenem
  - A carbapenem, stable to ESBLs, inactive vs. *P. aeruginosa*
  - Is indicated in cIAI, ABSSSI, CABP, cUTI
  - PK (including ELF data) looks acceptable for VAP

Scenario A (RCT, Design, 1 of 3)

- Subarms for cIAI and NP (HABP-VABP)
- X-1 + ertapenem vs. meropenem (non-inferiority)
  - cIAI: *May* add amikacin (mero arm) /placebo (X-1)
  - NP: *Must* add amikacin (*both* arms get active drug)
  - Both arms: amikacin stop by d4 (mero-susceptible)
    - Patient out of trial if *P. aeruginosa* is meropenem resistant
    - For discussion: BAT comparator arm instead
  - Can blind: X-1 and mero are q8h, can do both over 1h; erta/placebo qd as 4th study drug dose
- Both arms: Gram-positive coverage
  - May add linezolid or similar as desired (open-label)

Scenario A (RCT, Design, 2 of 3)

- Inclusions
  - Standard rules for cIAI and NP
  - Positive lateral flow or recent surveillance culture (patient stops study if baseline culture is negative)
  - No more than 24h of prior effective therapy
- Statistics
  - Primary analysis in microITT (positive culture for Pae)
    - Polymicrobial is not an exclusion
  - Endpoint: cIAI (clinical response), NP (28-d ACM)
  - Margins: 25% cIAI, 30% NP (see §2.3 and §A.2)
    - HABP-VABP: FDA M1 is 29% by 95-95 rule (argue for 30%)
    - cIAI: FDA M1 is conservative; KPC (Di Carlo 2013) data suggest stronger effect. Do more literature review and argue for 25%.

Scenario A (RCT, Design, 3 of 3)

- Success is defined as in
  - 95% CI of difference is within margin in both subarms
- Logic for approval would then be
  - Strong preclinical dose rationale
  - Target exposure proven in clinic (pop PK in entire program)
  - P1 (ELF) shows penetration
  - P2 (in bronchiectasis) has shown microbiologic effect
  - RCT in two diseases has shown effect
    - NP is partially confounded by concomitant amikacin
    - cIAI partially confounded by surgery but gives monotherapy data
  - Unmet Need label anticipated: Only for patients with LTO

Scenario A (RCT, Actual design)

- Power at 85%, assume 80% response rates
- Randomize 2:1 in both subarms
  - NP: Enroll 288 (192 X-1, 96 meropenem)
    - Of these, 48 and 24 should have a positive culture for Pae
  - cIAI: Enroll 624 (418 X-1, 209 control)
    - Of these, 69 and 34 should have a positive culture for Pae
- Actual study (Scenario A): Hits these parameters
  - Estimate: 36 months, 250 sites, screen close to 2000
  - Pop PK is on target
  - Amikacin (NP): 95% x 1d, 80% x 2d, 40% x 3, 20% x 4d

Results (Scenario A, §A.4.2)

RCT

Success / N (%)	X-1 + ertapenem	Meropenem	Delta
HABP/VABP	37/48 (77.1%)	19/24 (79.2%)	-2.1 (-22.2 to 18.1%)
cIAI	55/69 (79.7%)	27/34 (79.4%)	0.3 (-16.3 to 16.9%)

OL LTO

Success / N (%)	X-1 + ertapenem	% carbapenem-R P. aeruginosa
HABP/VABP	6/10 (60.0%)	8 of 10 are resistant
cIAI	10/15 (66.7%)	13 of 15 are resistant
cUTI	43/50 (86.0%)	45 of 50 are resistant

These patients were very complex and had multiple comordidities.

Safety: N on full dose/duration X-1 = 192 (P3) + 40 (P1-2) = 232. We're close enough to in the zone that we're probably OK unless a major new signal emerges

Noteworthy risks (§A.4.5)

- Is ertapenem at 1g acceptable for NP?
- N with *P. aeruginosa* is still small
- Margins of 30% and 25% are not agreed
  - Program easily exceeds 2000 if margins smaller
- <u>Enrolled</u> N likely needs to 30% larger
  - Unevaluable cases
  - Discontinuation from P3 RCT due to meropenem resistance (and hence a different 2nd drug)
  - Ultimately, the small N with *P. aeruginosa*
- We've not discussed pediatrics: Assume PK-based

Scenario A (90% CIs)

RCT

Success / N (%)	X-1 + ertapenem	Meropenem	Delta
HABP/VABP	37/48 (77.1%)	19/24 (79.2%)	-2.1 (-19.0 to 14.8%)
cIAI	55/69 (79.7%)	27/34 (79.4%)	0.3 (-13.6 to 14.2%)

Well, this does get the lower bound to < 20%

OL LTO

Success / N (%)	X-1 + ertapenem
HABP/VABP	6/10 (60.0%)
cIAI	10/15 (66.7%)
cUTI	43/50 (86.0%)

Scenario A (Discuss)

- What are the pros and cons of this approach & such data
  - from a clinical perspective?
  - from an investor perspective?
  - from a regulatory perspective?
- Data from two body sites! Pool (how?) or just take each as is?
- Impact of concomitant therapy in the HABP/VABP subset?
  - Monotherapy vs. dual therapy for P. aeruginosa? Impact of guidelines
  - Are there ways to reduce concomitant therapy?
  - Gram-positive coverage?
- What options exist to ertapenem as the companion to X-1?
- Handling of polymicrobial vs. monomicrobial infections?
- Could we focus on just MDR P. aeruginosa?
- Comparator: Best Available Therapy (BAT) vs. (blinded) meropenem?

Scenario B (a bit of drift from zero due some heterogeneity, perhaps)

RCT

Success / N (%)	X-1 + ertapenem	Meropenem	Delta
HABP/VABP	34/48 (70.8%)	19/24 (79.2%)	-8.3 (-29.1 to 12.4%)
cIAI	50/69 (72.5%)	27/34 (79.4%)	-7.5 (-24.5 to 9.4%)

OL LTO

Success / N (%)	X-1 + ertapenem
HABP/VABP	6/10 (60.0%)
cIAI	10/15 (66.7%)
cUTI	43/50 (86.0%)

Greatest possible delta within the already very generous margins.

It's a very small program. This much wobble is entirely plausible.

Scenario B (and now, reverse the drift. Is this superiority?)

RCT

Success / N (%)	X-1 + ertapenem	Meropenem	Delta
HABP/VABP	38/48 (79.2%)	17/24 (70.8%)	8.3 (-13.2 to 29.8%)
cIAI	55/69 (79.8%)	24/34 (70.6%)	9.1 (-8.9 to 27.1%)

OL LTO

Success / N (%)	X-1 + ertapenem
HABP/VABP	6/10 (60.0%)
cIAI	10/15 (66.7%)
cUTI	43/50 (86.0%)

If the previous slide made you to say "Hmmm – not sure I want this drug", what do you say to this reversal of fortunes?

Scenario B (side-by-side)

<div style="float:right; background:red; color:white;">
Very tiny shifts have big impact
</div>

Tilt right

Success / N (%)	X-1 + ertapenem	Meropenem	Delta
HABP/VABP	38/48 (79.2%)	17/24 (70.8%)	8.3 (-13.2 to 29.8%)
cIAI	55/69 (79.8%)	24/34 (70.6%)	9.1 (-8.9 to 27.1%)

Tilt left

Success / N (%)	X-1 + ertapenem	Meropenem	Delta
HABP/VABP	34/48 (70.8%)	19/24 (79.2%)	-8.3 (-29.1 to 12.4%)
cIAI	50/69 (72.5%)	27/34 (79.4%)	-7.5 (-24.5 to 9.4%)

Scenario C (Lower rate of culture-positive cases → smaller N)

RCT

Success / N (%)	X-1 + ertapenem	Meropenem	Delta
HABP/VABP	22/29 (75.9%)	11/14 (78.6%)	-2.7 (-29.3 to 23.8%)
cIAI	33/41 (80.5%)	16/20 (80.0%)	0.5 (-20.8 to 21.8%)

Delta is ~0, but margins as wide as in Scenario B.

OL LTO

Success / N (%)	X-1 + ertapenem
HABP/VABP	6/10 (60.0%)
cIAI	10/15 (66.7%)
cUTI	43/50 (86.0%)

Scenario D

- Culture-positive rate ~5%

- Program sizes rapidly balloon
  - At 30% margin and 1:1, might get down to 1276 for any one indication
  - At margins ≤ 25%, study sizes exceed 2k patients
  - So, pick one indication (NP) and do what you can
  - Perhaps really enrich for high-risk cases (renal failure, more comorbidities)

- The Animal Rule?
  - A validated ventilated piglet model is developed
  - The clinical trial is effectively the field trial
  - Could even add in some External Control Data

Scenario D (Results)

- Ventilated piglet model
  - Survival rate of 18/20 (X-1) vs. 0/10 (placebo), p = 0.005
- P3 RCT in NP (*can we consider this as a field trial?*)
  - Assume 80% success, 35% NI, 95% CI, 80% power, 2:1 randomization, and 5% culture positive
  - 484 vs. 242 (n=726) yields 24 & 12 on X-1 & control
  - Result: 19/24 (79%) vs. 10/12 (83%)
    - Delta of 4.2%, 95% CI = -27 to +18%
  - Boundary case is at 18/24 (75%). Essentially no buffer for heterogeneity or other random behavior
- Do these two things together create a Tier C- or D+?

Scenario E

- As in Scenario D
  - But, can't create an animal model that really seems a good mimic for human disease

- So,
  - Small RCT (after the fashion of Scenario D)
  - Or, just an OL trial that puts all the cases on X-1?
  - Would compare with External Controls

Scenario F

- What else?