Lead Criteria

Go criteria:

SCOPE

- New class of antibacterials active on Gram(-) bacteria without significant cross-resistance with existing classes of antibiotics and preferentially acting by a new MoA
- Broad spectrum covering WHO critical priority non-fermenters and enterobacteriaceae.
- Single-pathogen, non-fermenter TPPs possible

EXCELLENCE

- MIC90 against panels of ~50-100 strains representative of the major contemporary TPP pathogens, including MDR pathogens, at or below 4µg/ml for key enterobacteriaceae (indicative list: *Escherichia coli, Klebsiella pneumoniae, Citrobacter freundii, Enterobacter cloacae, Morganella morganii, Providencia stuartii, Serratia marcescens and Proteus mirabilis*), and with reference antibiotics for comparisons.
- and at, or below 8 µg/ml for key non-fermenters.
- MICs against other pathogens (eg anaerobes, Gram(+), other Gram(-)) documented
- Cidal/static effect documented
- Serum, pH, inoculum and cations effects documented for key TPP pathogens.
- Activities vs efflux-deficient and hyperpermeable strains documented.
- FoR of major TPP pathogens below 10^{-8} and if not, resistance risk shown to be manageable based on MIC shifts, MPCs or fitness costs…
- In vivo efficacy demonstrated (eg stasis or one-log reduction at doses < 100 mg/kg/day) by the iv/sc route at least in one TPP-relevant model of infection (eg thigh, septicemia, RTI or UTI) caused by a TPP-relevant pathogen and with concomitant tolerability at efficacious doses.
- PK (iv/sc in relevant mammalian species, used for efficacy studies) and ADMET properties across species (including metabolic stability, CYP liabilities, ion channel inhibitions, plasma stability and PPB) documented
- ELF concentrations (if possible) and/or urinary excretion compatible with TPP
- Aqueous solubility/formulability and chemical stability compatible with iv administration at sufficiently high doses (eg solubility in formulation above 5 mg/ml).
- Potential for oral route documented.
- TC50 vs HepG2 cells at least ten fold higher with respect to MICs in the presence of human serum vs the key TPP pathogens
- No major alerts at 10 µM vs a panel of enzymes, transporters … (eg CEREP panel)
- No genotox alert in a MNT assay up to 500 µg/ml (with and without metabolic activation)
- Hemolysis of human red blood cells < 1% at 100 µg/ml
- No more than 3-4 alerts in the Phys-Chem/ADMET profile of the series
- Chemistry routes, scales and efficiency compatible with further optimization of the series, L2C optimization strategy, flow-chart, Go/NoGo criteria for candidate selection, derisking-and mitigation plans and timelines up to candidate selection defined, taking into consideration specificities and issues associated to the series
- Acceptable IP position at this stage.

These lead criteria are indicative meaning that the Lead compound may not satisfy exactly all the listed quantitative criteria, or a few properties may not be properly documented. The lead dossier will be evaluated as a whole and with respect to the distance with the ideal Lead profile.

Preclinical-Development Candidate Criteria

(ready for IND-enabling studies)

Go criteria (in addition to or modified vs lead criteria)

- MIC90s against panels of at least 100 diverse and representative strains of the major TPP pathogens at, or below 2µg/ml for key enterobacteriaceae and at, or below 4 µg/ml for key non-fermenters.
- Manageable risk of rapid emergence of resistance for all key TPP pathogens
- Mechanism(s) of resistance documented
- Demonstrated capacity to deliver 5-10g batches of the candidate
- No major in vitro ADMET warnings (eg genotox, cytotoxicity, hemolysis, CYP liabilities, human hepatocyte clearance, in vitro pharmacology …)
- Suitable formulation to carry on a 5-7 day toxicology study
- In vivo efficacy demonstrated by the iv/sc route for multiple strains and in multiple infection models representative of the targeted clinical indications. Eg: stasis or a 1-log reduction at doses < 30 mg/kg/day in *Kp* thigh or *Ec* UTI models and ED_{50} <100 mg/kg in *Pa* RTI models
- PK data (iv/sc), including plasma protein binding, urine excretion and ELF concentrations available for several species including rats
- Rat exposures at the NOEL/NOAEL in a 7-day tox study below 4-fold the exposure corresponding to the dose inducing stasis or a 1-log CFU reduction in a TPP-relevant infection model caused by a MIC90 strain of the most difficult key TPP species
- In case of hERG alert, no or limited effects on QTC seen in an animal model (eg guinea pig) at a dose corresponding to 10x the C_{max} concentrations associated to efficacy in infection models
- Efficacy driver determined based on first PK/PD studies
- Reasonable active doses in human (< 3g/day) as estimated from expected human PK and from PK/PD studies
- IP position compatible with future FTO
- First clinical development plans available (preferably)