



SPERO[®] THERAPEUTICS

Ladenburg Thalmann Healthcare Conference

July 13, 2021

Forward-looking Statements

This presentation contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995 regarding, among other things, the design, initiation, timing and submission to the U.S. Food and Drug Administration (FDA) of a New Drug Application (NDA) for tebipenem HBr and the potential approval of tebipenem HBr by the FDA; future commercialization, the potential number of patients who could be treated by tebipenem HBr and market demand for tebipenem HBr generally; expected broad access across payer channels for tebipenem HBr; the expected pricing of tebipenem HBr and 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 direct and indirect impact of the pandemic caused by an outbreak of a new strain of coronavirus on the Company's business and operations; 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; objectives of management; potential growth opportunities; potential market size; reimbursement matters; possible or assumed future results of operations; projected costs; and the Company's cash forecast 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: 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 outcome of discussions with the FDA regarding the Phase 2a clinical trial of SPR720 and Spero's ability to proceed with such trial; the potential impact of the COVID-19 pandemic; the Company's ability to retain key personnel and to manage its growth; 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; 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 development milestone payment under its agreement with Everest Medicines; whether BARDA elects to exercise its second option under the Company's agreement with BARDA; 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.

Spero: Robust Infectious Disease and Rare Disease Portfolio led by Oral Tebipenem HBr

Tebipenem HBr (previously SPR994): *oral* carbapenem

ADAPT-PO Phase 3 met its primary endpoint in landmark trial – Oral tebipenem HBr demonstrated noninferiority to IV ertapenem in cUTI and AP; safety results similar to intravenous ertapenem

NDA submission planned for 2H21

Pipeline of assets supported by positive Phase 1 data

SPR720: First potential oral therapy for NTM infections; granted orphan designation

SPR206: Novel therapy for MDR Gram-negative infections; Phase 1 BAL and renal impairment trials initiated 2Q21

Multi-billion dollar opportunity for cUTI and NTM

Large unmet needs in infectious disease

No approved branded or generic oral competition within carbapenem class

Marketed primarily outside the hospital

cUTI = complicated urinary tract infections; ancillary supportive studies also required for tebipenem HBr in addition to single Phase 3 trial;
NTM = non-tuberculous mycobacterial ; PK = Pharmacokinetic; MDR = multidrug resistant infections; Tebipenem HBr = tebipenem pivoxil hydrobromide (formerly SPR994)

Leadership Team

Ankit Mahadevia, MD | Chief Executive Officer

Prior Venture Partner at Atlas Venture; Arcion Therapeutics, Genentech, McKinsey
Formed eight companies in the life sciences sector; three as Acting CEO
Background in healthcare policy

Genentech McKinsey & Company

Cristina Larkin | Chief Operating Officer

Prior Vice President, Infection, Forest Laboratories
25+ years of commercial expertise with multiple antibiotic launches including Teflaro, Dalvance, Avycaz, Levaquin
Launched seven products across variety of therapeutic categories in retail and hospital
FOREST LABORATORIES, INC.

David Melnick, MD | Chief Medical Officer

Prior Vice President Clinical Development for anti-infectives; Allergan, AstraZeneca
18 years in anti-infective drug development including 16 Phase 3 trials
Seven successful anti-infective drug approvals

Allergan AstraZeneca

*Trademarks are properties of their respective owners



Tom Parr, PhD | Chief Scientific Officer

Prior CSO at Fedora Pharma and Targanta; Microcide, Head of Antibacterials, Eli Lilly
Worked on a broad range of antibiotic classes and marketed antibiotics (oritavancin, vancomycin, ceftazidime, daptomycin, cephalexin, cefaclor, loracarbef, anidulafungin)

fedora[®] Lilly

Timothy Keutzer | Chief Development Officer

Prior VP Program and Portfolio Management, Cubist
Extensive antibiotic development experience from pre-clinical to approval
Over 20 years in the pharmaceutical industry

CUBIST
PHARMACEUTICALS

Sath Shukla | Chief Financial Officer

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

VERTEX

Tamara Joseph | Chief Legal Officer









Over 20 years of leadership and legal experience in the biotech sector
Prior General Counsel at several biotechnology companies including Millendo Therapeutics, Enzyvant Therapeutics, InVivo Therapeutics, and Cubist

CUBIST
PHARMACEUTICALS



Multiple Catalysts Across the Pipeline

Positive Tebipenem HBr ADAPT-PO Phase 3 Topline Data Support Expected NDA Submission in 2H21

Program	Target Indication	Preclinical	Phase 1	Phase 2	Phase 3	Upcoming Milestone	Partnerships/Alliances
Oral Carbapenem for Gram Negative Multidrug Resistant (MDR) Infections							
Tebipenem HBr	Complicated UTI (cUTI)	<div></div>				NDA submission for the treatment of cUTI planned for 2H21	 
Oral DNA Replication Inhibitor for Non-tuberculous Mycobacterial (NTM) Disease							
SPR720	NTM	<div></div>				Respond to FDA clinical hold notification	 
Direct Acting IV Potentiator for Gram Negative MDR Infections							
SPR206	MDR Infections	<div></div>				Phase 1 BAL and renal impairment trials initiated 2Q21; data readouts expected in early 2022	   

As of July 1, 2021

Spero Pipeline Assets Share Common Attributes With Other Successful ID Drugs



*Estimated Peak Year Worldwide Sales
*Trademarks are properties of their respective owners

Oral Carbapenem

Tebipenem HBr

SPERO 
THERAPEUTICS



Tebipenem HBr: Positive ADAPT-PO Phase 3 Trial Results

Robust Results Support NDA Submission and Potential Treatment Shift from IV to Oral in cUTI

Landmark ADAPT-PO Trial Met Primary Endpoint

- Positive results in landmark study unprecedented for the field
- Overall combined response rate: Oral tebipenem HBr response rate of 58.8% versus 61.6% for IV ertapenem (-3.3%; -9.7, 3.2; -12.5% NI margin)*
- Tebipenem HBr safety results similar to ertapenem

Potential to Transform How cUTI Patients are Treated

- Tebipenem HBr, if approved as the first oral carbapenem, could allow appropriate patients the opportunity to receive treatment in the community setting
- Provides an important value proposition that could benefit patients, hospitals and payers

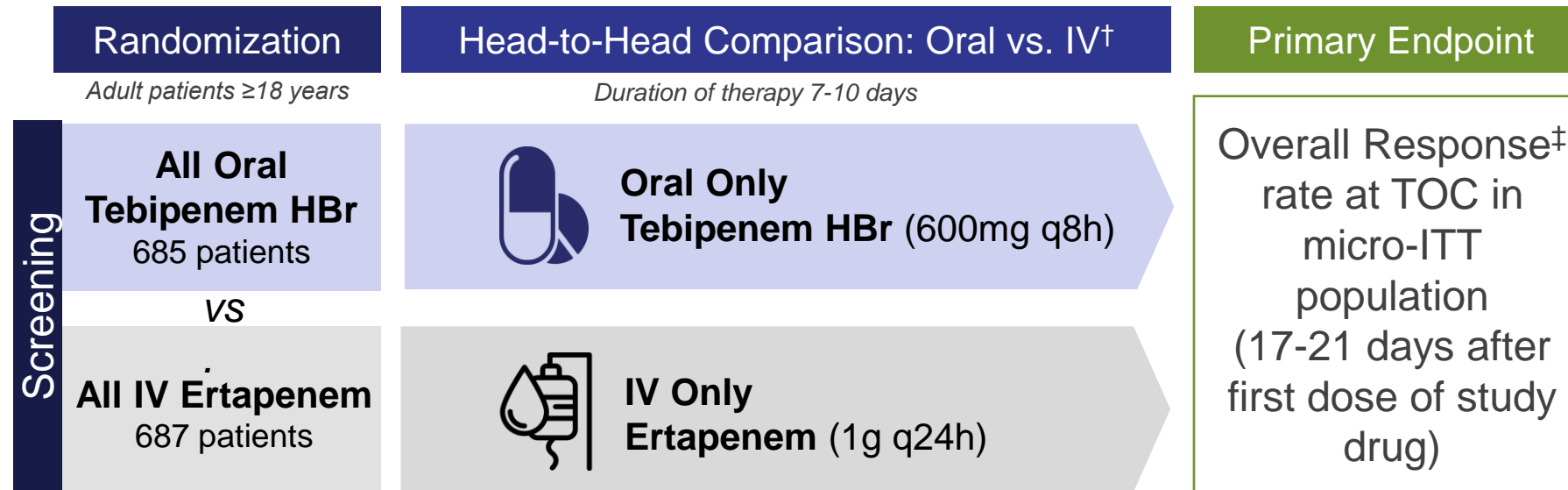
Positive ADAPT-PO Trial Results Support an NDA Submission in 2H21

- One well-controlled pivotal trial to form the basis for an NDA submission as per FDA interactions
- Expect completion of a new drug application (NDA) submission to the FDA in the second half of 2021

If approved, tebipenem HBr would be the only oral carbapenem approved for treatment of complicated urinary tract infections (cUTI) and acute pyelonephritis (AP)

Pivotal Phase 3 Trial Design: Evaluation of *Oral* Tebipenem HBr compared to *IV* Ertapenem

Innovative Trial Design Compares an Oral-Only Regimen Directly Against an IV Regimen for cUTI and Acute Pyelonephritis (AP)



[†]Showing active treatment arms only; study is placebo-controlled double-blind, double-dummy

[‡] Combined Clinical Cure and Microbiological Eradication

Additional evaluation at LFU (23-27 days after first dose of study drug)

Non-inferiority margin of -12.5%

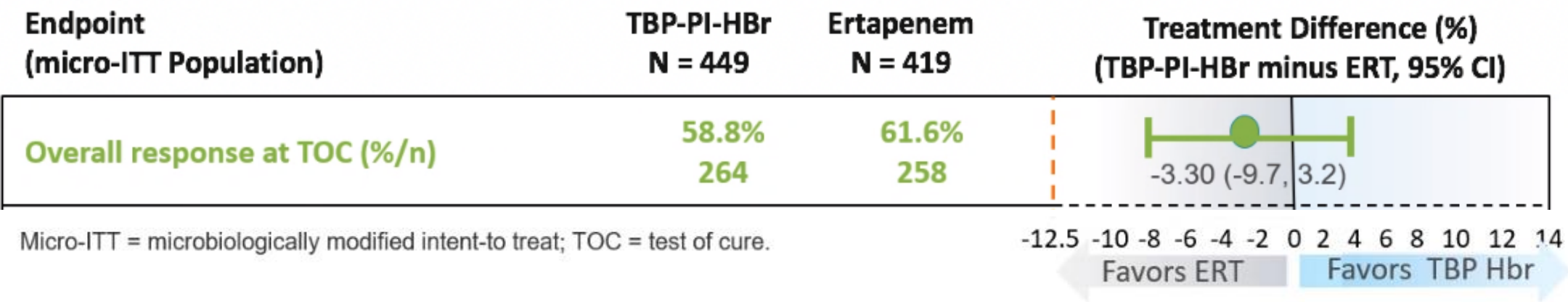
Masked individual and composite PK data reviewed by an independent review committee after enrolling the first 70 patients to confirm dose

ADAPT-PO Met Its Primary Efficacy Endpoint

Tebipenem HBr Demonstrated Statistical Non-inferiority Compared to Ertapenem

ADAPT-PO primary endpoint:

Clinical cure + microbiological eradication at test-of-cure in micro-ITT population



Demonstrated non-inferiority at margin of -12.5%*

Results were similar between treatment arms across all subgroups of patients

ADAPT-PO Key Secondary Endpoints Evaluating Patient Outcomes

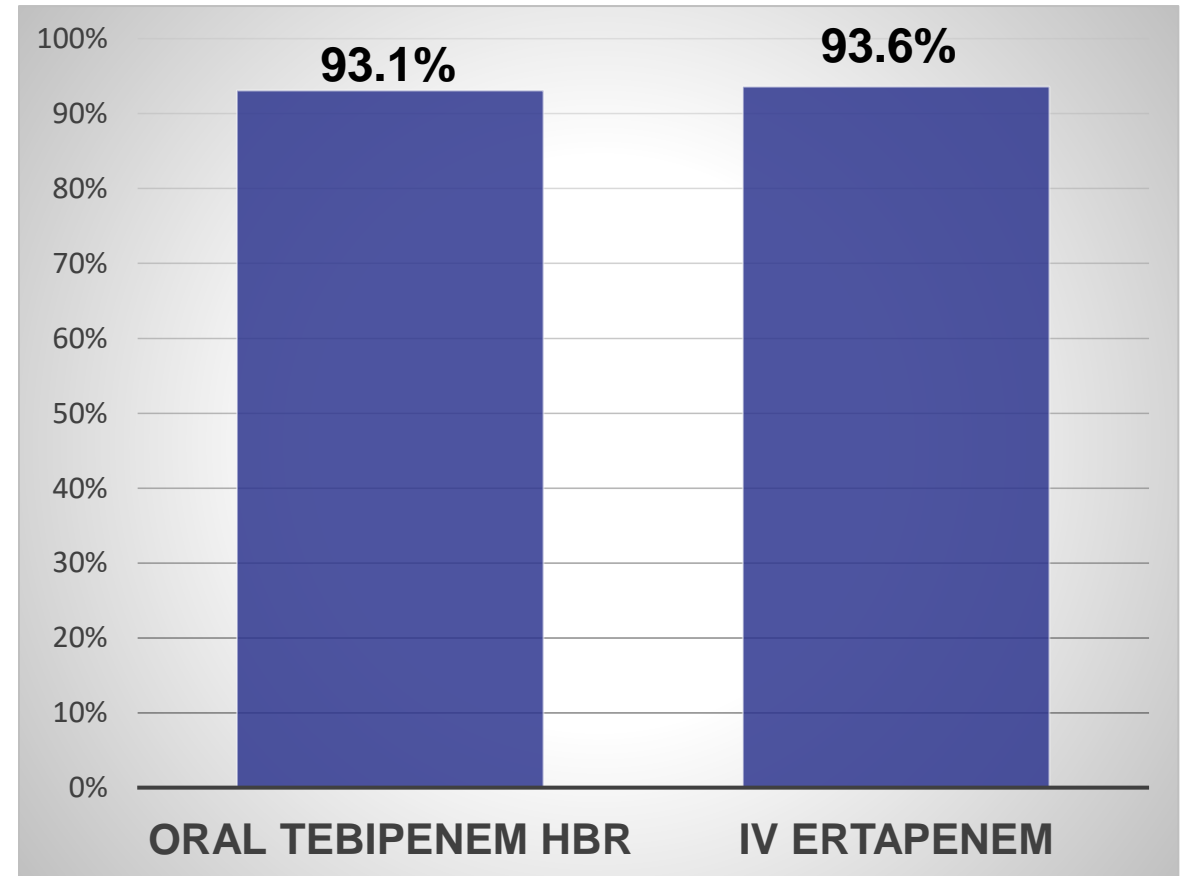
Clinical cure rate is a key determinant in routine clinical management of cUTI patients

Clinical cure rates at test-of cure (TOC) for micro-ITT groups comparable between the oral tebipenem HBr and IV ertapenem treatment arms

Durable clinical response observed with high clinical cure rates at TOC sustained through late follow-up visit

Median duration of therapy was similar for both treatment groups

Comparable Clinical Cure Rates at TOC



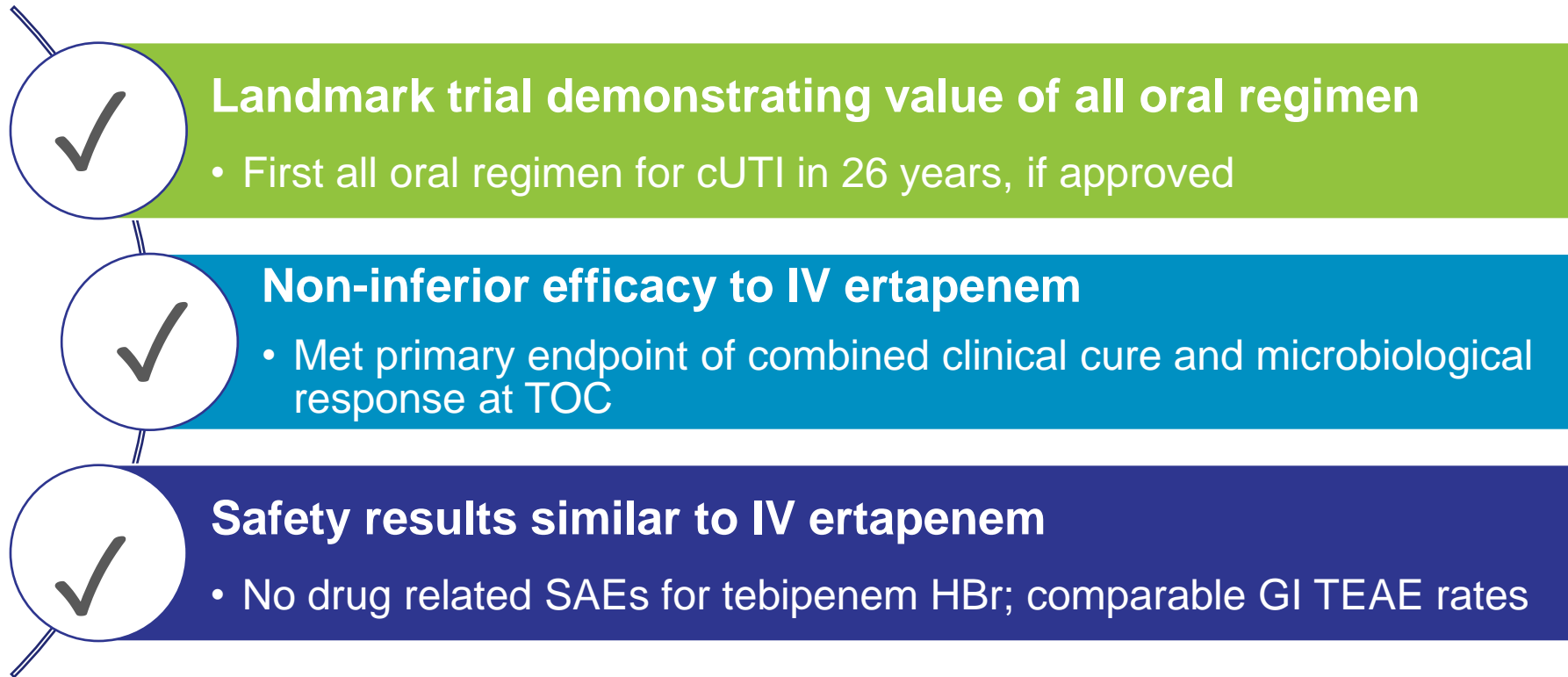
ADAPT-PO Safety and Tolerability Results

Safety and tolerability profiles similar across the oral tebipenem HBr and IV ertapenem arms

	Oral Tebipenem HBr	IV Ertapenem
Patients with at least one TEAE	25.7%	25.6%
Diarrhea	5.7%	4.4%
Headache	3.8%	3.8%
ALT increase	1.0%	1.0%
AST increase	1.0%	0.7%
Serious TEAEs	1.3%	1.7%
Drug-related SAEs	0.0%	0.3%

- TEAE rates generally consistent with that of the carbapenem/beta-lactam class
- Diarrhea and headache were the most commonly reported TEAEs in both treatment groups
- No *C. difficile* infections in tebipenem HBr arm
- No deaths reported

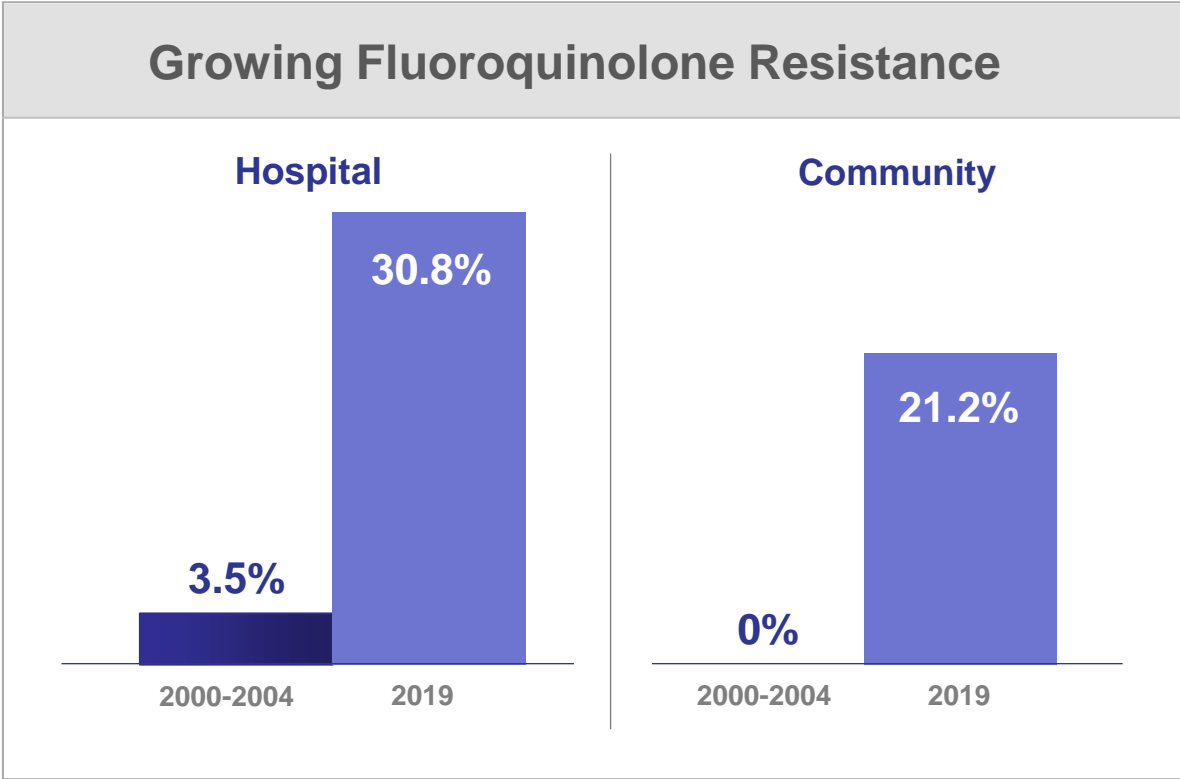
ADAPT-PO: Landmark Trial with Potential to Change Clinical Practice



Head-to-head results support regulatory submission of tebipenem HBr for the treatment of cUTI/AP

Lack of Oral Options for cUTI is Widespread, Costly, and Addressable

If approved, tebipenem HBr could help shift care back to outpatient setting: Helping patients to [Go Home or Stay Home](#)



Resistance + No Viable Oral cUTI Option = 2.3M Potentially Avoidable Hospitalizations

QuintilesIMS NDTI and MIDAS Database; Quintiles/IMS Market Assessment 2017, Simmering, Jacob E. et al. "The Increase in Hospitalizations for Urinary Tract Infections and the Associated Costs in the United States, 1998–2011." *Open Forum Infectious Diseases* 4.1 (2017): ofw281. PMC. Web. 15 Mar. 2018.; (Simmering et al. 2011). STEWARD 2019 Hospital resistance Data on file; BD 2019 community resistance data on file. Avoidable hospitalization estimates derived primarily from QuintilesIMS market assessment (August 2017); *Resistance estimates directly from market assessment. cUTI= Complicated urinary tract infection

Tebipenem HBr has the Potential to be a Highly Differentiated Therapy if Approved



No branded or generic oral substitutes in the carbapenem class



Existing, large, and growing unmet need



Primary reimbursement outside of the hospital



Current practice and financial incentives support usage



Prescriber base beyond infectious disease specialists

Tebipenem HBr Developed to Address a Large and Existing UTI Population

Stay Home: Hospital Avoidance

***Katrina**, college student at the University of Kansas, experienced “a U.T.I. that did not respond to three different rounds of antibiotics.” “It got so bad that I was out of school for months and had to get a medical withdrawal,” she said.*

Treatment currently includes:

- Evaluation for systemic involvement requiring hospitalization
- Referral to urologist to evaluate structure abnormalities
- Cycling through available oral antibiotics to avoid hospital admittance

Go Home: Get Home Sooner From Hospital

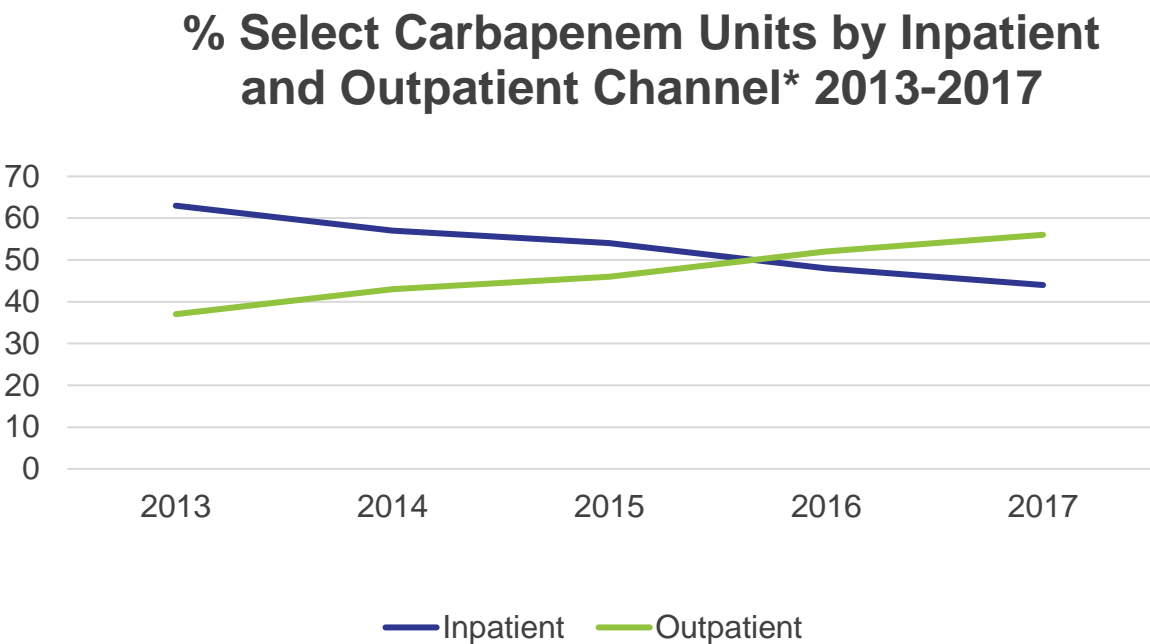
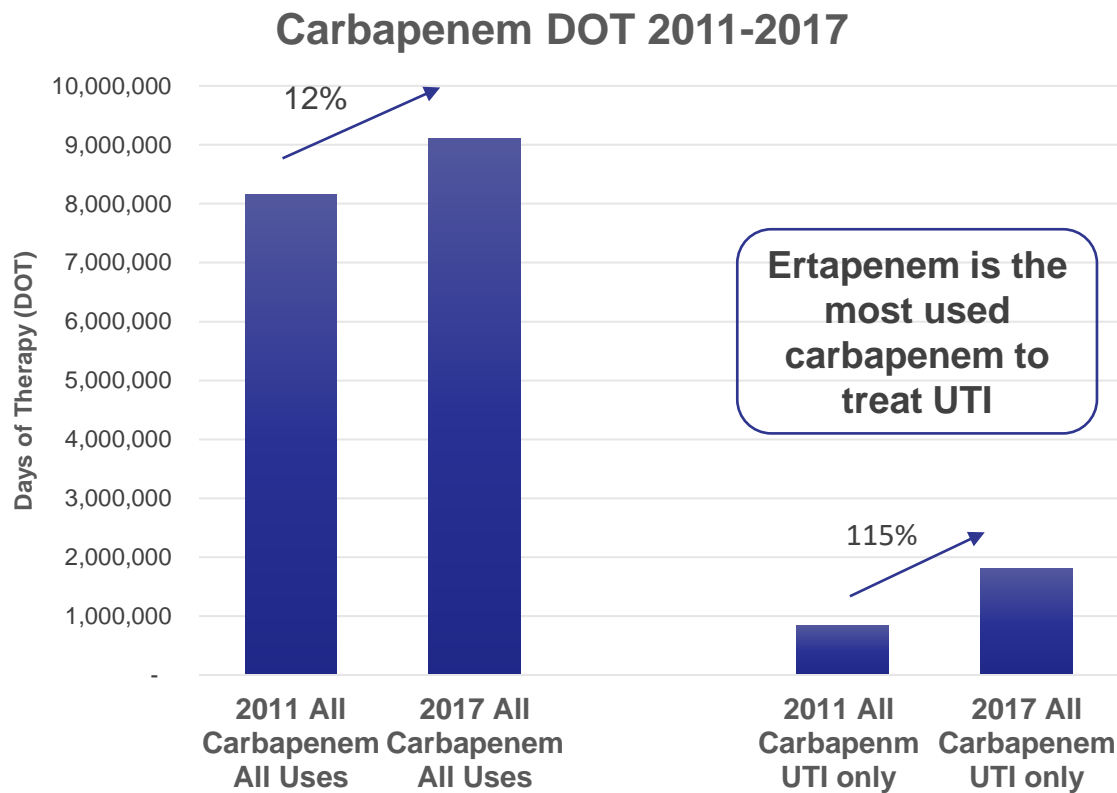
***“Timothy**, a medical student, was hospitalized with *E. coli* that was highly resistant to a wide variety of antibiotics. His discharge was delayed because the resistant nature of the bacteria would require insurance approval of home IV antibiotics.”*

Treatment currently includes:

- Full course of IV antibiotics within the hospital
- OR
- Transition from hospital to outpatient IV antibiotic therapy and monitor for complications

Carbapenem Market Estimated at \$3B in United States Alone*

Carbapenem use in UTI and in outpatient setting has increased significantly



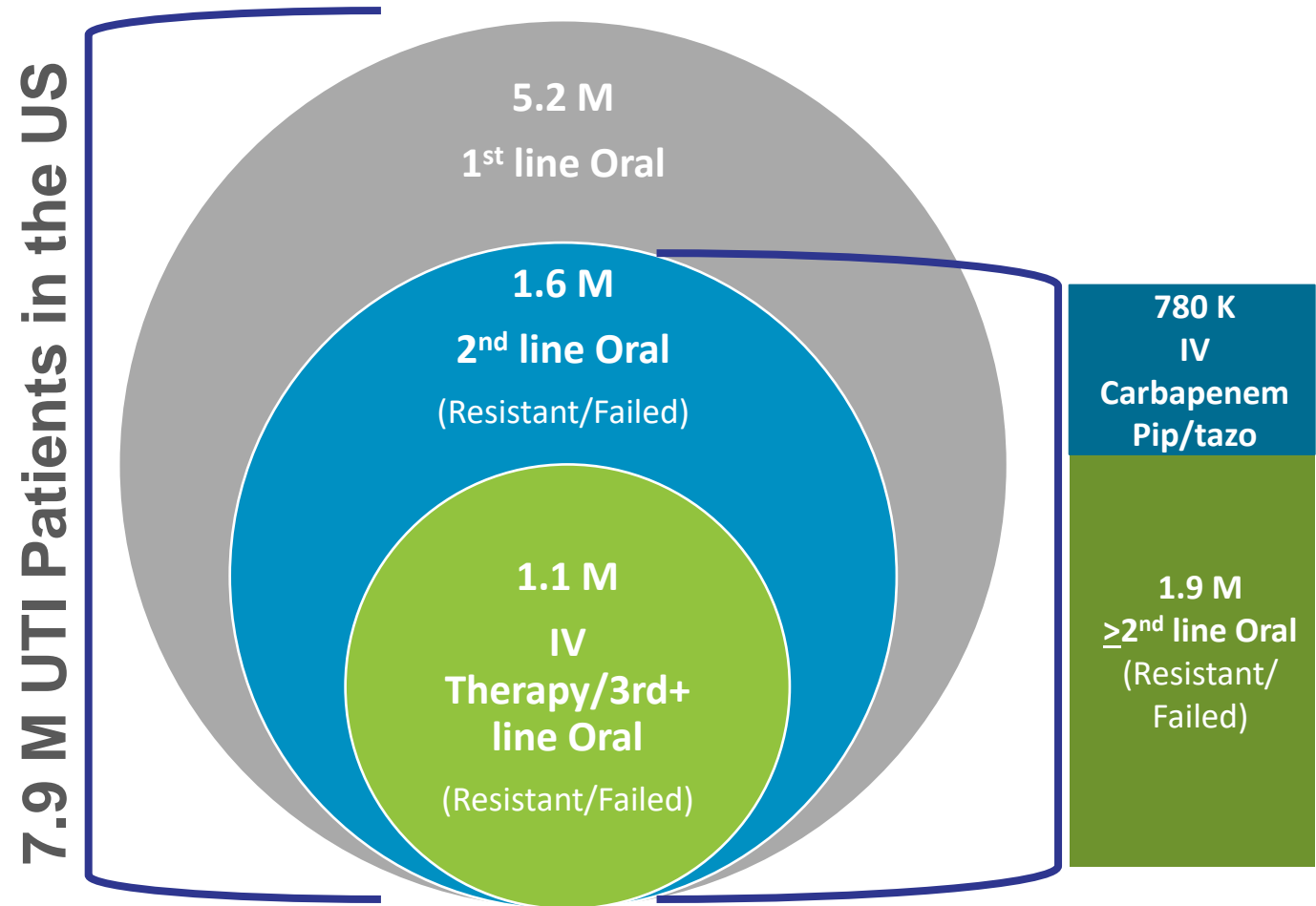
*9M DOT x \$350/day = \$3 billion

Source: IQVIA NDS Database, Accessed 11/06/2018; AMR data on use by indication; 2017 UTI data projected
Source: IQVIA NDS Database, accessed 11/06/2018

Outpatient calculated as volume in "Clinics" and "Home Health and Long Term Care" channels
*Analysis excludes Meropenem – price, dosing regimen and stability data do not make it a widely used outpatient option

Large Market Opportunity for Patients Able to Be Treated at Home

Targeted patients often cycle through multiple therapies



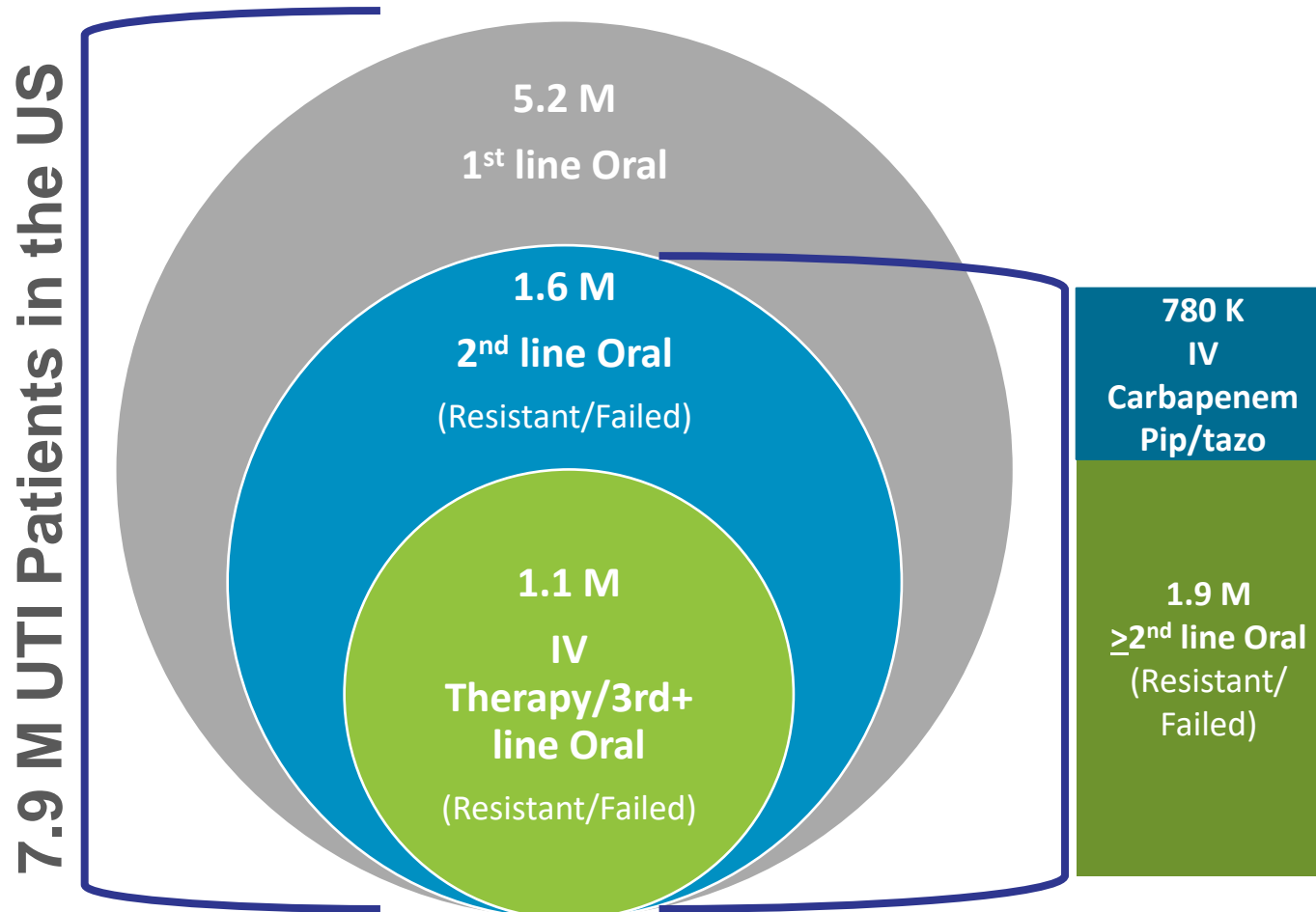
Lack of effective oral treatment options has resulted in increased...

- Outpatient visits
- Emergency department visits
- Unwarranted outpatient IV use
- Unnecessary hospitalizations
- Hospital days
- Home Health and LTC stays post-hospitalization

Spero Focus
2.7M UTI prescriptions 2nd line + Oral or IV therapy

Targeted Launch Based on Concentrated Prescribers and Focus on Urology

Initial sales team focused on high volume retail practices and hospitals



Spero will implement staged ~100-125 FTE field force by further segmenting for:

- Resistance (zip code level data)
- Favorable payer mix
- Adoption readiness, e.g. use of carbapenems

Spero Focus

50% patients in high-decile accounts
Highly concentrated opportunity in both retail (4,000 accounts) and hospital (1,000 accounts)

Urologists:

Largest treaters for 2nd line UTI patients across retail and hospital outlets²

Unmet Need Identified by Healthcare Providers; Expect Broad Access Across Payer Channels

Interactions with 100+ Health Care Professionals and 150M Payer Lives

There is high agreement that relapsed, failed cUTI patients could be treated at home

*"We need more drugs for UTI beyond Macrobid for lower UTI, Keflex and Cipro. **There is a lot of resistance to FQ**, so if we want an oral, we need something new." - Urologist*

HCPs identify carbapenems as a preferred drug class for our target patients

*"**Switching to PO** would be far preferable to a PICC and Home Health or having them return to an infusion center..." - KOL*

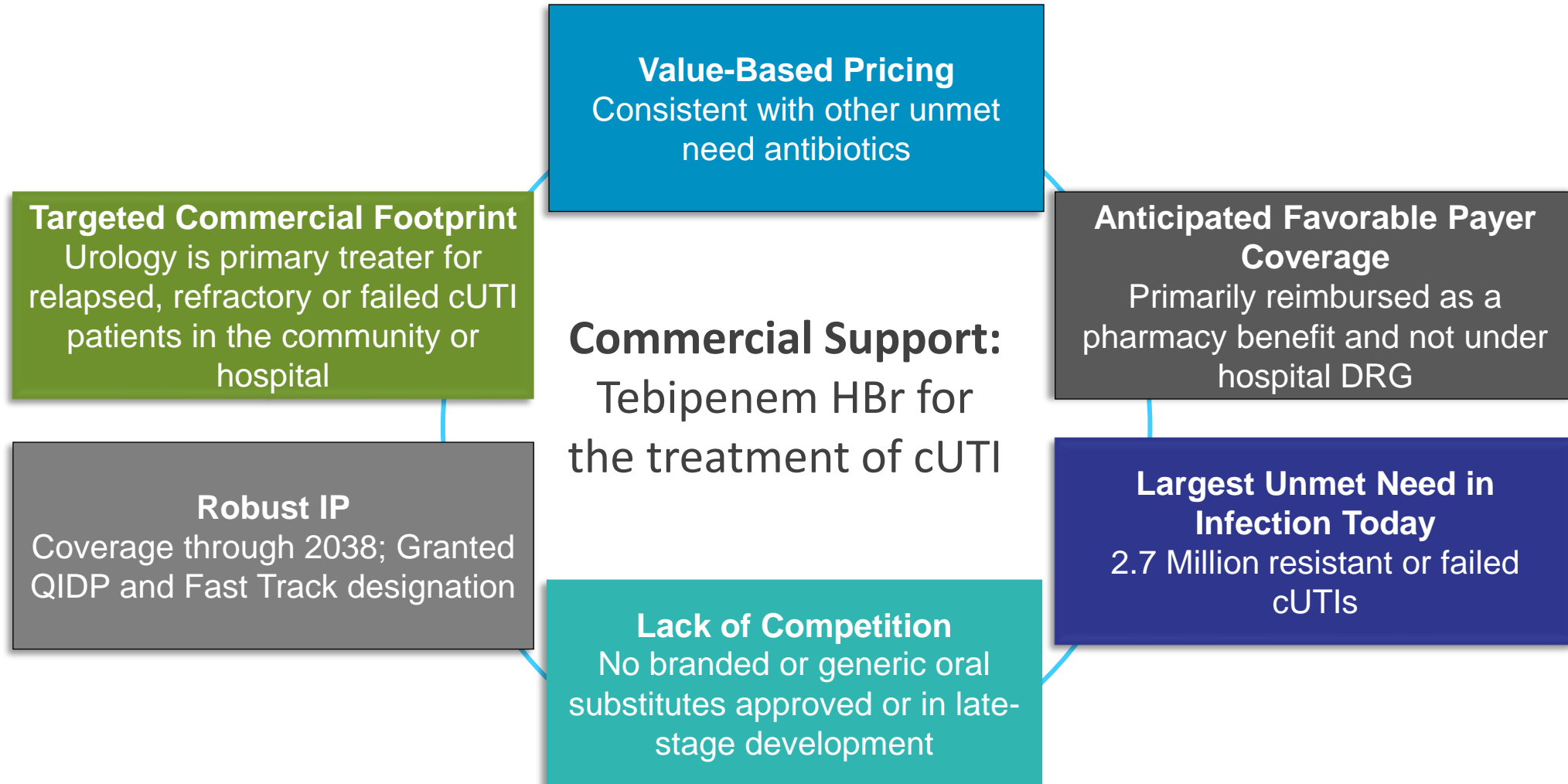
HCPs and Payers see potential value of tebipenem HBr

*"We don't have any oral carbapenems now to send them home. This would **shorten length of stay markedly and it covers ESBLs for hospital and community!**" – Hospitalist*

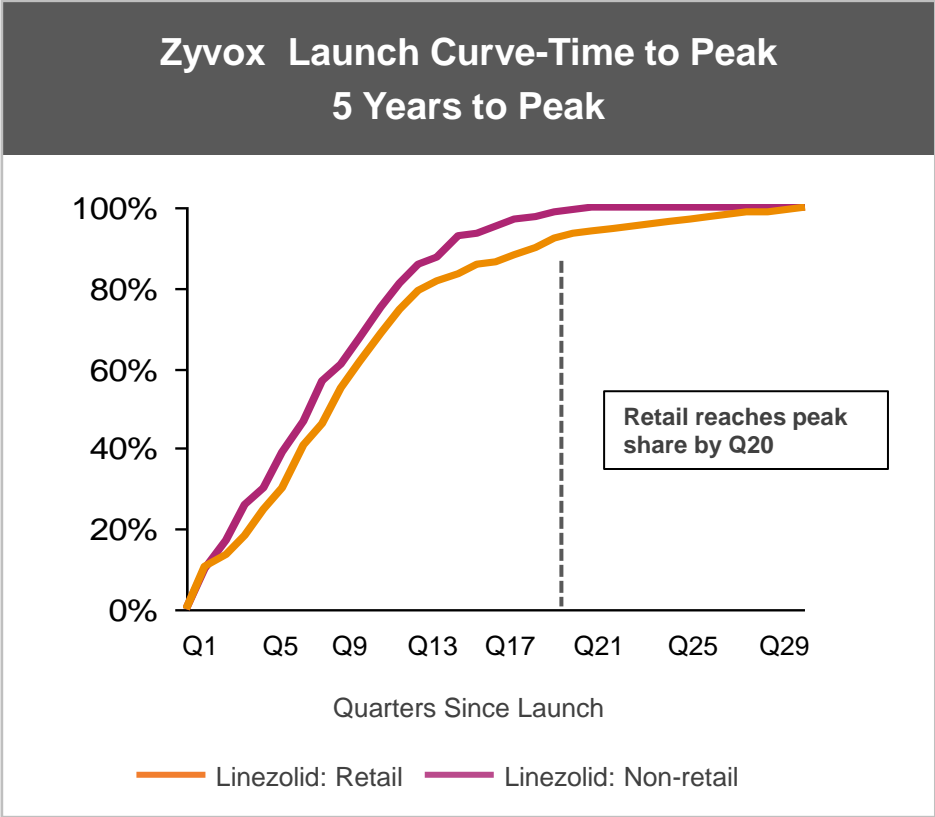
If approved, payers expect to broadly cover tebipenem HBr due to unmet need for new oral therapy

*"The value proposition here is that you can avoid using the IV which I think certainly has some **clinical benefit and may be even some economic benefit as well.**" - National Payer*

Tebipenem HBr Well Positioned to Recognize Significant Market Opportunity Upon Approval



Zyvox \$1.4 B Peak Year “Go-Home/Stay Home” Analogue for Tebipenem HBr Launch



	Zyvox MRSA Gram-positive Market	Tebipenem HBr FQ-R Gram-negative Market
Mkt size (pts)	1.8 M	2.2 M
Resistance to oral options at launch	29%	36%
Resistance to oral options at peak	64%	66%*
Reimbursement landscape	Restricted	Restricted
Pricing model	Premium	Premium

*Estimated for tebipenem HBr column based on 5.5% growth rate
Market Size for Zyvox is based on 14 M community cSSSI visits @ 5% resistance & 3.3 M hospital visits @ 29%. MS extended units and sales for linezolid; Resistance trends, Moran, *New England Journal Med* 355:7;2006; Monique R. Bidell et al. *Antimicrob. Agents Chemother.* 2016;60:3170-3173; OFID • Simmering et al; 2017 Winter.

Next Steps for Tebipenem HBr

Pre-NDA meeting complete in 1Q21; NDA filing remains on track for submission in 2H21



Complete NDA package and submit to FDA (expected in 2H21)



Exploring lifecycle management opportunities – Microbiological surveillance and clinical studies



Manufacturing readiness – Process validation and launch planning



Launch readiness – Market development work, pricing research, distribution strategy, key hires

Rare Disease Pipeline: SPR720



NTM: Absence of Effective and Well-tolerated Drugs Leaves Patients Without Options

Non-tuberculous mycobacterial disease (NTM) causes chronic and serious lung disease with debilitating symptoms that leads to a decline in lung function. It can have a significant physical and emotional impact on patients.

SPR720 has orphan drug designation and, if approved, could be the first and **only oral treatment for NTM**

Severe cough

“It [coughing] could go on for a good 90 minutes, and I'm just down on the floor, on my knees, grabbing my ribs, hacking.”

Fatigue

“I've been in the grocery store with the shopping cart, but I didn't have the energy to wait in line to check out.”

Dyspnea

Limits the types of activities that people are able to do, including walking, shopping, or traveling.

Source: The voice of the Patient; Non-Tuberculous Mycobacterial (NTM) Lung Infection Public Meeting: October 15, 2015 Report Date: April 2016

SPR720: First Novel Oral Candidate Designed to Treat NTM Infections

Broad spectrum, oral candidate: applicable to both non-refractory and refractory patients

More than **75%** of NTM patients are non-refractory; lack any approved options to treat NTM

Once daily dose supported by clinical and non-clinical studies

Selected 500 - 1000mg once daily dose range for Phase 2 supported by concordant *in vivo* and *in vitro* PK/PD models

BAL study in non-human primates supports lung exposure; macrophage data shows intracellular and extracellular activity

Safety/tolerability data

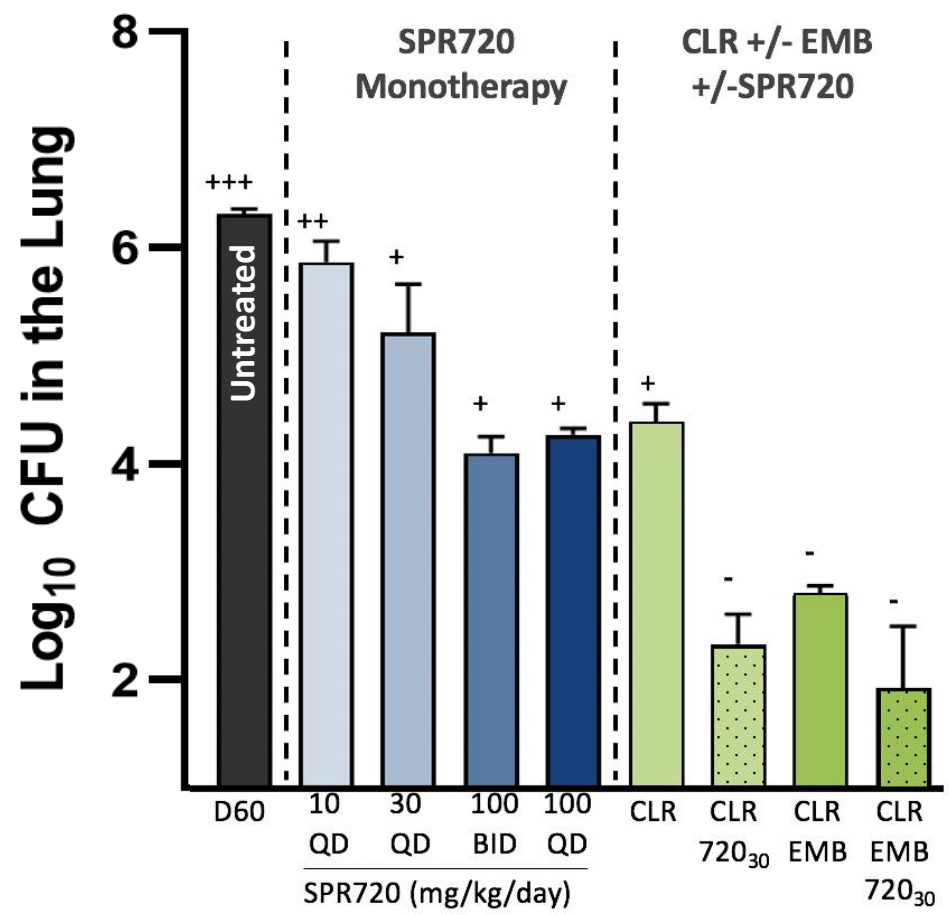
Data at 500 - 1000mg once daily in Phase 1 SAD/MAD studies supportive of advancement to Phase 2 clinical studies

Next Steps for the Development Plan

Evaluate toxicology study findings in non-human primates in conjunction with the FDA to determine next steps for the program

SPR720 Pulmonary Activity versus *M. avium* ATCC 700898 in a Murine Chronic Infection Model

SPR720 as monotherapy and in combination with SOC agents



- CLR and SPR720 monotherapy at 30 – 100 mg/kg/day reduced bacterial burden versus the untreated control
- SPR720 at 30 mg/kg/day improved the activity of CLR and was similar to CLR + EMB
- SPR720 at 30 mg/kg/day + CLR + EMB produced the greatest reduction in pulmonary burden

From the lab of Diane Ordway (CSU) Clarithromycin (CLR): QD x 28d at 250 mg/kg; Ethambutol (EMB): QD x 28d at 100 mg/kg

**Direct Acting IV
Potentiator:**
SPR206

SPERO 
THERAPEUTICS

SPR206: Safer Alternative for Patients Suffering from Serious Drug Resistant Infections

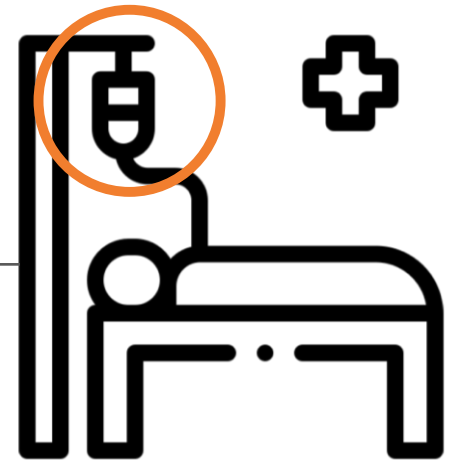
DR-*Acinetobacter* Treatment

TODAY

- Carbapenem; or
- Amp-sulbactam
- +/-Colistin

FUTURE

- Carbapenem; or
- Amp-sulbactam
- +/-**SPR206**



Significantly improved safety profile compared to colistin, enhances the activity of carbapenems and BL/BLIs¹

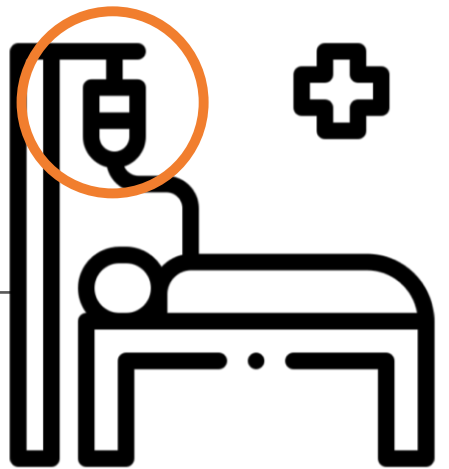
DR-*Pseudomonas* Treatment

TODAY

- Carbapenem; or
- BL/BLI¹
- +/-Colistin
- +/- AMG²

FUTURE

- Carbapenem; or
- BL/BLI¹
- +/-**SPR206**



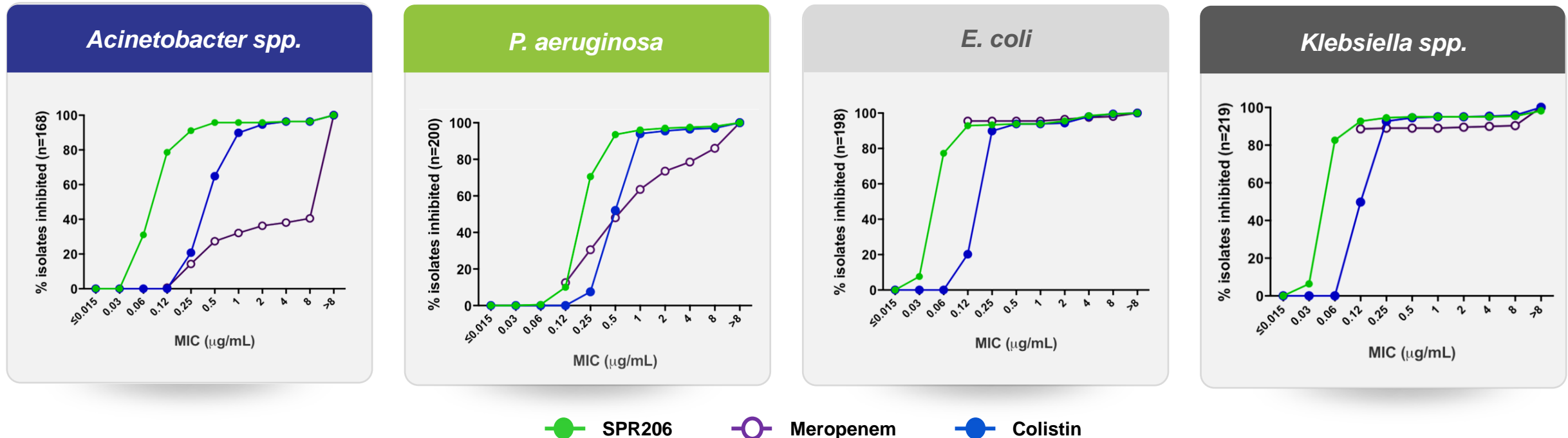
Significantly improved safety profile compared to colistin, enhances the activity of carbapenems and BL/BLIs¹

SPR206 Phase 1 Data and Preclinical Potency Against XDR Gram-Negative Pathogens Support Advancement

Phase 1 SAD/MAD Preliminary Data (N = 96)

- Successful Phase 1 doses likely to be within a therapeutic range for MDR Gram-negative bacterial infections
- Mean plasma drug exposures concordant with models predictive for clinical efficacy against target Gram-negative pathogens
- No evidence of nephrotoxicity at predicted therapeutic dose levels, providing clear differentiation over other polymyxin antibiotics

Preclinical Data Support Increased Efficacy Beyond Traditional Antibiotics



SPR206 Next Steps: Complete BAL and Renal Impairment Clinical Trials

Phase 1 trials initiated in 2Q21; results expected by early 2022

Bronchoalveolar Lavage (BAL) Trial



Trial Overview

Target Enrollment: 30

Number of Cohorts: 5

Dosing: 3 doses (100 mg, q8h) in one day

Objective: Evaluate intrapulmonary PK, including epithelial lining fluid and alveolar macrophage concentrations of SPR206 compared to plasma concentrations

Data to inform dose requirements for clinical efficacy of SPR206 in future trials

Renal Impairment Trial



Trial Overview

Target Enrollment: 40

Number of cohorts: 5, each with varying degrees of renal insufficiency

Dosing: Single 100 mg dose

Objective: Evaluate PK in healthy subjects and those with various degrees of renal insufficiency, including end stage renal disease

Data to help determine if concentrations of SPR206 are impacted by differences in renal function

Financial Overview

\$ in 000's

Income Statement	Three Months Ended March 31, 2021	Twelve Months Ended December 31, 2020
Total Revenue	\$7,300	\$9,330
R&D Expense	\$18,404	\$67,003
G&A Expense	\$8,299	\$21,440
Loss from Operations	\$(19,403)	\$(79,113)
Net Loss Attributable to Common Stockholders	\$(19,423)	\$(78,829)

Balance Sheet	As of March 31, 2021
Cash, Cash Equivalents and Marketable Securities	\$115,676

- With the recently announced (6/30/2021) \$40M transaction with Pfizer, Spero is funded into the second half of 2022
- BARDA/DTRA non-dilutive funding award for tebipenem HBr up to \$56.7M; NIAID award for SPR206 of up to \$23M; additional awards and alliances provide funding for pipeline

Key Investment Highlights



Experienced management team



Pipeline products with a solid value proposition



Accelerated path to market



Multiple drugs in clinical development



Significant near-term catalysts



Large and existing market opportunities