SPERO THERAPEUTICS

Corporate Presentation

April 2025

Forward-looking Statement

This presentation contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended, including without limitation, statements regarding, among other things, the potential number of patients who could be treated by tebipenem HBr and market demand for 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 continued development and commercialization of SPR720 and SPR206; 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; cash runway, 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

Clinical stage portfolio

- Indications with high unmet need in addressable patient populations
- Orphan drug and/or QIDP designations
- Strong global intellectual property

Tebipenem HBr in Phase 3 for cUTI

- In development, with potential to be the first and only oral carbapenem for complicated urinary track infections (cUTI)
- Pre-planned IA expected in 2Q 2025
- Phase 3 data readout and regulatory submission (US) expected in 2H 2025[1]
- GSK commercial partnership with strong economics

Strong financial foundation

- Cash runway into 2Q-2026
- Potential for additional regulatory and commercial milestones

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1. GSK Q3 results https://www.gsk.com/media/11646/q3-2024-results-announcement.pdf

Maturing Pipeline with Differentiated Clinical Assets

Asset	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Anticipated Milestone
Partnered Assets						
Tebipenem HBr GSK Worldwide, ex. Asia meiji Asia	**cUTI**					Pre-specified Interim Analysis 2Q 2025
Wholly Owned						
SPR720	**First-line NTM-PD**					Complete data analysis & determine next steps[1]

Non-dilutive Funding Alliances

cUTI: complicated urinary tract infection; NTM-PD: non-tuberculous mycobacterial pulmonary disease;
1. The company has elected to suspend its current development program for the oral dosing of SPR720, as it completes Phase 2a data analysis.

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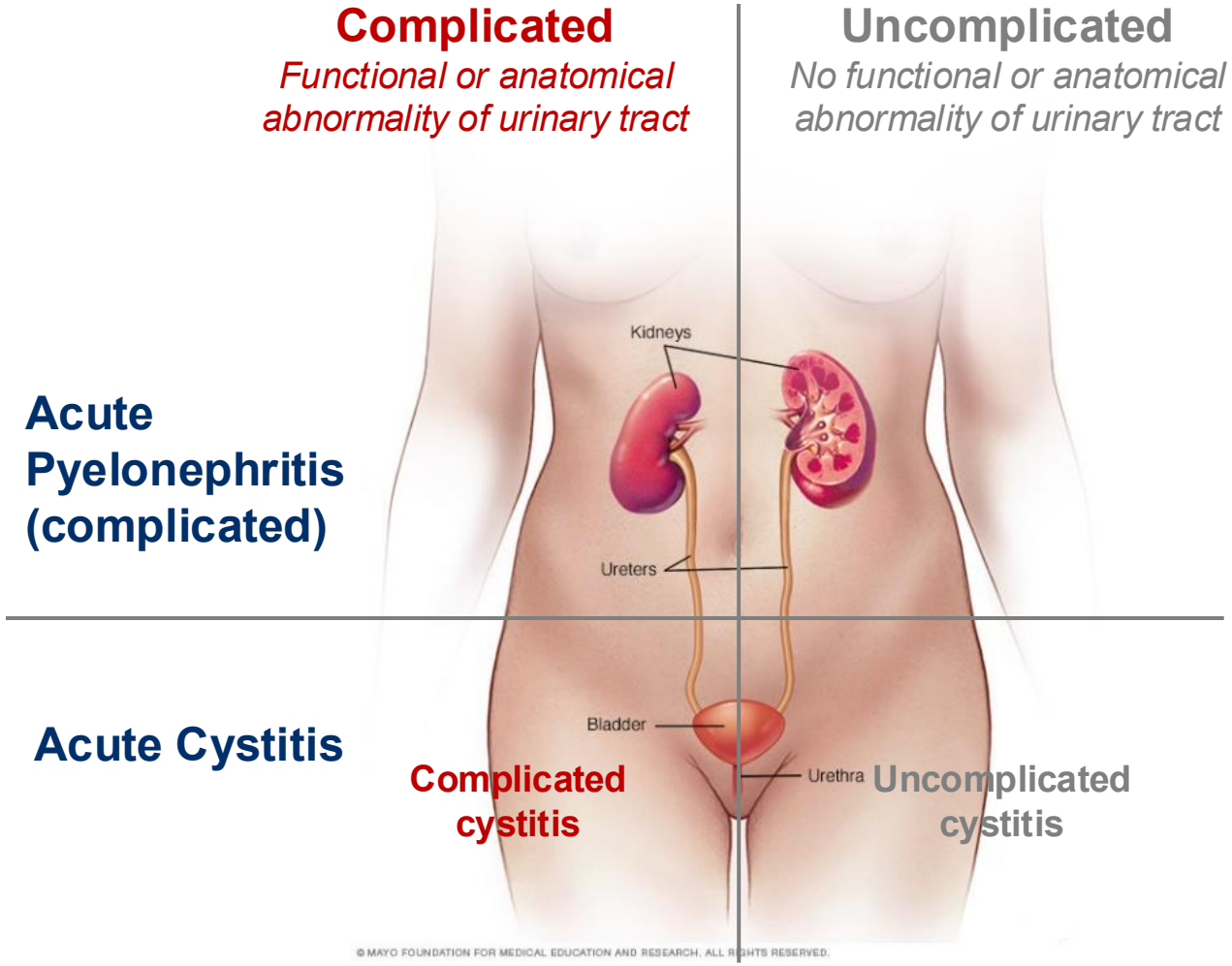
Tebipenem HBr

Oral Carbapenem for cUTI

Complicated Urinary Tract Infection (cUTI)

- cUTIs are associated with an **abnormality of the urinary tract** or in the presence of catheterization
- Patients with **pyelonephritis**[1], regardless of underlying abnormalities of the urinary tract, **are considered a subset of cUTI patients**
- cUTIs are more likely caused by resistant pathogens and have a higher risk of recurrence and progression to severe infection



1. Pyelonephritis – acute kidney infection. Source: Mayo Clinic website

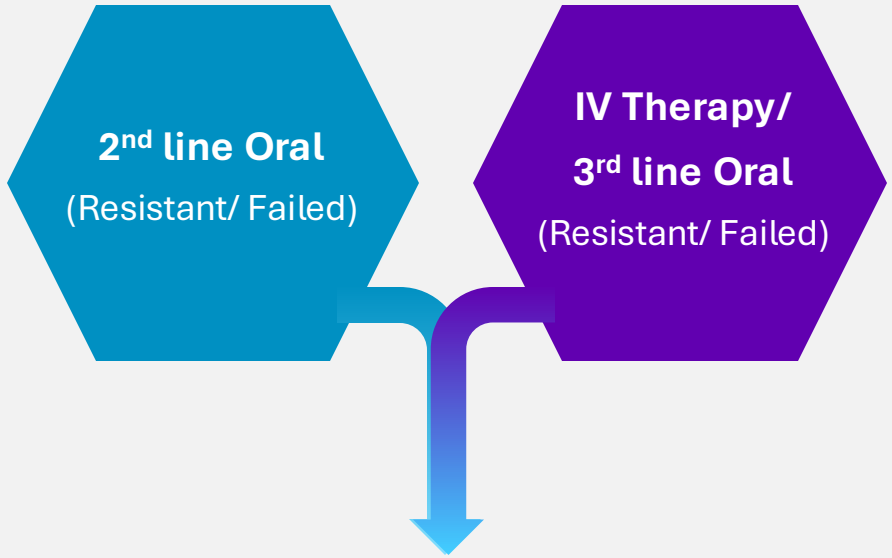
Overview of cUTI Therapeutic Landscape

Lack of effective oral treatment options has resulted in increased –

- Outpatient visits
- Emergency department visits
- Outpatient IV use
- Hospitalizations
- Hospital days
- Home health and long-term care stays post-hospitalization

All translating to patient suffering and high financial burden

Resistance and lack of effective treatments result in a large addressable cUTI patient population



Annual cUTI treatment episodes estimated to be 3.4M[1]

IV: intravenous; tebipenem HBr: tebipenem pivoxil hydrobromide (formerly SPR994); UTI: urinary tract infection

1. GSK Epidemiology data - fy-2023-epidemiology-report.xlsx (live.com)

Tebipenem HBr: Potential to Reduce Treatment Burden for cUTI Patients

Potential first-to-market oral carbapenem

- Orally bioavailable carbapenem prodrug that rapidly converts to active moiety tebipenem
- Potential treatment of complicated UTI in outpatient setting vs current hospitalized setting
- Robust IP through 2041
- QIDP designation

Phase 3 enrolling

- PIVOT-PO trial protocol approved under FDA Special Protocol Assessment (SPA)
- Global trial with centers in the North and South America, Europe, Africa, and Asia

Global commercial partnership

- Out-licensed global commercial rights ex-Asia to GSK
- Japan and certain other Asian countries retained by Meiji
- Robust financial terms including developmental, regulatory, and commercial milestones, as well as tiered sales royalties

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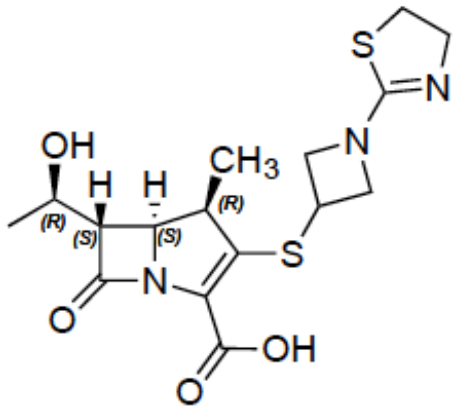
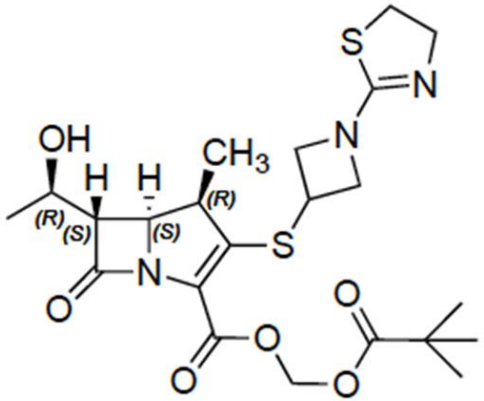
QIDP: qualified infectious disease product.

Compound Structures and Definitions



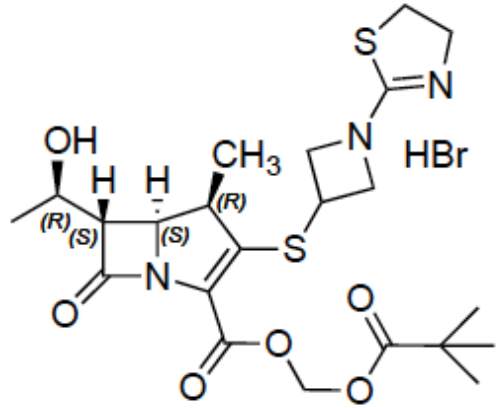
Tebipenem

Active drug



Tebipenem Pivoxil

Orally bioavailable prodrug of tebipenem (Orapenem® fine granules for pediatrics; Meiji Seika, Japan)



Tebipenem Pivoxil Hydrobromide

Spero's orally bioavailable prodrug + HBr salt, enabling high dosage and room temperature-stable product

- **TBP-PI-HBr is an orally bioavailable carbapenem prodrug** that rapidly converts in enterocytes to active moiety tebipenem
- **Tebipenem has *in vitro* activity against multidrug-resistant (MDR) Gram-negative pathogens**, including extended-spectrum ß-lactamase (ESBL)-producing, fluoroquinolone-resistant, and TMP-SMX-resistant Enterobacterales

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TMP-SMX = Trimethoprim-Sulfoxazole. Source: Kazuhiko Kato et. al., Molecular Pharmaceutics, vol. 7, no. 5, 1747–1756, doi.org/10.1021/mp100130b

Clinical Experience Supports Safety, Efficacy of Tebipenem[1]

Tebipenem Pivoxil evaluated in 23 trials enrolling over 1,300 subjects (Meiji-Seika experience)

- 741 Adult subjects evaluated, across 17 efficacy and pharmacology trials
- 440 pediatric subjects evaluated, across 6 efficacy and pharmacology trials
- Generally well tolerated, comparable to common, approved oral beta lactam antibiotics and IV carbapenems
- Met its primary endpoint in 3 double blind controlled efficacy trials in pediatric pneumonia, otitis media, and sinusitis

Tebipenem Pivoxil approved in Japan since 2009

- Approved for pediatric pneumonia, otitis media, sinusitis, over 4 million patients dosed to date
- Extensive post-marketing safety and efficacy surveillance completed, covering 3,331 patients
- No issues of safety were observed, and adequate efficacy was demonstrated

Tebipenem HBr evaluated in 10 trials enrolling over 950 subjects till date (Spero experience)

- 964 subjects have received at least one dose of TBP-PI-HBr
- 279 healthy volunteers or patients with renal impairment across Phase 1 studies
- 685 patients with cUTI/AP in a previous Phase 3 study (SPR994-301; ADAPT-PO)

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1. Akash Jain, Luke Utley, Thomas R. Parr, Thomas Zabawa & Michael J. Pucci (2018): Tebipenem, the first oral carbapenem antibiotic, Expert Review of Anti-infective Therapy, DOI: 10.1080/14787210.2018.1496821

Activity of Tebipenem and Comparator Carbapenems against Gram-negative and -positive Uropathogens

Pathogen	N	MIC_{90} (µg/mL)			
		Tebipenem	Imipenem	Meropenem	Ertapenem
Enterobacterales (Surveillance US & EU, 2022)					
E. coli	1,444	0.03	≤0.12	0.03	0.015
K. pneumoniae	404	0.12	0.5	0.06	0.25
P. mirabilis	170	0.25	4	0.12	0.015
E. cloacae (species complex)	72	0.25	0.5	0.12	2
K. oxytoca	69	0.06	0.25	0.03	0.03
K. aerogenes	40	0.12	1	0.06	0.25
S. marcescens	22	0.25	2	0.12	0.5
C. koseri	43	0.03	≤0.12	0.03	0.008
Gram-positive uropathogens (NCRPT-0089)					
E. faecalis	30	0.5	NA	4	>4
S. aureus (MSSA)	20	0.03	NA	0.25	0.25
S. Saprophyticus (MS)	25	0.25	NA	0.25	1

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* Spero data on file. MIC = Minimum Inhibitory Concentration; MSSA = Methicillin Susceptible Staph Aureus; MS = Methicillin Susceptible

Tebipenem is Active Against Clinically Important Resistant Enterobacterales UTI Pathogens from Europe and the USA in 2022

Organism/ phenotype	Phenotype	N	MIC_{90} (µg/mL)			
			Tebipenem	Imipenem	Meropenem	Ertapenem
Enterobacterales	All	2,447	0.12	1	0.06	0.06
E. coli	All	1,444	0.03	≤0.12	0.03	0.015
	ESBL*	205	0.03	0.25	0.03	0.12
	Levofloxacin-NS*	317	0.03	0.25	0.03	0.06
	TMP-SMX-R*	399	0.03	≤0.12	0.03	0.03
K. pneumoniae	All	404	0.12	0.5	0.06	0.25
	ESBL*	96	0.12	0.5	0.12	1
	Levofloxacin-NS*	74	0.25	0.5	0.12	1
	TMP-SMX-R*	102	0.06	0.5	0.06	0.25

*Non-CRE (Imipenem-susceptible, MIC ≤1 µg/mL): 2022 European and US Surveillance Isolates (JMI Laboratories)

* Spero data on file. ESBL = Extended spectrum beta-lactamases; TMP-SMX = Trimethoprim-Sulfoxazole; R = Resistant; NS= Non susceptible; CRE = Carbapenem Resistant Enterobacterales; MIC = Minimum Inhibitory Concentration

Tebipenem Pharmacokinetic Profile

- Prodrug rapidly converts to tebipenem in enterocytes of GI tract
- Plasma Half-life ~1 hour
- Dose-proportional PK relationship when administered fed or fasted state
- Low potential for drug-drug interactions
  - No CYP450-dependent metabolism
  - No induction of CYP450 enzymes
- Elimination through fecal and renal excretion
  - No dose adjustment for hepatic impairment
  - Dose adjustment for moderate and severe renal impairment
- Oral bioavailability of tebipenem ~60%

Spero data on file

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)

Treatment Population

Patients with a diagnosis of cUTI (incl. AP)
Approximately 2648 patients
(stratified by age, baseline diagnosis, etc.)
7-10 Days of Dosing

R

patients randomized 1:1 (blinded)

Treatment Arms

- TBP-PI-HBR (600 mg) orally and "dummy" infusion IV, every 6 hours, days 1-10, (n=1324)
- Imipenem-cilastatin (500 mg) IV and matched "dummy" tablets, orally every 6 hours, days 1-10, (n=1324)

Endpoints

Primary Endpoint:

Overall response at TOC in micro-ITT population

Primary Analysis:

Assessment of non-inferiority (NI) in micro-ITT population, based on a 10% NI margin

Entered FDA Special Protocol Assessment Agreement (SPA):

The FDA has indicated that positive and persuasive results from PIVOT-PO, along with previously completed studies[1], could be sufficient to support approval of tebipenem HBr as a treatment for cUTI, including pyelonephritis, for a limited use indication.

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1. supported by confirmatory evidence from PK/PD and breakpoint package

AP: acute pyelonephritis; cUTI: complicated urinary tract infection; NI: non-inferiority; TBP-PI-HBr/tebipenem HBr: tebipenem pivoxil hydrobromide (formerly SPR994)

Tebi Well Positioned As First Oral Carbanepenem for cUTI

Oral candidates for Complicated UTIs :

Company	Product	Pharmacological Class	Development Stage
Spero	Tebipenem HBr	BL (Carbapenem)	Phase 3
VenatoRx	Ceftibuten-ledaborbactam etzadroxil	BL/BLI	Phase 1
Shionogi/Qpex	Ceftibuten-xeruborbactam oral prodrug	BL/BLI	Phase 1

Oral candidates for Uncomplicated UTIs :

Company	Product	Pharmacological Class	Development Stage
Iterum	Sulopenem etzadroxil and probenecid (Orlynvah)	BL (Penem)	NDA Approved (Oct 2024)
Utility	Pivmecillinam (Pivya)	BL (Aminopenicillin)	NDA Approved (Apr 2024)
GSK	Gepotidacin	Triazaacenaphthylene	NDA Approved (March 2025)

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BL = Beta-lactam; BLI = Beta-lactamase Inhibitor

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 FPFD, Spero qualified to receive $95 Million in development milestones payable in four equal installments over two years; $47.5M remaining to be received in 2025*

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

FPFD: first patient first dose. SPA: Special Protocol Assessment

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SPR720

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

The company has suspended its current development for SPR720

SPR720: Inhibits Gyrase B in Bacterial Cells

- Novel mechanism of action for NTM-PD not exploited by current antibiotics
- No evidence of cross resistance against marketed antibiotics based on *in vitro* trials
- Low propensity for development of resistance as monotherapy and in combination with SOC antibiotics *in vitro*
- Currently formulated as an oral drug

Preclinical Studies

Support activity against a broad spectrum of NTM-PD pathogens, as well as low propensity for development of resistance

Proof of Concept Phase 2a oral study

While the data showed antimicrobial activity associated with SPR720, an interim analysis did not show sufficient separation from placebo, highlighted potential oral dose limiting safety issues in subjects dosed at 1,000 mg orally once daily

Next Steps

The Company plans to complete data analysis of all enrolled patients (n=25) and determine the next steps for the SPR720 program

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1. Keith A. Rodvold et. Al., Antimicrobial Agents and Chemotherapy, https://doi.org/10.1128/aac.01103-24

Leadership Team

Fulcrum Therapeutics
BANK OF AMERICA
UBS

Esther Rajavelu

President and Chief Executive Officer; Chief Financial Officer

- Twenty-five years of life science sector experience, combining equities research, investment banking, strategy consulting, and operations
- Prior CFO at Fulcrum Therapeutics. Senior equity research analyst at UBS, Oppenheimer and Deutsche Bank. Healthcare Investment Banker at Bank of America Merrill Lynch

CUBIST

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

uniQure
Intarcia
SANOFI GENZYME

James Brady

Chief Human Resource Officer

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

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Thank You