Drug X-1: Hypothetical case of an antibacterial targeting a single bacterial species

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Overview of Drug X-1

- Injectable antibacterial with activity limited to *P. aeruginosa*
- No activity vs. Gram-positives or other Gram-negatives, including Enterobacteriaceae
- New mechanism of action: acts on a novel ribosomal target unique to *P. aeruginosa*

Nonclinical Safety

- Hepatic and hematologic toxicity identified in mice and dogs
- Hepatic:
  - Dose-dependent increase in liver enzymes associated with macrophage infiltration (mid & high doses), reversible focal hepatocellular necrosis (high dose)
  - Safety margins:
    - Liver enzyme elevations: **4x's** targeted therapeutic dose
    - Focal hepatocellular necrosis: **8x's** targeted therapeutic dose
- Hematologic:
  - Some evidence of neutropenia
  - Safety margin: **8x's** targeted therapeutic dose

Nonclinical Microbiology & PK/PD

- Drug X-1 is mainly active vs. *P. aeruginosa*
- MICs have bimodal distribution
  - 0.06 – 1 mg/L for wild type
  - > 4 mg/L for non-wild type
- 99% of isolates had MIC ≤ 1 mg/L in global survey of 850 recent isolates
- MIC distribution for wild type
  - Centered on MIC of 0.25 mg/L
  - 5% of isolates at low (0.06 mg/L) and high (1 mg/L) ends of spectrum
  - Therefore, both MIC_{90} and MIC_{99} = 1 mg/L

Nonclinical Microbiology & PK/PD (2)

- Frequency of emergence of resistance < 1 in 10^{10} organisms
  - Mechanism not yet determined
- Drug X-1 has variable activity vs. other *Pseudomonas* species (MICs 0.03 to > 8 mg/L)
- No activity vs. other Gram-negatives (MICs > 16 mg/L) or Gram-positives (MICs > 256 mg/L)

Nonclinical Microbiology & PK/PD (3)

- In animal infection models, Drug X-1 was effective in treating *P. aeruginosa* infections (MICs 0.03 – 16 mg/L)
  - Based on reduction of CFU/g: thigh, pneumonia, peritonitis
  - Based on survival: sepsis

- The PK/PD index associated with bacterial killing:
  - Percent time that free-drug concentrations are above the MIC over a dose interval (%fT > MIC)
    - Observed in hollow-fiber, as well as, murine thigh and pneumonia infection models

Clinical Studies

- Sponsor has completed some Phase 1 studies and one Phase 2 study

- Phase 1:
  - Completed: healthy volunteer (HV), lung epithelial lining fluid (ELF), renal and hepatic impairment studies
  - Planning Thorough QT and drug-drug interaction studies

Population PK Model

- Simulations of a population PK model based on Phase 1 data showed that a 100 mg IV infusion over 1 hour every 8 hours would provide $\geq$ 40% fT > MIC for MIC of 1 mg/L in more than 90% patients using parameter estimates from HVs and with 40% inflated variance

- Drug X-1 is excreted renally and $\geq$ 90% target attainment is possible for varying degrees of renal impairment based on dose adjustment

Additional Data

- Terminal elimination half-life of Drug X-1 in healthy subjects was approx. 2 hours
- No significant drug-drug interactions predicted
  - *In vitro* metabolism study showed that Drug X-1 does not inhibit or induce CYP enzymes or have transporter liabilities
- ELF to plasma concentration ratios of Drug X-1 were approx. 40% and 25% in humans and mice, respectively

Phase 2 Proof of Concept Study

- 14-day uncontrolled study conducted in patients with non-CF bronchiectasis
- Drug X-1 was given as monotherapy in 10 patients
- At proposed dose, the predicted PK parameters were observed
- Microbiologic activity was assessed in terms of log reduction (CFU/g) of *P. aeruginosa* in sputum:
  - > 1 $\log_{10}$ reduction in 9 of 10 subjects
  - > 2 $\log_{10}$ reduction in 4 of 10 subjects
- No adverse events of concern observed

And now for perspectives on the development program…

- Academia – Helen Boucher
- Industry – John Tomayko
- FDA – Sumathi Nambiar
- EMA – Marco Cavaleri