3 Overview of the Phase 3 program scenarios

Six scenarios will be discussed:

Scenario	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) NP, cIAI, and cUTI in OL LTO study	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		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 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. Can the Animal Rule be applied (perhaps with External Controls)?
E		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 (supported by External Controls)?
F	??	??	??	1. Audience choice! What other path(s)?

NP = Nosocomial Pneumonia = Hospital-associated bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia

A P3 Program, Scenario A

A.1 General considerations

1) The P1 program has involved 120 subjects. Of these, 80 received doses / durations less than then full proposed clinical dose. The remaining 40 have received the full therapeutic dose for 14 days.
2) The Phase 2 program enrolled 10 patients and all received a full therapeutic dose for two weeks.
3) A rapid selection device has been invented. It is a based on a lateral flow immunochromatographic assay that uses an antibody to detect the presence of pyocyanin, a metabolite that is distinctive for *P. aeruginosa* (actually, it detects 1-hydroxyphenazine, a metabolite of pyocyanin itself; Pastells et al. "Immunochemical determination of pyocyanin and 1-hydroxyphenazine as potential biomarkers of *P. aeruginosa* infections." Anal Chem 88:1631-1638, 2016). The test can be conducted in 20 minutes at the bedside and a positive result increases the likelihood of growing *P. aeruginosa*. Available data suggest that the test is 80% sensitive for the presence of *P. aeruginosa* (only 1 in 5 culture positive cases are missed) and that a positive bedside test is associated with these rates of subsequent positive culture (PPV, or positive predictive value):
   a) HABP-VABP: 25% (up by 66% from 15%)
   b) cIAI: 16.5% (up by 66% from 10%)
   c) cUTI: 6% (up by 100% from 3%)
   d) Note: ***The described pyocyanin-based test does not exist!*** *For avoidance of doubt, the case scenario has been created with the assumption that only imperfect tools for patient identification are available. As will be seen below, achieving a higher % culture-positive rate is key to keeping the program < ~1000 subjects. To achieve this, we invented a test to help with this, we assume the test is convenient (20-30 mins), but we also assume that it still has a pretty high false-positive rate. In short, it's just good enough to get to a program of this size.*
4) For further avoidance of doubt, the pyocanin-based test is not used as a definitive diagnostic, but only for enrichment. As noted above, a large cohort must be screened to find those with a positive culture.
5) Treatment guidelines for nosocomial pneumonia due to *P. aeruginosa* unanimously recommend use of two active drugs as part of initial therapy.
6) It is important to get at least some data using X-1 as monotherapy for *P. aeruginosa.*

On the basis of these considerations, an approach is proposed based on combination of an RCT vs. a standard comparator and an open-label study in patients with limited treatment options (OL LTO).

A.2 P3 Randomized controlled trial in cIAI, hospital-associated bacterial pneumonia, and ventilator-associated bacterial pneumonia

Title: A prospective, randomized, blinded comparative study of X-1 in combination with ertapenem vs. meropenem for complicated intraabdominal infection (cIAI), hospital-associated bacterial pneumonia (HABP), and ventilator-associated bacterial pneumonia (VABP)

Note: Ertapenem lacks activity vs. P. aeruginosa. It can be thought of as otherwise equal to meropenem. Activity vs. P. aeruginosa in the X-1 arm can thus be attributed to X-1.

Inclusions:
1) Standard rules for cIAI, HABP, VABP
2) Positive lateral flow assay (or recent positive surveillance culture for *P. aeruginosa*)
3) Patient is taken out of the study (and off study drug) if baseline cultures do not yield *P. aeruginosa* after 96h of incubation (safety data are collected from these patients).
4) Less than or equal to 24h of prior effective therapy (all disease subsets)

Endpoints and statistics
- Primary analysis in microITT population (all with a positive baseline culture for *P. aeruginosa*)

- cIAI: Standard clinical response rules (complete resolution or significant improvement in signs & symptoms at the TOC visit between 28 and 35 days after randomization)
- HABP-VABP: All-cause mortality at 28 days after randomization
- Success will be declared if both infection subsets achieve non-inferiority within the bounds of the proposed (Wide! See below!) margins.

Treatment arms:

- cIAI: ertapenem[1] + X-1 vs. meropenem + placebo
  - Amikacin may be added to the meropenem arm if there is a substantial concern about meropenem resistance. It is given as placebo #2 (X-1 group) or amikacin (meropenem group).
- HABP/VABP: ertapanem[1] + X-1 vs. meropenem* + placebo
  - Amikacin is always given for up to the first 4 days in both study arms — it is stopped when it is confirmed that the non-amikacin therapy is active. Investigator training sessions and study monitors ensure that all understand need to stop amikacin as soon as possible.
  - If the isolate is found to be meropenem resistant (in either study arm: this is a blinded study), the patient is removed entirely from the trial so that an appropriate open-label best-available regimen can be devised for the patient. It is permitted to transfer the patient to the Open-label study for patients with limited treatment options (see next section).
  - The sponsor understands the possibility that labeling may state the X-1 should be used in combination with amikacin as part of initial therapy for HABP-VABP.

Footnotes to treatment arms

1) Ertapenem is used at its full dose of 1g every 24h. It is indicated for CABP and lung penetration data suggest it should be active in nosocomial pneumonia due to Enterobacteriaceae, including ESBL-producing strains.
   a) Bassetti, M., E. Righi, et al. (2007). "Efficacy of ertapenem in the treatment of early ventilator-associated pneumonia caused by extended-spectrum beta-lactamase-producing organisms in an intensive care unit." J Antimicrob Chemother 60(2): 433-435.
   b) Artero, A., A. Atienza, et al. (2016). "Ertapenem therapy for pneumonia requiring hospital admission in elderly people." Rev Esp Quimioter 29(1): 8-14.
   c) Boselli, E., D. Breilh, et al. (2006). "Pharmacokinetics and lung concentrations of ertapenem in patients with ventilator-associated pneumonia." Intensive Care Med 32(12): 2059-2062.
   d) EUCAST breakpoint rationale document (v1.3, 2009).
   e) *For avoidance of doubt, note that further work should be done on the PK-PD of ertapenem. But, the aggregate data above suggest it is plausible.*
2) Although meropenem is not approved for NP in the United States, this is a global trial and the investigators have agreed to use meropenem at its maximal dose of 2g every 8h. This also enables blinding (rather than using imipenem q6h).

These designs are considered (see also tables above):

Infection	Margin	Power	Ratio	N1 / N2 (Total N)	% Culture+	MicroITT: N1/N2
HABP/VABP	20%	85%	1:1	287 / 287 (574)	25%	72 / 72
	30%	85%	2:1	192 / 96 (288)		48 / 24
		85%	1:1	128 / 128 (256)		32 / 32
cIAI	14%	85%	1:1	888 / 888 (1776)	16.5%	147 / 147
	25%	85%	2:1	418 / 209 (627)		69 / 34
		85%	1:1	279 / 279 (558)		46 / 46
cUTI	30%	85%	1:1	532 / 532 (1064)	6%	32 / 32
	35%	85%	2:1	586 / 293 (879)		35 / 18
		85%	1:1	391 / 391 (782)		23 / 23

Based on a review of these data, the sponsor has elected:

1) To power at 85%
2) To estimate a response rate of 80% for all diseases.
   a) *This is an arbitrary simplification. The goal was to show plausible but difficult statistics.*
   b) The case also does not consider in detail the split between HABP and VABP — all are lumped into nosocomial pneumonia (NP).
3) To study only HABP/VABP and cIAI in the randomized trial — inclusion of cUTI in the randomized program costs too much to be justified.
   a) The OL LTO study (see next section) will enroll for these infections as well as for cUTI.
      i) The OL LTO is not randomized – instead, it focuses on enrolling very clearly defined infections due to pathogens often resistant to carbapenems. It is felt that randomization would just further subdivide the expected small numbers.
   b) Studying two indications permits acquisition of data with concomitant active therapy (HABP/VABP) and without concomitant active therapy (cIAI).
   c) Recall: The P2 program has shown the selected dose can have activity in the lung.
4) To propose margins of 30% and 25% for HABP/VABP and cIAI, respectively. These margins are wider than FDA's estimate of M1, but are justified on the basis of
   a) Unmet Need
   b) The 95-95 rule for the HABP-VABP data gives an undiscounted M1 of 29%.
   c) Di Carlo 2013 (see Section 2.3, above) shows a *mortality* benefit of 50% in cIAI, thus justifying a modest uplift to the conservative approach taken to M1 in the FDA Guidance.
5) To randomize at 2:1 in both indications:
   a) The P3 RCT will enroll 288 (HABP/VABP) + 627 (cIAI) = 915 subjects.
   b) The P3 RCT at 2:1 will treat 117 *P. aeruginosa* cases with X-1 vs. only 78 at 1:1.
   c) This will lead to a total safety database for X-1 at full dose / duration of 40 (Phase 1) + 10 (Phase 2) + 48 (HABP/VABP, P3 RCT) + 69 (cIAI, P3 RCT) + 75 (P3 OL LTO) = 242.

A.3 P3 Open-label study for patients with limited treatment options

Title: A prospective non-comparative study of X-1 for intraabdominal infection (cIAI), hospital-associated bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), or complicated urinary tract infection (cUTI) in patients with limited treatment options.

Inclusions:

1) Standard rules for cUTI, cIAI, HABP, VABP
2) Positive culture for *P. aeruginosa*
3) Susceptibility pattern of the isolate combined with the clinical picture of the patient makes other agents inappropriate (i.e., the patient has limited treatment options)

Endpoints and statistics

- Descriptive statistics only
- Same endpoints as for P3 RCT
- For context, a comparison with historical response rates (e.g., the rates provided in the FDA guidance summaries) is proposed by the sponsor. It is noted that any such comparisons will need to be interpreted with great caution given the likely differences in the patients enrolled in this open-label study (the likelihood of worse prognosis in patients with no other treatment options and the likelihood of greater co-morbidities) compared to the populations from which response rates were derived in FDA guidance documents.

Treatments:

- cUTI: X-1 (+ ertapenem if needed)
- cIAI: X-1 (+ ertapenem if needed)
- HABP/VABP: X-1 + 2nd agent if appropriate (+ ertapenem if needed)

A.4 Results

A.4.1 Overview

The trial program was implemented over a 36-month period at 250 sites in 20 countries. *(Note: detailed feasibility work has not been done for this case study — estimates are taken from recent experience. Assumed rate for HABP/VABP is ~0.06 per site/month; for cIAI is ~0.14/month. These are reductions from usual rates due to presumption that not all will pass the Pseudomonas screen.)*

The rate of positive baseline culture was as predicted and the by-indication subgroups were all enrolled to the target N. (*Note: No allowance made in these numbers for case evaluability, major protocol violations, and such. It may be appropriate to plan to slightly over enroll by ~1-2%.)*

Patient disposition was thus (see A.4.1.1 for more on the math):

- 1888 patients who met all other criteria were evaluated by the rapid test.
  - HABP/VABP: 600 screened (assumes true rate of 15%, test sensitivity of 80%, test PPV of 25%, 72 culture-positive needed; hence screen 72/0.15/0.80 = 600)
  - cIAI: 1288 screened (assumes true rate of 10%, test sensitivity of 80%, test PPV of 16.5%, 103 culture-positive needed; hence screen 103/0.10/0.80 = 1288)
- Of these, 915 were enrolled: 288 with HABP/VABP and 627 with cIAI
- Of the 288 with HABP/VABP, 192 were randomized to X-1 and 96 to control
  - Of these, 48 and 24, respectively, had a positive culture for *P. aeruginosa*
- Of the 627 with cIAI, 418 were randomized to X-1 and 209 to control
  - Of these, 69 and 34, respectively, had a positive culture for *P. aeruginosa*

PK: Population PK was done in the program and the target exposures were achieved.

Prior therapy: 75% of the subjects in the HABP/VABP subgroup received at least one dose (but less than 24h) of prior effective therapy.

Concomitant therapy: 95% of subjects in the HABP/VABP subgroup received amikacin for one day, 80% for 2 days, 40% for 3 days, and 20% for 4+ days. 80% of isolates were amikacin susceptible. *For purposes of this scenario, we assume all isolates are meropenem susceptible. In reality, the numbers would need to be inflated 10-30% to compensate for loss of cases due to carbapenem resistance.*

A.4.1.1 Sidebar on screening math (not the focus of the day, but may help to see)

Background Theory

		True pathogen positive		
		Y	**N**	
Diagnostic	**Y**	A	B	A+B
	N	C	D	C+D
		A+C	B+D	N

PPV (% Diag+ who truly have pathogen) =A/A+B;
NPV (% Diag- and truly no pathogen) =D/C+D

Sensitivity (% true positives identified) = A/A+C;
Specificity (% true negatives correctly ID'd as negative) =D/B+D

Example with N=600, true positive rate of 15%

		True pathogen positive		
		Y	**N**	
Diagnostic	**Y**	72	216	288
	N	18	294	312
		90	510	600

1. True positive pathogens: 15% of 600 = 90.
2. Sensitivity of 80% means A/A+C = **72**/90 = 80%
3. PPV of 25% means A/A+B = 25% (→ 72/288)
4. Specificity = D/B+D = 294/510 = 58%
5. NPV = D/C+D = 294 / 312 = 94%

Note that sensitivity and specificity are fixed for a particular type of test whereas PPV/NPV depend upon prevalence: If prevalence=100%, every positive is true → PPV=100%; if prevalence=0%, every positive is false → PPV=0%.

A.4.2 Efficacy in the patients with a positive culture for *P. aeruginosa*

P3 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%)

Commentary: The differences in results are centered on zero but the 95% CI for the delta extends slightly below M1 for each indication (M1 is 20% for HABP/VABP, 14% for cIAI).

P3 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 comorbidities.

Integrated*

Success / N (%)	X-1 + ertapenem
HABP/VABP	43/58 (74.1%)
cIAI	65/84 (77.4%)
cUTI	43/50 (86.0%)

*The OL LTO cases are different in character from the patients enrolled in the P3 RCT, but the aggregate data are shown just in case you want to see them.

A.4.3 Safety

P3 RCT

28-day All-Cause Mortality (ACM)	X-1 + ertapenem	Meropenem
HABP/VABP	10/48 (21.3%)	5/24 (20.8%)
cIAI	3/69 (4.3%)	1/34 (2.9%)

P3 OL LTO

28-day All-Cause Mortality (ACM)	X-1 + ertapenem
HABP/VABP	4/10 (40.0%)
cIAI	1/15 (6.7%)
cUTI	1/50 (2.0%)

Integrated

- The total safety population on X-1 is 610 patients. Of these, 493 received only 2-4 days of therapy before being removed from the study for lack of a positive culture. 117 remained on study drug for the full course of therapy.
- Similar rates of discontinuations for AEs (3-4%, both arms)
- No duration-related patterns of AEs
- Slightly higher number of patients had elevated (mainly 2-3-fold; none > 5-fold; no changes in bilirubin) transaminases in X-1 arm
- No other differential pattern of AEs between the two arms

A.4.4 Microbiology

- All isolates were susceptible either to X-1 or to the combination of meropenem + amikacin. That is, initial randomized (and sometimes combination therapy) was predicted to have microbiologic activity in both arms. In reality, there might be a portion of cases where the control arm was inactive and hence a limited comparison with initial placebo is available, but such data would serve to simplify the case and this possibility is ignored for today.
- Similar rates of culture clearance in the two arms
- Similar rates of emergence of resistance (1-2 cases in each arm)

A.4.5 Noteworthy risks

1) Is ertapenem at 1g daily as efficacious as meropenem at 1g every 8 h for the non-*Pseudomonas* component of HABP/VABP?
   a) The available data suggest so, but formal modeling should be undertaken.
2) Despite the size of the program, the N with *P. aeruginosa* is actually small.
   a) Single patient changes are impactful.
3) The margins of 30% and 25% have not been agreed with the agencies
   a) The proposed 30% for NP is strong: This is M1 using the 95-95 rule but before discounting.
   b) The proposal for 25% for cIAI seems plausible (puts the effect size in the same range as other major infections; has some literature basis) but needs more review & discussion
      i) At a margin of 20%, need 982 in cIAI (+358) for a total program of 1270
      ii) At a margin of 15%, need 1739 in cIAI (+1115) for a total program of 2027
      iii) At a margin of 14%, need 2000 in cIAI (+1376) for a total program of 2288
4) On top of the margin question, the program may need to be as much as a further 30% bigger as the sample size math has not been adjusted for either of the following issues:
   a) Unevaluable cases
   b) Rates of discontinuation from the P3 RCT due to meropenem resistance (and hence the need to add a different second drug to amikacin)
   c) Predicted response rate of 80% might be too high — numbers would need to be a larger if 65-70% response rates are anticipated.

A.4.6 Discuss!

- What are the pros and cons of such data from a clinical perspective?
- What are the pros and cons of such data from a regulatory perspective?
- How do you think about using the data from the two body sites (e.g., pooling vs. take each as is)?
- How do you weight (and analyze) the impact of concomitant therapy in the HABP/VABP subset?
  - Are there ways to reduce concomitant therapy?
- What options exist to the use of ertapenem as the companion to X-1?
- Could the comparator be a Best Available Therapy (BAT) rather than meropenem?

A.4.7 The same data could be seen through a different lens

It is sometimes suggested that we use a larger alpha. To model the effect of this, use alpha of 0.10 (instead of 0.05) and hence use 90% CIs to describe the data:

P3 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%

These confidence limits now sit within M1 for both indications. Does this change your view?

B P3 Program, Scenario B

B.1 Overview

All conditions are identical to Scenario A. The only differences are in the efficacy results.

B.2 Efficacy in the patients with a positive culture for *P. aeruginosa*

P3 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%)

Commentary: These are the worst possible results within the limits of the already generous margins that were proposed in Scenario A (30% for HABP/VABP and 25% for cIAI).

P3 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 comorbidities.

Integrated

Success / N (%)	X-1 + ertapenem
HABP/VABP	40/58 (69.0%)
cIAI	60/84 (71.4%)
cUTI	43/50 (86.0%)

B.3 Safety

P3 RCT

28-day ACM	X-1 + ertapenem	Meropenem
HABP/VABP	14/48 (29.2%)	5/24 (20.8%)
cIAI	3/69 (4.3%)	1/34 (2.9%)

P3 OL LTO

28-day ACM	X-1 + ertapenem
HABP/VABP	4/10 (40.0%)
cIAI	1/15 (6.7%)
cUTI	1/50 (2.0%)

Integrated

- Otherwise similar to Scenario A.
- The 28-day ACM (All-Cause Mortality) is the inverse of the success rate. In relative terms, the mortality rate is thus 40% higher in the X-1 arm.

B.4 Discuss!

- What are the pros and cons of such data from a clinical perspective?
- What are the pros and cons of such data from a regulatory perspective?
- How do you think about using the data from the two body sites (e.g., pooling vs. take each as is)?
- How do you weight (and analyze) the impact of concomitant therapy in the HABP/VABP subset?

B.5 And here is the math for a 90% CI

P3 RCT

Success / N (%)	X-1 + ertapenem	Meropenem	Delta
HABP/VABP	34/48 (70.8%)	19/24 (79.2%)	-8.3 (-25.7 to 9.1%)
cIAI	50/69 (72.5%)	27/34 (79.4%)	-7.5 (-21.4 to 7.5%

Does this alter your view?

C P3 Program, Scenario C

C.1 Overview

All conditions are identical to Scenario A. The only difference is that the patient selection device fails in practice and the actual rates of positive cultures for *P. aeruginosa* are 15% and 10% for HABP/VABP and cIAI. The sponsor is aware of the unblinded culture rate but does not have funding to increase the trial size by 2/3rd to compensate. Hence the trial is run to the planned size and the resulting smaller N for analysis is anticipated.

C.2 Efficacy in the patients with a positive culture for *P. aeruginosa*

P3 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%)

Commentary: These are the worst possible results within the boundaries of the already very generous margins. Deltas are ~0, but margins are as wide as in Scenario B.

P3 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 comorbidities.

Integrated

Success / N (%)	X-1 + ertapenem
HABP/VABP	28/39 (71.8%)
cIAI	43/56 (76.8%)
cUTI	43/50 (86.0%)

C.3 Safety

P3 RCT

28-day ACM	X-1 + ertapenem	Meropenem
HABP/VABP	7/29 (24.1%)	3/14 (21.4%)
cIAI	2/41 (4.8%)	1/20 (5.0%)

P3 OL LTO

28-day ACM	X-1 + ertapenem
HABP/VABP	4/10 (40.0%)
cIAI	1/15 (6.7%)
cUTI	1/50 (2.0%)

Integrated 5) Otherwise similar to Scenario A.

C.4 Discuss!

- What are the pros and cons of such data from a clinical perspective?
- What are the pros and cons of such data from a regulatory perspective?
- The stats could be reworked to use a larger alpha (e.g., 0.1 instead of 0.05). Is this helpful?

D P3 Program, Scenario D

D.1 Overview: Very rare pathogen

In this Scenario (and in Scenario E to follow), the agent has narrow-spectrum activity vs. a rare Gram-negative bacterium (perhaps *Acinetobacter*). The maximum rate of positive cultures for the target pathogen is 5% in any indication.

Preclinical data are as for the main case. Phase 1 data and good preclinical data in support of exposure (dose) selection are available. It may not be possible to do the non-CF bronchiectasis program due to the infrequency of the pathogen.

D.2 Possible designs (80% success, 85% power)

Infection	Margin	Ratio	N1 / N2 (Total N)	% Culture+	Culture+ N1/N2 (ME)
Any	35%	1:1	469 / 469 (938)	5%	23 / 23
		2:1	704 / 352 (1056)		35 / 18
	30%	1:1	638 / 638 (1276)		32 / 32
		2:1	958 / 479 (1437)		48 / 24
	25%	1:1	919 / 919 (1838)		46 / 46
		2:1	1380 / 690 (2070)		69 / 35

D.3 Sponsor: Typical amounts of clinical data can't be generated in man

1) The small number of cases will struggle to be convincing
2) Even a single indication would approach or exceed 2000 patients with margins ≤ 25%.

D.4 The Animal Rule is considered

Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible (21 CFR 314.600 for drugs and 21 CFR 601.90 for biological products)): This subpart applies to certain new drug products that have been studied for their safety and efficacy in ameliorating or preventing serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances. This subpart applies only to those new drug products for which definitive human efficacy studies cannot be conducted because it would be unethical to deliberately expose healthy human volunteers to a lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substance; and field trials to study the product's effectiveness after an accidental or hostile exposure have not been feasible.

The following four criteria have to be met if evidence from animal studies is used to provide substantial evidence of effectiveness:

1. There is a reasonably well-understood pathophysiological mechanism of toxicity of the substance and its prevention or substantial reduction by the product;
2. The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single species that represents a sufficiently well-characterized animal model for predicting the response in humans;
3. The animal study endpoint is clearly related to the desired endpoint in humans, generally the enhancement of survival or prevention or major morbidity; and
4. The data or information on the PK & PD of the product or other relevant data or information, in humans and animals, allows selection of an effective dose in humans.

Adequate and well-controlled animal efficacy studies are required for approval under the Animal Rule. The animal efficacy studies substitute for efficacy trials in humans, and therefore, the assessment of efficacy in animals should use endpoints that demonstrate an important clinical benefit,

generally the enhancement of survival or prevention of major morbidity. Studies should be designed to mimic the ultimate clinical use of the investigational drug and to achieve meaningful outcomes similar to the effectiveness desired in humans. Data from in vitro studies, other types of animal studies, and human studies may be supportive.

The animal species selected for the adequate and well-controlled efficacy studies must exhibit key characteristics of the human disease when the animal is exposed to the challenge agent and the drug's effect in the animal species should be expected to be predictive of the effect in humans. This allows extrapolation from the animal data to an effective dose and regimen for humans. Generally, the efficacy of the drug should be demonstrated in more than one animal species expected to react with a response predictive for humans.

For a drug approved under the Animal Rule, there are three additional requirements:

1. Postmarketing studies (e.g., field studies) to provide evaluation of safety and clinical benefit if circumstances arise in which a study would be feasible and ethical (i.e., in the event an emergency arises and the drug is used).
2. Restrictions to ensure safe use, if needed (e.g., restricting distribution to facilities or health care practitioners with special training, requiring specified types of follow up, or imposing record keeping requirements).
3. Information to be provided in the labeling that explains that for ethical or feasibility reasons, the drug's approval was based on efficacy studies conducted in animals alone.

See http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm399217.pdf for more details on the requirements for the supporting animal model.

Based on natural history studies and animal model development work, the ventilated piglet model using a pedigreed strain of ***P. aeruginosa*** and survival endpoint was found to be an appropriate animal model reflective of human VABP. In a study of 30 piglets, a humanized exposure of X-1 was superior to placebo therapy (18/20 X-1 treated and 0/10 placebo-treated piglets survived, p = 0.005).

D.5 A clinical program in nosocomial pneumonia is proposed

As all indications have the same low pathogen rate, a small P3 program in nosocomial pneumonia is proposed because of the clarity of the endpoint and the importance of the disease. At 80% success, 35% NI margin, 95% confidence interval, 80% power, 2:1 randomization, and 5% culture positive:

3) A study of 484 vs. 242 (total 726) would yield 24 and 12 on X-1 and control, respectively.
   a) At parity: 19/24 (79%) vs. 10/12 (83%), difference of 4.2%, 95% CI = -27 to +18%
   b) At boundary case: 18/24 (75%) vs. 10/12 (83%), difference of 8.3%, 95%CI = -31 to 15%

As in Scenario A, most patients receive an initial concomitant antimicrobial agent. A small OL LTO program is implemented and gives data similar to Scenario A. Safety data similar to Scenario C.

D.6 Discuss!

1) What are the pros and cons of such data from a clinical perspective?
2) What are the pros and cons of such data from a regulatory perspective?
3) Effectively, the clinical data are the field trial that accompanies AR-approved drugs when used. How do you weight the Animal Rule-compliant animal model data relative to the human data?
4) Could data like this compensate for issues of interpreting the impact of concomitant therapy?
5) The hypothetical program in this scenario was conducted in nosocomial pneumonia. Would you prefer to see it conducted in cIAI? Please discuss the trade-off of lack of concomitant therapy (cIAI) vs. impact of surgery and drainage.
6) Would it be better to replace the RCT with an OL study with External (Historical) Controls? This would put more subjects on X-1. Might also enrich for co-morbidities to strengthen the story.

E P3 Program, Scenario E

E.1 Overview

The situation is the same as for Scenario D.

E.2 The problem that emerges

The Sponsor considers the various animal models of infection currently available and is unable to identify a fully satisfactory animal model in HABP/VABP for the target organism. Development of such a model will take 2-3 years (if it is possible at all).

The Sponsor is now weighing the options and considering if a Scenario D-like program alone in humans might be the best path forward. The program would have the typical data from preclinical PK-PD programs, but a fully validated Animal Rule-compliant preclinical model would not be available.

E.3 Proposed program design

All you have are the clinical efficacy and safety data from Scenario D. No piglet model data.

The sponsor could either run the RCT with a comparator or simply run it is an open-label trial with external (historical) controls. The latter path has the strength of putting more patients on X-1. Having a greater severity of illness in the enrolled cases might also strengthen the story.

E.4 Discuss!

See questions from Scenario D.

F Scenario F

Audience choice!

For discussion: What other program options could be considered?