Target Product Profile –Therapeutic Product (Gram-Negative Lower Respiratory Infections)

Variable	Minimal Requirement	Ideal Requirement
Product Indication	Treatment for hospital-acquired bacterial pneumonia (HABP) or ventilator-associated bacterial pneumonia (VABP) and associated bacteremias.	Treatment for hospital-acquired bacterial pneumonia (HABP) or ventilator-associated bacterial pneumonia (VABP) and associated bacteremias. Preferred expansion to treatment for hospitalized community-acquired pneumonia (hCABP).
Organisms Covered	**Product must target** antibiotic-susceptible and -resistant isolates of *Pseudomonas aeruginosa* (incl. MDR). Enterobacterales spp. (incl. MDR, CRE, and ESBL-producing) and *Acinetobacter baumannii* (incl. CRAB) are considered a bonus.	**Product must target** antibiotic-susceptible and -resistant isolates of **either** *Pseudomonas aeruginosa* (incl. MDR) **or** Enterobacterales spp. (incl. MDR, CRE, and ESBL-producing). If *P. aeruginosa* is not covered, then *K. pneumoniae* must be among the covered Enterobacterales. Preferred additional coverage: antibiotic-susceptible and -resistant isolates of: A. baumannii (incl. CRAB); *Streptococcus pneumoniae* (incl. penicillin non-susceptible); *Staphylococcus aureus* (incl. MRSA); *Haemophilus influenzae* (incl. ampicillin-resistant); *Moraxella catarrhalis*; *Legionella spp.; Mycoplasma pneumoniae; Chlamydophila pneumoniae.*
Patient Population	Adults in a healthcare setting for the treatment of a confirmed serious Gram-negative infection.	Adults and children (>1 yr) in a healthcare setting for the treatment of a confirmed serious Gram-negative infection, with the possibility of early discharge with a PO step-down treatment
Treatment Duration	10 – 14 days	5 – 10 days
Delivery Mode	IV (NOTE: IV-only products must target *P. aeruginosa*)	Oral and IV
Dosage Form	Solution or powder for reconstitution	Tablet, capsule (oral), solution or powder for reconstitution (IV)
Regimen	Up to 3 doses/day	Up to 3 doses/day for IV treatment, then up to 2 doses/day for oral treatment
Efficacy	Equal to the standard of care for all targeted indications	Greater than or equal to the standard of care for all targeted indications
Risk/Side Effects	Manageable drug interactions; clean safety profile; minimum safety margin 3X over effective dose	Manageable drug interactions; clean safety profile; minimum safety margin >5X over effective dose
Stability	At least 3-month solid state stability at 4 °C	At least 3-month solid state stability at 4 °C and 25 °C
Cost	Equivalent to current treatment regimens in HICs	COGs that are compatible with launch in LMICs
Specific Population Claims		
Overall Value Proposition: Effective IV, Oral, or IV/Oral antibiotic active against antibiotic-resistant Gram-negative pathogens enabling timely transition from hospital to outpatient setting		

Target Product Profile – Therapeutic Product (Urinary Tract Infections)		
Variable	Minimal Requirement	Ideal Requirement
Product Indication	Treatment of acute UTI or complicated UTI, including pyelonephritis and associated bacteremia	Treatment of acute UTI or complicated UTI, including pyelonephritis and associated bacteremia
Organisms Covered	*E. coli* and *K. pneumoniae* (including MDR, CRE, and ESBL-producing isolates)	*E. coli, K. pneumoniae,* other Enterobacterales, and *P. aeruginosa* (including MDR, CRE, and ESBL-producing isolates)
Patient Population	Acute UTI in adult women or men with and without signs or symptoms of infection beyond the bladder	Acute UTI in adult women or men with and without signs or symptoms of infection beyond the bladder
Treatment Duration	Up to 5 days for acute UTI confined to the bladder, and up to 10 days for pyelonephritis and complicated UTI	Up to 5 days for acute UTI confined to the bladder, and up to 10 days for pyelonephritis and complicated UTI
Delivery Mode	Oral, or IV/oral	Oral, or IV/oral
Dosage Form	Tablet, capsule (oral), solution or powder for reconstitution (IV)	Tablet, capsule (oral), solution or powder for reconstitution (IV)
Regimen	Up to 3 doses/day for IV treatment, then up to 2 doses/day for oral treatment	Up to 3 doses/day for IV treatment, then up to 2 doses/day for oral treatment
Efficacy	Non-inferior to SOC (e.g., nitrofurantoin, pivmecillinam, fosfomycin, trimethoprim-sulfamethoxazole, quinolones, BL-BLI therapies, and cefiderocol)	Non-inferior to SOC (e.g., nitrofurantoin, pivmecillinam, fosfomycin, trimethoprim-sulfamethoxazole, quinolones, BL-BLI therapies, and cefiderocol)
Risk/Side Effects	Comparable to current therapies with β-lactams, no toxicity signals in preclinical reproduction toxicity studies; minimum safety margin 3X over effective dose	Comparable to current therapies with β-lactams, no toxicity signals in preclinical reproduction toxicity studies; minimum safety margin >5X over effective dose
Stability	Heat stable, 3-year shelf life	Heat stable, 3-year shelf life
Cost	Equivalent to current treatment regimens	Equivalent to current treatment regimens
Population Claims	Contraindicated in pregnant women, catheterized patients and patients with comorbidities	Safe in pregnant women, catheterized patients and patients with comorbidities
Overall Value Proposition: Safe, effective and affordable therapy against hard-to-treat, antibiotic-resistant UTI infections in HIC and LMICs		

Target Product Profile – Therapeutic Product (Diarrheal Diseases)		
Variable	Minimal Requirement	Ideal Requirement
Product Indication	Treatment for diarrhea	Treatment for diarrhea
Organisms Covered	Antibiotic-susceptible and -resistant isolates of *Shigella* spp. and *Salmonella* spp.	Antibiotic-susceptible and -resistant isolates of *Shigella* spp. and *Salmonella* spp., plus coverage of *Campylobacter jejuni* and diarrhea-causing *Escherichia coli* pathovars (Enterotoxigenic *E. coli*, Enteropathogenic *E. coli*, Enteroinvasive *E. coli*, Enteroaggregative *E. coli*, and/or Shiga toxin-producing *E. coli*)
Patient Population	Children (>6 months) and immunocompetent adults suffering from diarrhea	Children (>1 month) and both immunocompetent and immunocompromised adults, including pregnant women, suffering from diarrhea
Treatment Duration	5-7 days	1-3 days
Delivery Mode	Oral, tablet/capsules	Oral, liquid formulation and parenteral where oral administration is not possible
Dosage Form	Tablet or capsule (oral)	Tablet or capsule and liquid formulation for children (oral). Another parenteral dosage form that can be used in cases where oral dosing may not be feasible.
Regimen	Up to 3 doses/day	Daily dose
Efficacy	Equal to the standard of care for resolution of symptoms (diarrhea, fever)	Superior to standard of care for resolution of symptoms (diarrhea, fever), including a lower relapse rate
Risk/Side Effects	Safety profile equivalent to standard of care in target populations with safety margin >3X over effective dose; manageable drug-drug interactions	Safety profile equivalent to standard of care treatment in target populations with safety margin >5X over effective dose; manageable drug-drug interactions
Stability	At least 6-month solid state stability in ICH Zone IVb (30 °C and 75% relative humidity environment)	At least 12-month solid state stability in ICH Zone IVb (30 °C and 75% relative humidity environment)
Cost	COGs that are compatible with launch in UMICs	COGs that are compatible with launch in LMICs/LDCs
Population Claims		
Overall Value Proposition: Effective oral or oral/parenteral antibiotic active against antibiotic-resistant and antibiotic-susceptible Gram-negative pathogens, enabling safe treatment of diarrhea in vulnerable populations		

CARB-X
Combating Antibiotic Resistant Bacteria

Development Stages in Scope
Therapeutics

The earliest eligible stage for CARB-X funding is Hit-to-Lead, and CARB-X defines a "Hit" as meeting the following minimal entry criteria.

- Scaffold(s) demonstrated to act against a defined target in at least in one relevant assay, has ample chemical space to explore, shows indications of Structure-Activity Relationships that can be optimized.
- Active upon resynthesis; >90% purity
- Demonstration of activity against wild-type pathogen(s) relevant to the desired target indication in a biologically appropriate assay (e.g., MIC assay for direct-acting therapeutics)
- Demonstration that cell-based antibacterial activity is due to the stated mechanism of action (i.e., is on-target).
- Low cytotoxicity against a relevant human cell line, suggesting selectivity will be achievable (CC_{50}:MIC ratio ≥10).
- Suitable physicochemical properties to support formulation work in-line with anticipated route of administration.
- If an oral product is proposed, quantitative experimental data supporting either (a) or (b) is required. Units must be provided for all numerical data.
    a. In vitro data supporting potential for oral bioavailability, e.g.: medium-to-high Caco-2 cell (or equivalent) permeability. For permeability data, transport in both directions (apical to basolateral and basolateral to apical) must be shared to underscore the extent to which efflux will be an optimization driver.
    b. If in a class where transport or efflux liabilities are a consideration, or if in a later stage of development, positive baseline exposure (≥10 %F) in appropriate compartments when dosed in vivo in an acceptable preclinical formulation (not containing DMSO) within a typical experimental range (e.g., 1-3 mg/kg IV and 10 mg/kg PO).
    c. Any proposed prodrug strategy must be explicit and well-defined, with baseline demonstration of conversion to the parent drug at a rate consistent with pharmacological efficacy.
- If an IV product is proposed, demonstration of physicochemical properties providing adequate aqueous solubility at a clinically acceptable pH.

<u>Typical activities during Hit-to-Lead (Lead Generation)</u>

- Explore initial structure-activity relationship and chemical design across a number of lead scaffolds, and identify areas to improve on *in vitro* potency, selectivity, chemical stability and synthetic tractability, cytotoxicity, and other drug-like properties.
- Demonstrate *in vitro* activity against wild-type representatives of all TPP-targeted pathogen(s).
- Generate preliminary in vivo proof-of-concept efficacy data in relevant infection model showing statistically significant efficacy (minimum endpoint = stasis). Where a positive control is available, demonstration of model validation.
- *In vitro* ADME suggests no obvious liabilities with respect to microsomal stability, plasma stability, and protein binding across relevant species (minimum of rat, dog, and human).
- Synthetic route suggests compound scale-up will be possible to support LO and IND enabling studies and source of relevant starting materials/intermediate(s) identified.
- If an oral product is proposed, positive baseline exposure (≥10 %F) in appropriate compartments when dosed orally in vivo, plus evidence of efficacy in a relevant infection model via the oral route.

Typical activities during Lead Optimization

- Synthesize compounds from selected lead scaffold(s) - new analogs with improved potency, reduced off-target activities, and physiochemical/metabolic properties suggestive of reasonable in vivo pharmacokinetics compatible with human dose. SAR trends must remain consistent with mechanistic hypothesis.
- Expand microbiological understanding of lead molecules (spontaneous resistance frequency, serial passaging for resistance, defining mechanisms of resistance, killing kinetics, population MIC determination, including testing against contemporary, molecularly characterized antibiotic-resistant pathogens); confirmation of antimicrobial mechanism of action in targeted pathogens).
- Identify suitable toxicological species and conduct non-GLP *in vivo* toxicity (MTD and repeat dosing) in accordance with the product's intended use.
- Initiate experiments to identify correlate of efficacy (e.g., PK-PD driver) and suitable endpoints for further pre-clinical studies.
- Demonstrate *in vivo* activity and potential for efficacy consistent with the product's intended use (i.e. dose, schedule, duration, route of administration) against multiple TPP pathogens (or multiple isolates for narrow-spectrum agents) covering the range of activity seen in vitro. A positive antibiotic control should be included to confirm the performance of the infection model. Ideally, the efficacy endpoint should be comparable to or better than standard of care administered (when feasible) at humanized doses.
- Perform pre-formulation studies to identify an appropriate non-DMSO formulation for the non-GLP toxicity and efficacy studies.
- Profile in *in vitro* safety and secondary pharmacology assays.
- Prepare a defined strategy for interaction with regulatory agencies.
- Selection of candidate to progress into pre-clinical evaluation.

Typical activities during Preclinical (IND Enabling)

- Demonstrate acceptable Absorption, Distribution, Metabolism, and Elimination (ADME) characteristics in non-GLP animal studies as necessary for IND filing.
- Complete suitable microbiological IND package demonstrating appropriate differentiation.
- Conduct GLP non-clinical studies for toxicology, safety pharmacology, genotoxicity, and immunogenicity (as appropriate).
- Continue evaluation in animal models or *in vitro* systems with efficacy and dose-ranging studies to understand the range of PK/PD driver magnitudes required across a panel of isolates to provide confidence for clinical success.
- Develop a scalable and reproducible manufacturing process amenable to GMP. Manufacture GMP-compliant pilot lots.
- Initiate development of in-process assays and analytical methods for product characterization and release, including assessments of potency, purity, identity, strength, sterility, and quality as appropriate.
- Prepare and submit Investigational New Drug (IND) package to FDA or appropriate documentation to other relevant regulatory authorities.

Typical activities during Phase 1

- Conduct First-in-Human single ascending dose (SAD) and multiple ascending dose (MAD) clinical trial(s) to determine the safety and pharmacokinetics of the clinical test article in healthy volunteers (in certain circumstances, patients).
- Determine microbiological QC ranges and manufacture and test AST assays to support Phase II studies.
- Expand PK/PD understanding, refine population PK models and Monte Carlo simulation to refine Phase II dose selection.
- Conduct additional CMC, formulation, and analytical activities required to support further clinical development.