Overview

This document presents a realistic but entirely hypothetical candidate drug. The drug is of a novel class and has activity limited to *P. aeruginosa*. It offers very clean microbiology — resistance is uncommon and seems to develop only rarely.

The drug has an IV presentation with straightforward pharmacology. The PK-PD information identifies a well-justified 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 ELF study and is shown in a small Phase 2 study to have an effect on bacterial burden in adults with non-cystic fibrosis (CF) bronchiectasis.

In short, the drug is entirely plausible and appears useful. The problem is that the clinical development program is difficult due to the relatively low frequency of this pathogen.

The preclinical picture, Phase 1, and Phase 2 data are provided in detail in Section 1 of the document. Section 2 provides some data that are useful in thinking about options for a clinical program.

A variety of Phase 3 scenarios are presented in Section 3 (this section will be shared during the workshop). These scenarios show increasingly difficult situations built around the theme of a narrow-spectrum agent that targets a low-frequency pathogen. The ability to enroll patients with the target pathogen is progressively reduced in each scenario.

In the final scenarios, the rate of pathogen recovery becomes very low and thus makes the case representative of agents active only against really rare pathogens such as A. *baumannii*.

1 Drug X-1

1.1 Overview

Drug X-1 is an injectable antibacterial drug with activity limited to *P. 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*.

1.2 Nonclinical Data: General

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 is 8 times the targeted therapeutic dose.

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

1.3 Nonclinical data: Microbiology and PK-PD

Drug X-1 is mainly active against *P. aeruginosa.* The MICs have a bimodal distribution with the wild type ranging from 0.06 – 1 mg/L and the non-wild type with MICs >4 mg/L. In a

global survey of 850 recent *P. aeruginosa* isolates, 99% of isolates 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 and the MIC99 would be 1 mg/L.

In serial passage studies, the frequency of emergence of resistance is < 1 in 10^{10} organisms. 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 infection, Drug X-1 demonstrated antibacterial activity in treating infections caused by *P. aeruginosa* (MICs 0.03 – 16 mg/L) including thigh (on the basis of CFU/g reduction), lung (CFU/g reduction), peritonitis (CFU/g reduction), and sepsis models (on the basis of survival).

Dose fractionation studies in a hollow-fiber model and murine thigh and pneumonia infection models showed that the percent time that free-drug concentrations are above the MIC over a dose interval (%fT > MIC) is the PK/PD index associated with the bacterial killing effect. The magnitudes of the PK/PD index for bacterial stasis, 1-log kill and 2-log kill against *P. aeruginosa* determined in a murine thigh infection model were 30%, 40% and 50% fT>MIC, respectively. The corresponding values determined in a murine pneumonia infection model were similar.

1.4 Clinical Data

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

- Phase 1 studies include, HV studies, ELF, renal and hepatic impairment
- Thorough QT and Drug-drug interaction studies being planned

A population PK model established with data from Phase 1 PK studies and a simulation conducted with the population PK model showed that a 100 mg IV infusion over 1 hour every 8 hours would provide 40% fT>MIC for an MIC of 1 mg/L in more than 90% of patients using parameter estimates from HVs 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 finds that X-1 does not inhibit or induce CYP enzymes nor does it have any transporter liabilities. 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-CF bronchiectasis. The drug was given as monotherapy to 10 patients. At the proposed therapeutic dose, the PK parameters were essentially the same as in the healthy volunteer PK study. Over the course of the 14-day Phase 2 study in non-CF bronchiectasis, sputum CFU/g were reduced > 1 $\log_{10}$ in 9 of 10 subjects and by > 2 $\log_{10}$ in 4 of 10 subjects. No adverse events of concern were seen.

2 Designing the clinical program: Useful data

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.*

2.2 Consequences of these rate data

Although a rapid patient selection tool would be helpful when seeking out a rare pathogen, it is still necessary to screen enough patients to find the targeted subset. That is, if the target pathogen occurs at a rate of 10%, then accruing 100 patients with the target pathogen would require screening of at least 1000 patients.

Further, the target of 1000 assumes that the device has perfect sensitivity (that it never misses a case). If the sensitivity (probability of a positive test if the patient actually has the target condition) is < 100%, then the number to screen is even higher. This will impact running time of the program because it increases the number who need to be screened.

Here are some sample calculations:

Desired N with illness	100			10		
True rate of illness in the population	10%			15%		
Test sensitivity: TP / (TP + FN)	100%	80%	50%	100%	80%	50%
PPV of test: TP / (TP + FP)	15%	15%	15%	25%	25%	25%
N to screen: Desired N / True rate / Sensitivity	1000	1250	2000	667	833	1333
N to enroll: Desired N / PPV	667	667	667	400	400	400

2.3 Non-Inferiority Margins: M1 and M2

Response rates	Placebo	Active	DPE*	M1	M2
NP	38%	80%	42%	20%	10%
cIAI	61%	82%	21%	14%	10%
cUTI	33%	70%	37%	30%	10%

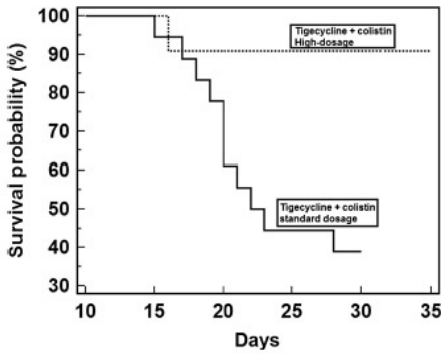
* DPE = difference in point estimates

FDA have reviewed available literature and estimated response rates for placebo (or inactive) therapy. Response rates for active therapy from other trials have been generated as well. The resulting estimates are shown in the table above.

- DPE is the difference in point estimates of response rates for placebo and active therapy. No adjustment is made for the precision of these two estimates.
- M1 is a margin less than DPE that is thought to be the largest reliable estimate of the treatment effect based on discounting that incorporates the uncertainty around the individual point estimates. This can be done using the "95-95" rule in which the extremes of the 95% CIs for active and placebo are used to estimate effect size.
- M2 is a margin less than M1 that is proposed as a clinically acceptable margin and reflects the degree of potential loss of efficacy that is acceptable.
- The values shown here for M2 are the margins recommended in FDA's indication-specific guidance for a standard development program.
- Larger values of M2 (wider margins) have been accepted for selected unmet need situations.

These further details on the estimation of M1 and M2 may be helpful:

1) HABP-VABP
   a) Mortality with placebo/inadequate therapy: 62%, 95% CI = 52-71%
   b) Mortality with adequate therapy: 20%, 95% CI: 18-23%
   c) Difference between upper and lower 95% CI bounds: 29%
   d) The 29% difference was reduced to an M1 of 20% to allow for uncertainty of the data.
   e) All figures must be inverted (subtract from 100%) to convert to the success rates used above.
2) cIAI
   a) Success with placebo/no treatment was 61% (57-65%).
      i) This estimate is believed very conservative as the placebo/no treatment estimate was taken from patients undergoing elective intra-abdominal surgery who did NOT have an infection at the time of the procedure.
   b) Success with treatment: 82% (79-84%)
   c) Difference between upper and lower 95% CI bounds: 14%
   d) M1 is maintained at 14% because the estimate is believed very conservative.
3) Di Carlo (2013) reports 30 patients who developed infections after open abdominal surgery
   a) KPC-producing *K. pneumoniae*. (Almost?) all with IAI. All with bacteremia. Some other sites.
   b) "ICU mortality" (time frame unclear): 40% (12/30)
   c) 28-day ACM was ~60% in those receiving a lower dose of tigecycline + colistin and ~10% in a group receiving higher doses (K-M at right, ~15/group).



References

a. FDA (2015). Guidance for Industry: cUTI.
b. FDA (2015). Guidance for Industry: cIAI.
c. FDA (2014). Guidance for Industry: HABP & VABP.
d. Di Carlo, P. et al. (2013). BMC Anesthesiol 13(1): 13.

2.4 Some sample sizes

Assume sizing for 80% response, 95% confidence intervals, 80% power, 1:1 randomization, and the specified non-inferiority margin. The final statistics are done only for patients from whom *P. aeruginosa* is cultured.

Calculations follow Pocock (Fundam Clin Pharmacol 2003;17:483-90) without continuity correction. On average, add another 7-8% to N to use continuity correction.

10% non-inferiority margin, 80% power						
% culture-positive	N/arm	Total N		% culture-positive	N/arm	Total N
100%	251	502		25%	1005	2010
75%	335	670		20%	1256	2512
50%	502	1004		15%	1674	3348
40%	628	1256		10%	2512	5024
30%	837	1674		6%	4186	8372

10% non-inferiority margin, 85% power						
% culture-positive	N/arm	Total N		% culture-positive	N/arm	Total N
100%	287	574		25%	1149	2298
75%	383	766		20%	1437	2874
50%	575	1150		15%	1915	3830
40%	718	1436		10%	2873	5746
30%	958	1916		6%	4788	9576

10% non-inferiority margin, 90% power						
% culture-positive	N/arm	Total N		% culture-positive	N/arm	Total N
100%	336	672		25%	1345	2690
75%	448	896		20%	1681	3362
50%	672	1344		15%	2242	4484
40%	841	1682		10%	3362	6724
30%	1121	2242		6%	5604	11208

12.5% non-inferiority margin, 80% power						
% culture-positive	N/arm	Total N		% culture-positive	N/arm	Total N
100%	161	322		25%	643	1286
75%	214	428		20%	804	1608
50%	321	642		15%	1072	2144
40%	402	804		10%	1607	3214
30%	536	1072		6%	2679	5358

12.5% non-inferiority margin, 85% power						
% culture-positive	N/arm	Total N		% culture-positive	N/arm	Total N
100%	184	368		25%	736	1472
75%	245	490		20%	919	1838
50%	368	736		15%	1226	2452
40%	460	920		10%	1839	3678
30%	613	1226		6%	3065	6130

12.5% non-inferiority margin, 90% power						
% culture-positive	N/arm	Total N		% culture-positive	N/arm	Total N
100%	215	430		25%	861	1722
75%	287	574		20%	1076	2152
50%	430	860		15%	1435	2870
40%	538	1076		10%	2152	4304
30%	717	1434		6%	3587	7174

15% non-inferiority margin, 80% power						
% culture-positive	N/arm	Total N		% culture-positive	N/arm	Total N
100%	112	224		25%	447	894
75%	149	298		20%	558	1116
50%	223	446		15%	744	1488
40%	279	558		10%	1116	2232
30%	372	744		6%	1860	3720

15% non-inferiority margin, 85% power						
% culture-positive	N/arm	Total N		% culture-positive	N/arm	Total N
100%	128	256		25%	511	1022
75%	170	340		20%	638	1276
50%	255	510		15%	851	1702
40%	319	638		10%	1277	2554
30%	426	852		6%	2128	4256

15% non-inferiority margin, 90% power						
% culture-positive	N/arm	Total N		% culture-positive	N/arm	Total N
100%	149	298		25%	598	1196
75%	199	398		20%	747	1494
50%	299	598		15%	996	1992
40%	374	748		10%	1494	2988
30%	498	996		6%	2491	4982

Remainder of handout to be shared during the meeting