Antibiotic X-1: A promising antibiotic for pan-drug resistant P. aeruginosa (From 2016 U.S. Food and Drug Administration Workshop on Antibiotic Clinical Tirals-Unmet Needs https://www.fda.gov/drugs/news-events-human-drugs/facilitating-antibacterial-drug-development-patients-unmet-need-and-developing-antibacterial-drugs

Background

This document presents a realistic but entirely hypothetical candidate antibiotic. The antibiotic is of a novel class and has activity limited to *P. aeruginosa,* including pan-drug resistant (PDR) strains. It offers very clean microbiology — resistance is uncommon and seems to develop only rarely.

The drug has an IV formulation with straightforward pharmacology. The pharmacokinetic/ pharmacodynamic data has established target exposure and a dose regimen is found that produces this exposure. The drug is found to penetrate into the lung in a Phase 1 lung epithelial lung fluid (ELF) pharmacokinetic study, and in a small Phase 2 study it was shown to reduce the bacterial burden in adults with non-cystic fibrosis (CF) bronchiectasis.

Overview

Drug X-1 is an injectable antibacterial drug with activity limited to *Pseudomonas aeruginosa*. It has no activity against Gram-positive organisms or other Gram-negative organisms including members of the Enterobacteriaceae family. Drug X-1 has a new mechanism of action: it acts on a novel target that is unique to *P. aeruginosa.*

Nonclinical data: General safety

Signals for hepatotoxicity and hematologic toxicity have been identified in the studies conducted so far. In both mice and dogs, a dose-dependent increase in liver enzymes was seen. Histopathologic examination of the liver showed macrophage infiltration and reversible focal hepatocellular necrosis. Hematologic toxicity with some evidence for neutropenia was seen only at the highest dose evaluated.

At the proposed dose, safety margin for liver enzyme elevation is 4 times the targeted therapeutic dose and liver histopathology changes occurs at 8 times the targeted therapeutic dose.

At the proposed dose, safety margin for hematologic events is 8 times the targeted therapeutic dose.

Nonclinical data: Microbiology

Drug X-1 is mainly active against *Pseudomonas aeruginosa.* The MICs have a bimodal distribution with the wild type (non-resistance gene mechanisms carrying isolates) ranging from 0.06 – 1 mg/L and the non-wild type (potential resistance mechanism carrying isolates) with MICs >4 mg/L.

In a global microbiology testing survey of 850 recent *P. aeruginosa* isolates, 99% of isolates tested had an MIC ≤ 1 mg/L. The MIC distribution for wild-type is centered on an MIC of 0.25 mg/L with ~5% of isolates at the low (0.06 mg/L) and high (1 mg/L) ends of the spectrum. Hence, both the MIC90 (concentration needed to inhibit 90% of isolates) and the MIC99 (concentration needed to inhibit 99% of isolates) would be 1 mg/L.

In serial passage studies used to induce antimicrobial resistance, the frequency of resistance emergence is < 1 in 10^10 organisms (one in 10 billion). The mechanism of resistance has not yet been determined. Drug X-1 has variable activity against other *Pseudomonas* species (MICs 0.03 to >8 mg/L). As predicted from its mechanism of action, Drug X-1 shows no significant activity against other Gram-negative bacteria (MICs, >16 mg/L) or Gram-positive bacteria (MICs > 256 mg/L).

In animal models of experimental infection, Drug X-1 demonstrated efficacy in treating infections caused by *P. aeruginosa* (X-1 mean inhibitory concentrations of 0.03 – 16 mg/L) including thigh infection models (on the basis of colony forming units/ gram tissue (CFU/g), lung (CFU/g reduction), peritonitis (CFU/g reduction), and sepsis models (on the basis of survival).

Human clinical trials data

The sponsor has completed Phase 1 studies and one Phase 2 study.

- Phase 1 studies include, healthy volunteer studies, epithelial lining fluid (ELF) pharmacokinetic studies (patients with ventilator-associated pneumonia), renal and hepatic impairment
- Thorough QT (effects on cardiac conduction-safety) and drug-drug interaction studies being planned.

A population pharmacokinetic model established with data from Phase 1 pharmacokinetic study and a simulation conducted with the population pharmacokinetic model showed that a 100 mg IV infusion over 1 hour every 8 hours would provide 40% free drug time>MIC for an MIC of 1 mg/L in more than 90% of patients using parameter estimates from healthy volunteers and 40% inflated variance. An appropriate dose adjustment that maintains the ≥ 90% target attainment is also possible for different degrees of renal impairment (X-1 is cleared by the kidneys, see next paragraph).

A mass balance study showed that Drug X-1 is primarily excreted by the kidney with negligible metabolism. The terminal elimination half-life of Drug X-1 in healthy subjects was approximately 2 hours.

An *in vitro* metabolism study found that X-1 does not inhibit or induce CYP enzymes nor does it have any drug transporter interactions. No significant drug-drug interactions are predicted.

The ELF to plasma concentration ratio of Drug X-1 was approximately 40% and 25% in humans and mice, respectively.

A Phase 2 proof of concept study was conducted in patients with non-cystic fibrosis bronchiectasis. The drug was given as monotherapy to 10 patients. At the proposed therapeutic dose, the pharmacokinetic parameters were essentially the same as in the healthy volunteer PK study. Over the course of the 14-day Phase 2 study in non-cystic fibrosis bronchiectasis, *Pseudomonas* bacterial sputum colony forming units/gram were reduced > 1 log10 in 9 of 10 subjects and by > 2 log10 in 4 of 10 subjects. No adverse events of concern were seen.

Clinical trial submitted for approval

1. Below are recently reported frequencies of Pseudomonas aeruginosa (includes both susceptible and MDR strains) from published studies of **nosocomial pneumonia (NP), complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI) and Acute bacterial skin and soft tissue infection (ABSSSI).**

2.1 Frequency of *P. aeruginosa* (% of all enrolled)

	Lit.	Recent drug #1	Recent #2	Recent #3	Kollef	Consensus
NP	20%[a, b]	13%	10%	23%	26%	15%
cIAI	10%[c]	7%				10%
cUTI	3%[d]	4.30%	2.00%	2.40%		3%
ABSSSI	Rare		Rare			Rare

References

a. Chastre J et al. Efficacy and safety of IV doripenem versus imipenem in ventilator-associated pneumonia: A multicenter, randomized study. Crit Care Med 36:1089–1096, 2008.
b. Brun-Buisson C et al. Treatment of ventilator-associated pneumonia with piperacillin-tazobactam/amikacin vs. ceftazidime/amikacin: A multicenter, randomized controlled trial. Clin Infect Dis 26;346-54, 1998.
c. Lucasti C et al. Efficacy and Tolerability of IV Doripenem Versus Meropenem in Adults with Complicated Intra-Abdominal Infection: A Phase III, Prospective, Multicenter, Randomized, Double-Blind, Noninferiority Study. Clin Ther 30:868-83, 2008.
d. Naber KG et al. Intravenous doripenem at 500 milligrams versus levofloxacin at 250 milligrams, with an option to switch to oral therapy, for treatment of complicated lower urinary tract infection and pyelonephritis. Antimicrob Agents Chemother. 53:3782-92, 2009
e. Kollef, M. H., J. Chastre, et al. (2014). "Global prospective epidemiologic and surveillance study of ventilator-associated pneumonia due to *Pseudomonas aeruginosa*." Crit Care Med 42(10): 2178-2187. *A higher rate, but note that non-standard VAP definitions were used.*

The company proposed to perform a randomized clinical trial of X-1 for intraabdominal infection (cIAI), hospital associated bacterial pneumonia ventilator-associated bacterial pneumonia (HABP)/VABP)

Patient inclusion criteria for the study:

1. Clinical signs and symptoms of 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)

Clinical response endpoints:

- **Primary analysis endpoint is microbiology-eligible population intent-to-treat population** (all patients with a positive baseline culture for *P. aeruginosa*)
- **cIAI: Standard clinical response rules** (complete resolution or significant improvement in signs & symptoms at the test of cure visit between 28 and 35 days after randomization)
- **HABP-VABP: All-cause mortality at 28 days after randomization**

Treatment Randomization:

- Treatment arms: **cIAI**:
    - **ertapenem + X-1 vs. meropenem + placebo** (ertapenem is a carbapenem without activity against P. aeruginosa, meropenem is a carbapenem with activity against *P. aeruginosa)*
    - **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 + 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
    - 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.

To randomize at 2:1 in both indications:

- The Phase 3 randomised controlled trial will enroll 288 (HABP/VABP) + 627 (cIAI) = **915 subjects total.**

Success will be declared if both infection subsets achieve non-inferiority within the bounds of the proposed wide study margins**-30% non-inferiority for HABP/VABP and 25% for cIAI.** These margins are larger than typically justified (although the FDA has agreed on the basis of a) Unmet Need b) The 95-95 rule for the HABP-VABP data gives an undiscounted M1 of 29%.

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

STUDY RESULTS

The trial program was implemented over a 36-month period at 250 sites in 20 countries.

1888 patients who met all other criteria were evaluated by the rapid test.

- **600 HABP/VAP patients screened → 288 enrolled**
    - 192 randomized to X-1 drug group (48 with positive P. aeruginosa cultures)
    - 96 randomized to control (24 with positive *P. aeruginosa* cultures)
- **1288 cIAI screened → 628 enrolled**
    - 418 randomized to X-1 (69 with positive *P. aeruginosa* cultures)
    - 209 randomized to control (34 respectively, had a positive culture for *P. aeruginosa*)

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 : 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.

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).

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

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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%)

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.

Similar rates of culture clearance in the two arms

Similar rates of emergence of resistance (1-2 cases in each arm)

QUESTIONS FOR GROUP DISCUSSION

1. **Do you think this study provides sufficient evidence for approving X-1 for the treatment of HABP/VABP or cIAI caused by Pseudomonas pneumonia?**
2. **Do you think this study provide sufficient data for using X-1 in the treatment of pneumonia or complicated intraabdominal infection caused by MDR P. aeruginosa?**
3. **Do you think their are sufficient numbers of patients with *P. aeruginosa* infections enrolled in the study? What do you think would be the effect of 1-2 patients changing outcome on the overall trial results?**
    1. Recall: HABP/VAP: 48 X-1 patients vs. 24 controls
    2. Recall: cIAI: 68 X-1 patients vs. 34 controls
4. **What is your impression about the possible effect of prior antibiotic therapy?... concomitant amikacin? Should it have been allowed?...Does it obscure evaluation of the efficacy of X-1 for *Pseudomonas aeruginosa*?**
5. **What are the pros and cons of this study from a clinical perspective? Would you feel comfortable using the drug for treatment of serious *P. aeruginosa* infections**
6. **Do you think this drug would be immediately available in low-middle income countries? What are the possible factors that would influence its availability?**