



# SPERO THERAPEUTICS

**Corporate Presentation**  
Sept 2024

# Forward-looking Statement

This presentation contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995 regarding, among other things, the future development and commercialization of SPR720 and SPR206; the potential number of patients who could be treated by SPR 720 and tebipenem HBr and market demand for SPR720 and tebipenem HBr generally; the potential regulatory path forward for tebipenem HBr, the potential approval of tebipenem HBr by the U.S. Food and Drug Administration (FDA) and the timing thereof; the potential commercialization of tebipenem HBr and its future value, the potential receipt of milestone payments and royalties on future sales of tebipenem HBr under the GlaxoSmithKline Intellectual Property (No. 3) Limited (GSK) license agreement; the effectiveness of tebipenem HBr and its potential impact on healthcare resource utilizations; the anticipated shift in treating patients from intravenous to oral administration; the initiation, timing, progress and results of the Company's preclinical studies and clinical trials and its research and development programs, including management's assessment of such results; the timing of the availability of data from the Company's clinical trials; the timing of the Company's filings with regulatory agencies; product candidate benefits; competitive position; business strategies; potential growth opportunities; potential market size; projected costs and the availability of additional non-dilutive funding from governmental agencies beyond any initially funded awards. In some cases, forward-looking statements can be identified by terms such as "may," "will," "should," "expect," "plan," "aim," "anticipate," "could," "intent," "target," "project," "contemplate," "believe," "estimate," "predict," "potential" or "continue" or the negative of these terms or other similar expressions. All statements other than statements of historical facts contained in this presentation are forward-looking statements. The Company may not actually achieve the plans, intentions or expectations disclosed in these forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements as a result of various factors, including whether the FDA will ultimately approve tebipenem HBr and, if so, the timing of any such approval; whether the FDA will require any additional clinical data or place labeling restrictions on the use of tebipenem HBr that would add costs for the Company, delay approval and/or reduce the commercial prospects of tebipenem HBr; the Company's need for additional funding; the lengthy, expensive, and uncertain process of clinical drug development; the Company's reliance on third parties to manufacture, develop, and commercialize its product candidates, if approved; the ability to develop and commercialize the Company's product candidates, if approved; the Company's ability to retain key personnel; whether results obtained in preclinical studies and clinical trials will be indicative of results obtained in future clinical trials and whether preliminary data from the Company's clinical trials will be predictive of final results from such trials; the Company's dependence on raising capital and whether the Company's product candidates will advance through the preclinical development and clinical trial process on a timely basis, or at all, taking into account such factors as the effects of possible regulatory delays, slower than anticipated patient enrollment, manufacturing challenges, clinical trial design, clinical data requirements and clinical outcomes; whether the results of such clinical trials will warrant submission for approval from the FDA or equivalent foreign regulatory agencies; decisions made by the FDA and equivalent foreign regulatory agencies with respect to the development and commercialization of the Company's product candidates; the commercial potential of the Company's product candidates; the Company's ability to obtain adequate third-party reimbursement for its product candidates; whether the Company will satisfy all of the pre-conditions to receipt of the milestone payments under its various license and collaboration agreements; the Company's ability to implement its strategic plans; the Company's ability to obtain, maintain and enforce intellectual property and other proprietary rights for its product candidates; the risks and uncertainties related to market conditions; whether the Company's cash resources will be sufficient to fund its continuing operations for the periods and/or trials anticipated; and other factors discussed in the "Risk Factors" section of the Company's periodic reports filed with the U.S. Securities and Exchange Commission (SEC), and risks described in other filings the Company may make with the SEC in the future. The forward-looking statements included in this presentation represent the Company's views as of the date of this presentation. The Company anticipates that subsequent events and developments will cause its views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, it specifically disclaims any obligation to do so. These forward-looking statements should not be relied upon as representing the Company's views as of any date subsequent to the date of this presentation.

# Developing Therapies for Rare and Multi-drug Resistant Infectious Diseases



## Diversified clinical stage portfolio

Indications with high unmet need in addressable patient populations

Late-stage development pipeline

Focused on oral, small molecule drugs

Orphan drug and/or QIDP designations

Strong global intellectual property



## SPR720, positioned for near-term inflection

Potential novel, oral, first-line treatment for non-tuberculous mycobacterial pulmonary disease (NTM-PD)

Rare disease with ~245,000 diagnosed patients in developed markets<sup>1</sup>

No first-line therapies approved

Proof-of-concept data anticipated in 4Q 2024



## Supported by world class partnerships

Partnership milestones, cash and cash equivalents are expected to provide runway into late 2025

# Maturing Pipeline with Differentiated Clinical Assets

Asset	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Anticipated Milestone
<b>Wholly Owned</b>						
SPR720	First-line NTM-PD					Preliminary Data (4Q 2024)
<b>Partnered Assets</b>						
<b>Tebipenem HBr</b>  Worldwide Rights (ex. Asia)	cUTI					Complete Enrollment (2H 2025)
<b>SPR206</b>  China  OUS, ex. China Spero Retains Rights in United States	HABP/VABP					Initiate Phase 2 <sup>1</sup>

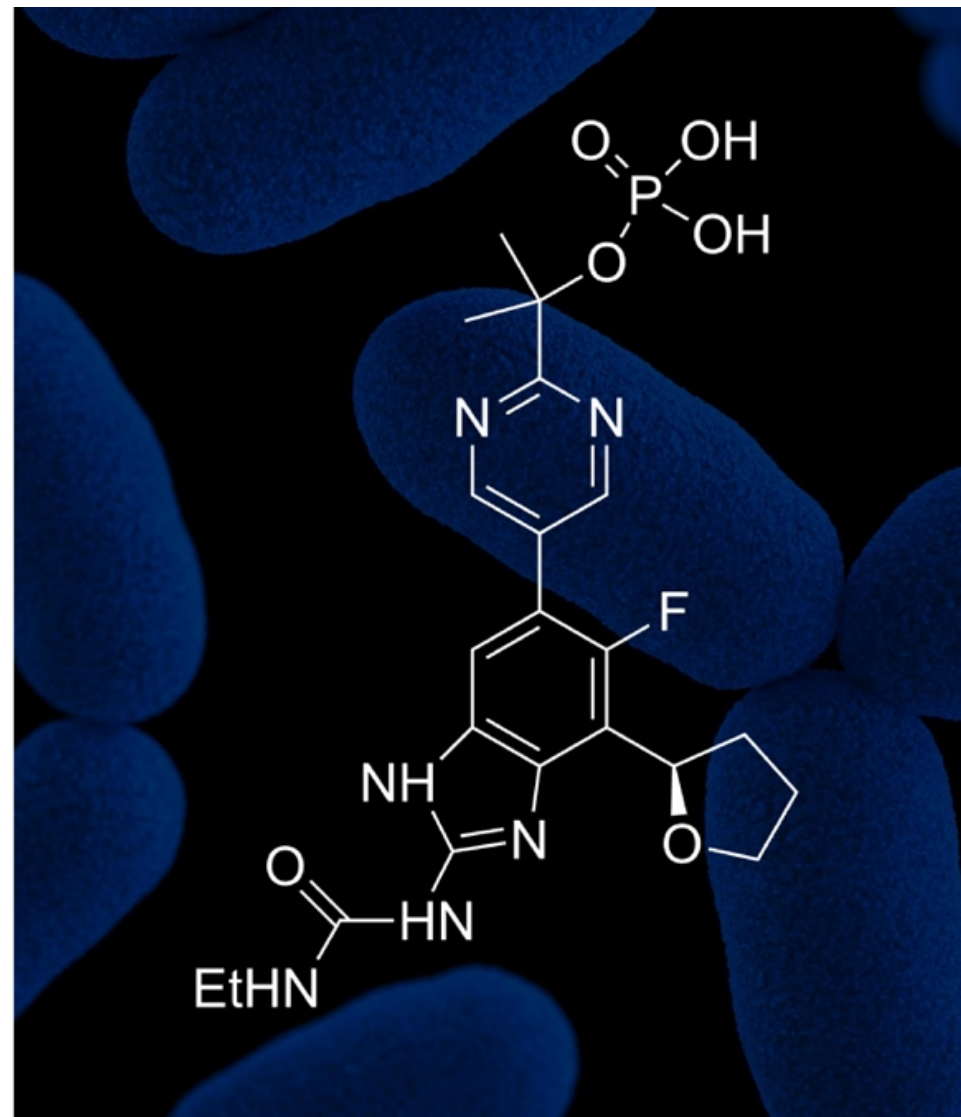
**Non-dilutive Funding Alliances**

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# SPR720

Oral Antibiotic for Non-Tuberculosis  
Mycobacterium Pulmonary Disease (NTM-PD)

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# NTM-PD: Chronic Debilitating Disease with Significant Patient Burden

## 1 Patient with existing structural lung damage and/or immunocompromised status

Select pre-existing indications include:

Bronchiectasis

COPD

Cystic fibrosis

## 2 Exposure to NTM species

*M. avium* complex (80-85%)\*

Additional species, including *M. abscessus*

## 3 Presentation of signs and symptoms of NTM-PD

Fatigue	83%
Cough	78%
Sputum (phlegm)	67%
Short of breath	65%
Night sweats	54%
Fever	44%
Hemoptysis	29%
Weight loss	3.7 ± 5.2 kg

## 4 Worsening of lung damage

High-Resolution CT Scans (HRCT) Confirms NTM-PD diagnosis and severity



5 First-line treatment options include 6-12 months (or more) on a combination of antibiotics, including a macrolide

6 Drug-resistance &/or exacerbations eventually leads to 5-yr all-cause mortality rate of ~35%<sup>1,2</sup>

# High Unmet Need in First-Line Patients With Long Treatment Duration, and Lack of Efficacy and Tolerability from Current Treatment Options

## Rare Disease with High Unmet Need

~245,000 diagnosed patients in developed markets<sup>1</sup>

~35% Five-year all-cause mortality rate<sup>2</sup>

Chronic condition requiring long-term treatment

## Current SOC Treatments Have Severe Limitations

Poor outcomes driven by emergence of resistance

Safety & tolerability concerns & high rate of treatment drop-offs

~50% of treated patients experience infection recurrence<sup>3</sup>

## No Approved First-Line Treatment

Off-label use of

- Azithromycin
- Ethambutol
- Rifampin

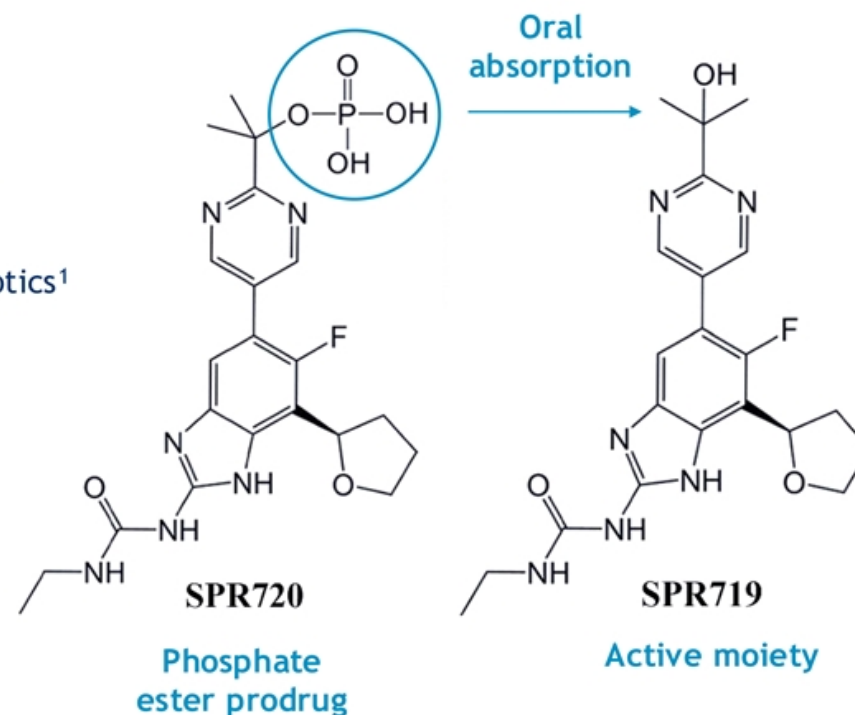
Inhaled amikacin in Phase 3 trial

**No other oral agent in clinical development**



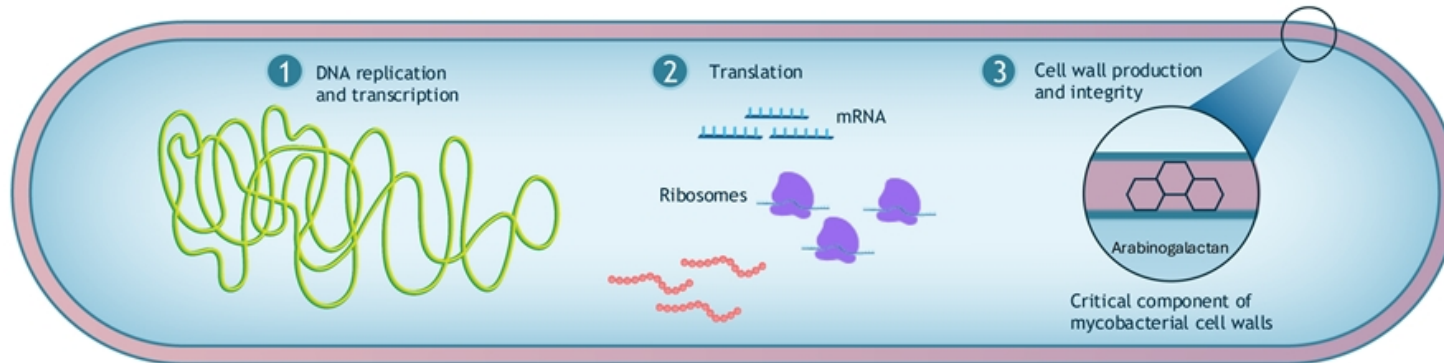
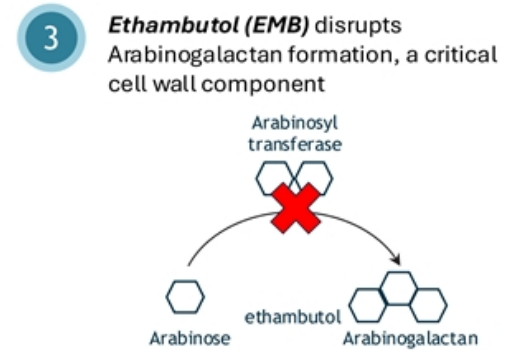
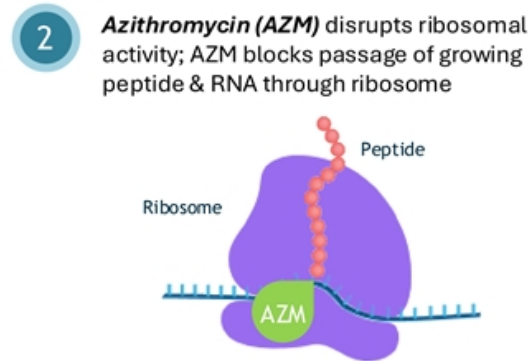
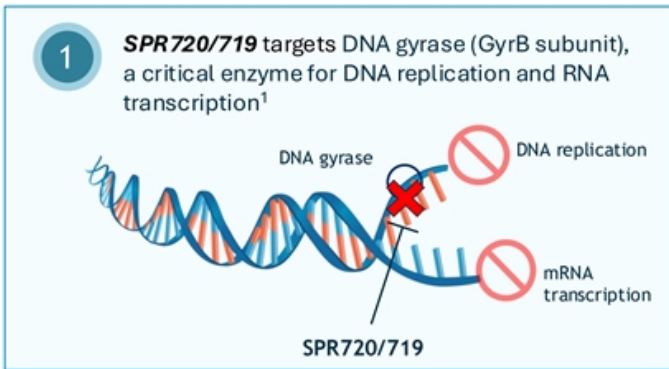
# SPR720, An Oral, Small Molecule Gyrase B Inhibitor in Development to Address Unmet Patient Need in First-line Setting

- ✓ Potency against multiple NTM pathogens, such as MAC (including macrolide-resistant MAC) and *M. abscessus*<sup>1</sup>
- ✓ Novel mechanism of action for NTM-PD not exploited by current antibiotics
- ✓ No evidence of cross resistance against marketed antibiotics<sup>1</sup>
- ✓ Low propensity for selection of resistance<sup>2</sup>
- ✓ Data support potential for efficacy, lung macrophage penetration, and safety/tolerability
- ✓ May be administered with or without food
- ✓ Composition of matter patent into 2032
- ✓ Granted Orphan Drug, QIDP and Fast Track designations





# SPR720's Novel Mechanism of Action Not Exploited by Existing Antibiotics for NTM-PD



Novel target and differentiated MOA potentially position SPR720 to improve current SOC regimen

## SPR719 Inhibits Growth of MAC Isolates at Lower Concentrations (MICs) than SOC Agents *in vitro*

MAC organism (n)	Agent	MIC 90% (µg/mL)
<i>M. avium</i> (12)	SPR719	2
	Amikacin	64
	Clarithromycin	8
	Linezolid	64
	Moxifloxacin	8
<i>M. intracellulare</i> (19)	SPR719	2
	Amikacin	>64
	Clarithromycin	>64
	Linezolid	64
	Moxifloxacin	8
MAC-X (10)	SPR719	1
	Amikacin	32
	Clarithromycin	4
	Linezolid	64
	Moxifloxacin	>8

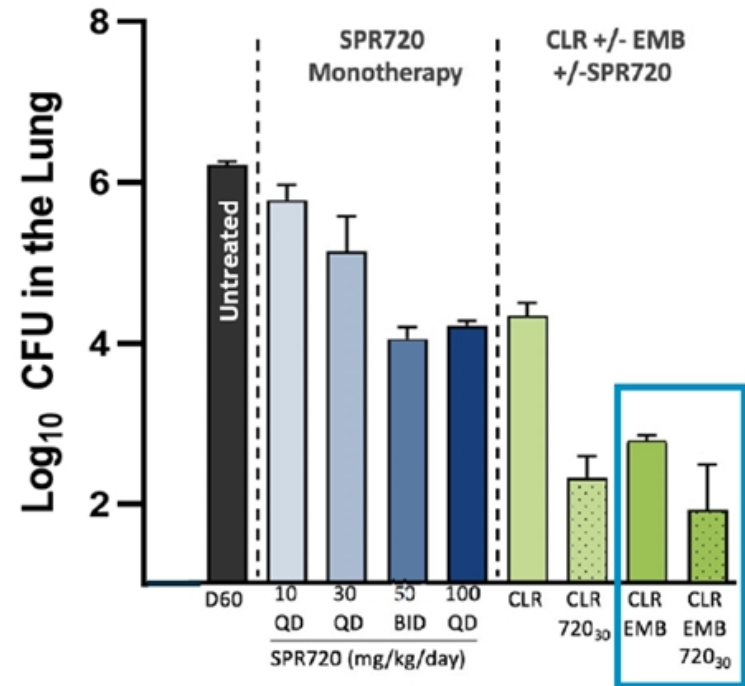
Low MIC<sub>90</sub> values for SPR719 suggest consistent activity against most clinically important NTM species

Low variability in MIC<sub>90</sub> values across species support thesis that SPR719 has a novel mechanism with minimal pre-existing drug resistance

# In Vivo Murine Data Demonstrate Increased Potency When Combined with SOC Agents

## SPR720 as monotherapy and in combination with SOC agents

- SPR720 active as monotherapy with evidence of dose response
- Demonstrates improved efficacy when used in combination with SOC agents



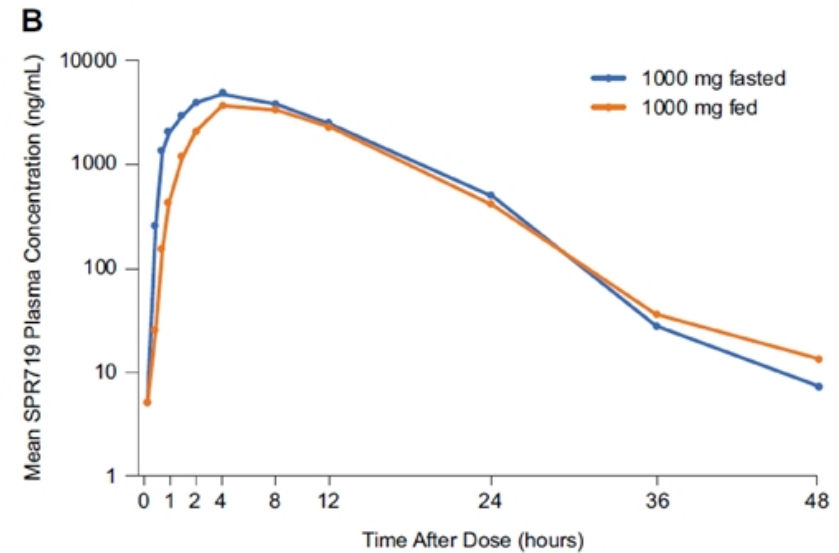
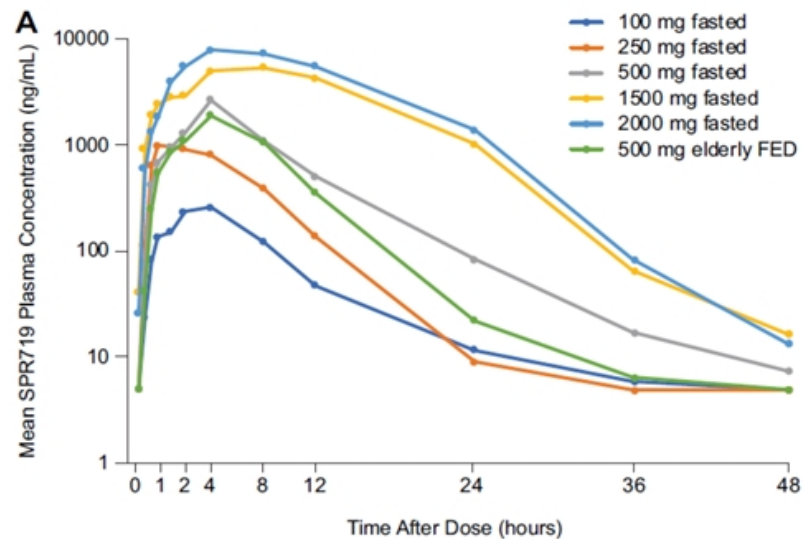
## Phase 1 SAD/MAD Study in 96 HV: Favorable Safety/Tolerability Profile

- SAD (100 to 2000 mg)
- MAD evaluated over 7 days (500, 1000 and 1500 mg) and over 14 days (500 and 1000 mg)
- Dose-dependent increase in plasma exposure observed
- No SAEs reported; generally well tolerated at doses up to 1000 mg
- One discontinuation of study drug at 1500 mg dose: Grade 2 pancreatic enzyme elevation that was asymptomatic, monitorable and reversible

SPR720 is Generally Well-tolerated with Predicted Therapeutic Exposures Attainable with 500 to 1000 mg

# SPR720 Plasma Concentration Increases with Dose Escalation; No Clinically Significant Food Effect Observed

Phase 1 SAD/MAD study



Mean plasma concentration-time curves following single ascending dosing (SAD) of SPR720

# SPR720 Aims to be the Foundation of First-line Combination Regimen for NTM-PD

## Therapeutic Landscape Challenges

- ❑ No approved oral therapy for newly diagnosed symptomatic patients, the majority with MAC infections
- ❑ Regimen tolerability
- ❑ Emergence of resistance even with combination therapy
- ❑ Limited efficacy in current SOC

## SPR720 Differentiation

- ✓ SPR720 is the only oral agent in clinical development for first-line treatment of NTM-PD patients infected with MAC
- ✓ Dosing to date support a tolerable profile
- ✓ SPR720 *in vitro* data suggest low evidence of emergence of resistance when used in combination with current oral SOC agents

## Areas of Ongoing Focus for SPR720 Clinical Development

### Question

Does SPR720 reduce MAC bacterial burden and demonstrate tolerability in 1<sup>st</sup> line patients?

Does SPR719 (active moiety of SPR720) get to the site of infection?

Does SPR720 exposure change when co-administered with primary SOC agents?

Does SPR720 provide a better resistance profile when used with SOC agents?

### Study



Phase 2a PoC study intended to *determine SPR720 monotherapy activity in MAC infected patients*



Phase 1 HV BAL study to *understand exposure in lung*



Phase 1 HV and HFIM SOC combo studies to *explore potential for therapeutic effectiveness when used with AZM and EMB*

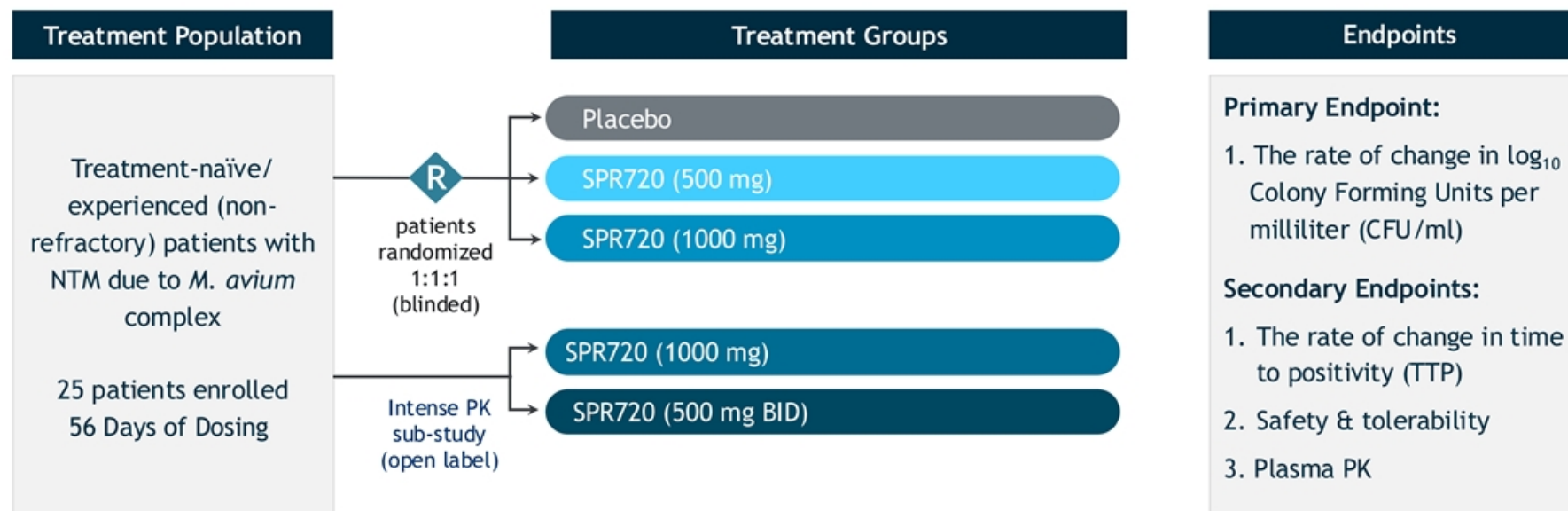


*In vitro* studies to evaluate resistance profile

## Phase 2a Designed to Achieve SPR720 Proof-of-Concept

- Study SPR720-202 (NCT05496374): Phase 2a study in NTM-PD

A study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of SPR720, as compared with placebo for the treatment of patients with *Mycobacterium avium* complex (MAC) pulmonary disease





## Phase 2a Focused on Non-refractory Patients

SPR720 is currently being developed for treatment-naïve and treatment-experienced non-refractory patients with MAC infection



Future indication expansion possibility in refractory NTM-PD

### Treatment-naïve

Never received SOC multidrug treatment for NTM-PD

### Treatment-experienced non-refractory

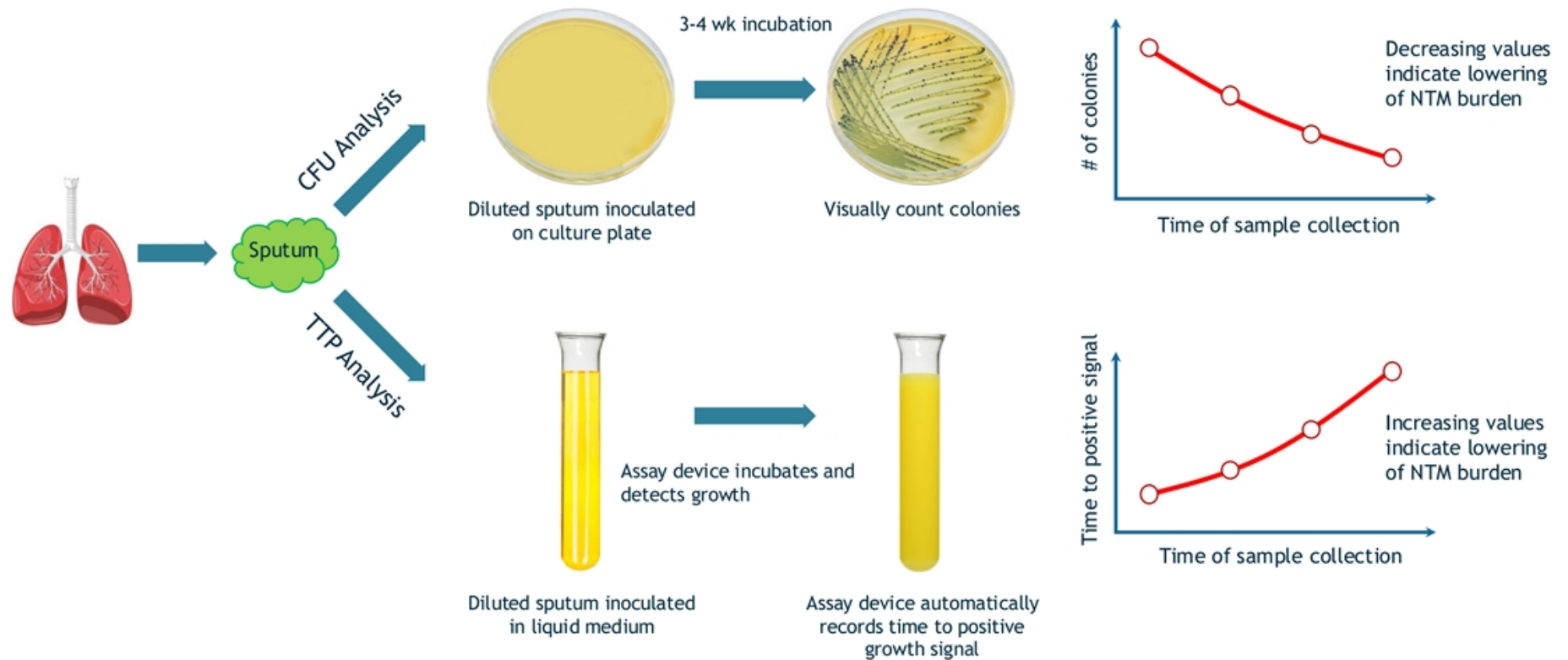
Received SOC multidrug treatment for NTM-PD and successfully converted cultures to negative

Culture conversion defined as: 3 consecutive lower respiratory cultures, obtained 1 month apart, negative for acid-fast bacilli (AFB)

### Refractory

Received multidrug SOC treatment for NTM-PD, but after 6 months of therapy, fail to convert cultures to negative

# SPR720 Efficacy Will be Evaluated via CFU and TTP Assays



## Spero Plans to Share a Comprehensive Dataset in the Fourth Quarter

### Question

Does SPR720 reduce NTM bacterial burden and demonstrate tolerability in 1<sup>st</sup> line patients?



### Study

Phase 2a PoC study to *determine SPR720 monotherapy activity in MAC infected patients*



### We hope to see

- 1) Numerical difference in key quantitative bacterial burden metrics
- 2) A well tolerated dosing regimen

Does SPR719 (active moiety of SPR720) get to the site of infection?



Phase 1 HV BAL Study to *understand exposure potential in lung*



Higher concentration of active drug in epithelial lining fluid and alveolar macrophages compared to plasma

Does SPR720 exposure change when co-administered with primary SOC agents?



Phase 1 HV and HFIM SOC combo studies to *explore potential for therapeutic effectiveness when used with AZM and EMB*



Consistent SPR719 plasma PK when SPR720 is administered as a monotherapy vs in combination with SOC agents

Does SPR720 provide a better resistance profile when used with SOC agents?



*In vitro* resistance study to *demonstrate lack of resistance development*



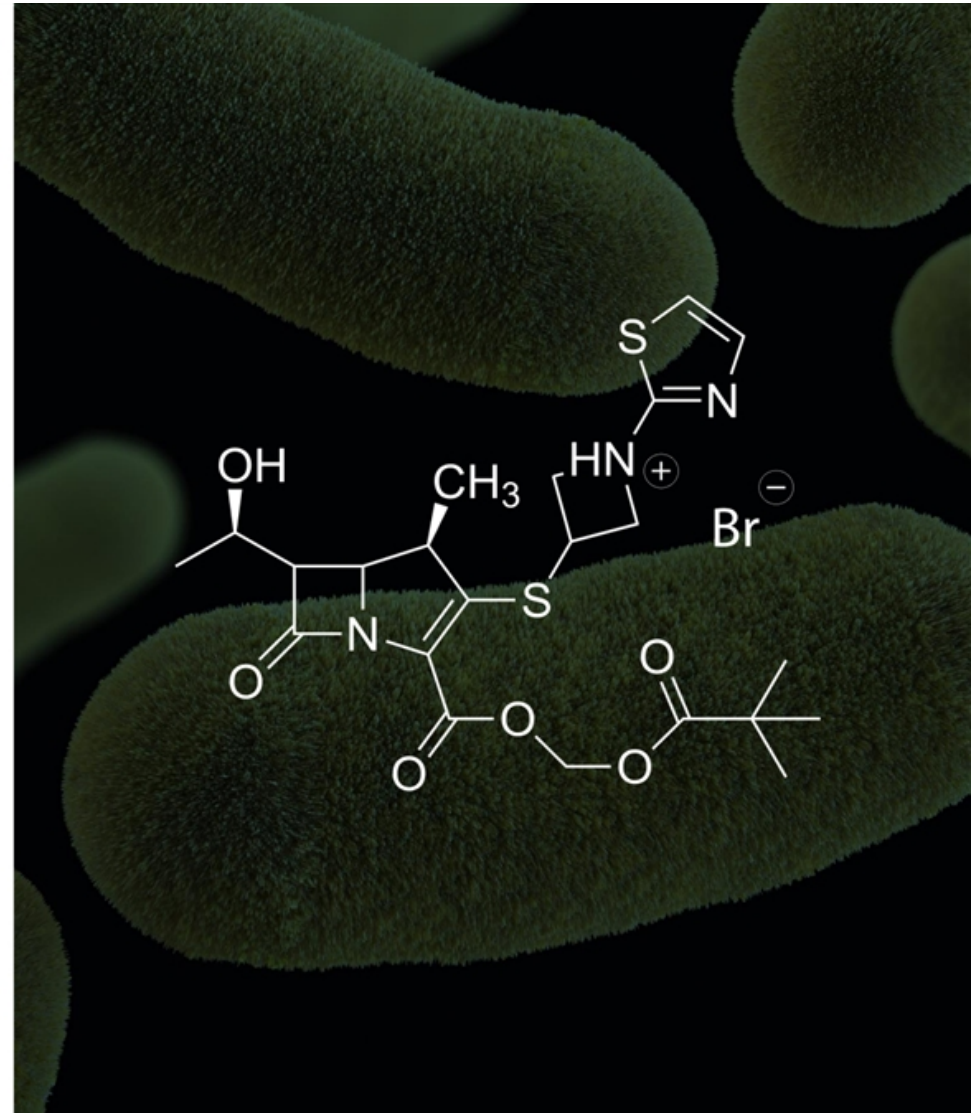
- 1) Low SMF values for SPR719 monotherapy
- 2) Ability of SPR719 to suppress resistance to SOC drugs

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# Tebipenem HBr

Oral Carbapenem

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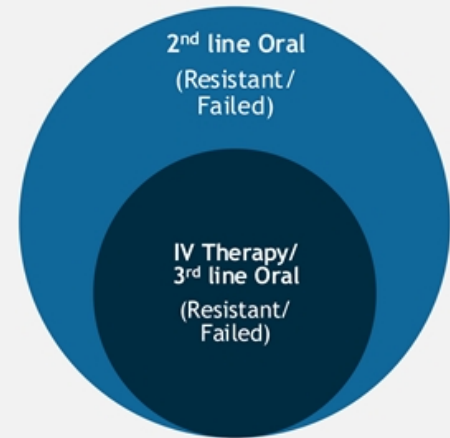
# cUTI Patients Often Cycle through Multiple Therapies

## Lack of effective oral treatment options has resulted in increased -

- Outpatient visits
- Emergency department visits
- Unwarranted outpatient IV use
- Unnecessary hospitalizations
- Hospital days
- Home health and long-term care stays post-hospitalization

All translating to patient suffering and high financial burden

## Tebipenem, in development to offer an oral alternative to cUTI patients



Annual cUTI treatment episodes estimated to be 3.4M<sup>1</sup>

# Tebipenem HBr: Potential to Reduce Treatment Burden for cUTI Patients, if Approved

## Potential first-to-market oral carbapenem

- Potential treatment of complicated UTI in outpatient setting vs current hospitalized setting
- Expand prescriber base beyond infectious disease specialists
- Robust IP through 2038
- QIDP designation

## Phase 3 enrolling

- PIVOT-PO trial protocol approved under FDA Special Protocol Assessment (SPA)
- Enrollment began with first patient dosed in Q4 2023
- Global trial with centers in the North and South America, Europe, Africa, and Asia

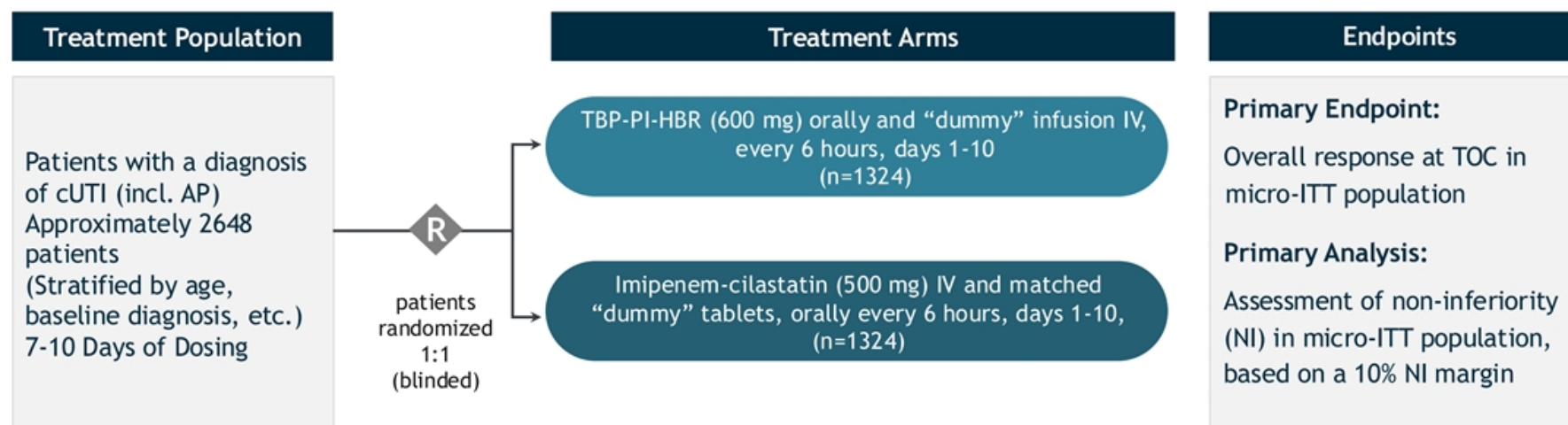
## Global commercial partnership

- Out-licensed global commercial rights (except Japan and certain other Asian countries) to GSK
- Robust financial terms including developmental, regulatory, and commercial milestones, as well as tiered sales royalties

## Phase 3 Clinical Trial PIVOT-PO: Pivotal Design

### Study Tebipenem HBr (NCT06059846): Phase 3 Clinical Trial in cUTI

A Phase 3, Randomized, Double-blind, Double-dummy, Multi-center Study to Assess the Efficacy and Safety of Orally Administered Tebipenem Pivoxil Hydrobromide (TBP-PI-HBr), Compared to Intravenously Administered Imipenem-cilastatin in Patients with Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)



#### Entered FDA Special Protocol Assessment Agreement (SPA):

The FDA has indicated that positive and persuasive results from PIVOT-PO, along with previously completed studies, could be sufficient to support approval of tebipenem HBr as a treatment for cUTI, including pyelonephritis, for a limited use indication

# Exclusive License Agreement with GSK for Tebipenem HBr and Equity Investment

## Global Collaboration (ex-Asia)

- Spero is responsible for execution and costs of the Tebipenem HBr Phase 3 in the United States
- GSK received exclusive license to:
  - Develop Tebipenem in territories outside of United States (not including Japan and certain other Asian countries where rights are held by Meiji Seika); and
  - Obtain regulatory approval and commercialize tebipenem HBr in all territories, except Meiji Seika Territories

## Financial Terms

- ✓ Received \$66 Million upfront and \$9 Million in common stock investment
- ✓ Received \$30 Million upon SPA agreement with the FDA
- ✓ Upon FPDF, Spero qualified to receive \$95 Million in development milestones payable in equal installments over two years

Spero is eligible to receive up to \$400 Million in additional potential regulatory, commercial and sales milestone payments, as well as royalties

- \$25 Million to be paid upon GSK's submission of tebipenem HBr's New Drug Application (NDA)
- Up to \$150 million in potential commercial milestones based on first commercial sales (US/EU)
- Up to \$225 million in sales related milestone payments
- Spero to receive tiered low-single digit to low-double digit (if sales exceed \$1 billion) tiered royalties on net product sales

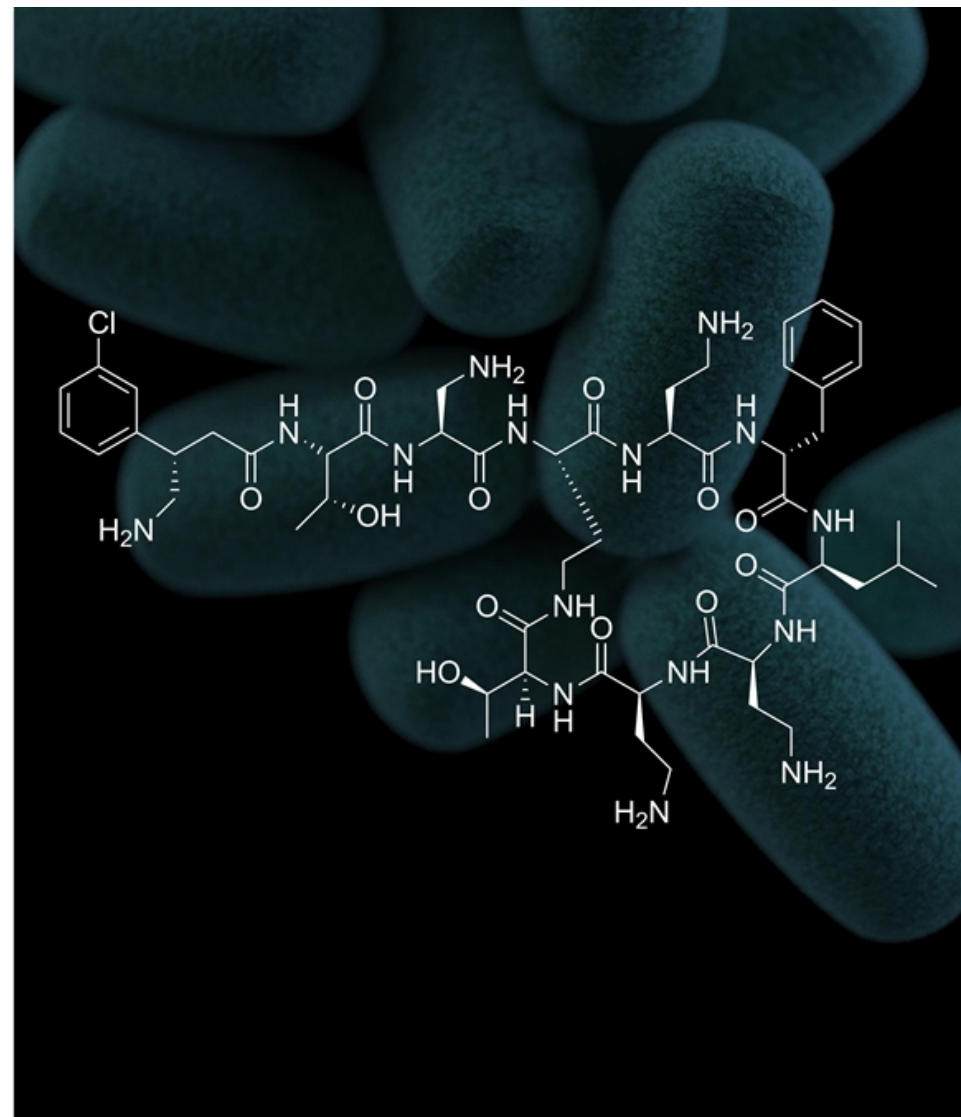


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# SPR206

Direct Acting IV Potentiator

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## SPR206: Ongoing Clinical Development Lends Potential to Address Significant Unmet Need

- Innovative, investigational IV direct-acting polymyxin antibiotic
- Destabilization of phospholipids and lipopolysaccharides (LPS) present
- Increased permeability, cell membrane disruption, bacterial cell death
- Received FDA Fast Track designation

Current standard of care involves drug combinations that are often associated with nephrotoxicity

### Preclinical Studies



Support increased efficacy beyond traditional antibiotics and potential for single agent activity

### SAD/MAD Phase 1 Trial<sup>1</sup>



No evidence of nephrotoxicity at predicted therapeutic dose levels

### Bronchoalveolar Lavage Phase 1 Trial<sup>2</sup>



Well-tolerated and achieved lung exposures consistent with predicted therapeutic levels

### Renal Impairment Phase 1 Trial<sup>3</sup>



Supportive of renal dosing in subsequent trials for patients impacted by differences in renal function

Next Steps: Phase 2 HABP/VABP Proof of Concept Study<sup>4</sup>

SPR206 has potential to fulfill unmet need for a well tolerated, efficacious therapeutic against carbapenem-resistant pathogens

# Leadership Team



## Sath Shukla

*President and Chief Executive Officer*

- Prior CFO at Spero Therapeutics; Prior CFO at Ziopharm Oncology; VP and Global Head of Corporate Finance at Vertex
- Over 20 years of financial leadership, executing within commercial and clinical companies



## Esther Rajavelu

*Chief Financial Officer  
Chief Business Officer*

- Over two decades of life science sector experience, combining equities research, investment banking, strategy consulting, and M&A
- Prior CFO at Fulcrum Therapeutics. Senior equity research analyst at UBS, Oppenheimer and Deutsche Bank. Healthcare Investment Banker at Bank of America Merrill Lynch



## Timothy Keutzer

*Chief Operating Officer*

- Previously, Spero's Chief Development Officer
- Prior VP Program and Portfolio Management, Cubist
- Extensive antibiotic development experience from pre-clinical to approval
- Over 30 years in the pharmaceutical industry



## James Brady

*Chief Human Resource Officer*

- Prior CHRO at uniQure Therapeutics; Vice President, Human Resources at Intarcia Therapeutics
- Over 30 years of senior human resources leadership with over 17 years in the life science space



**SPERO**  
THERAPEUTICS

Thank You