COMPANY OVERVIEW

Jefferies 2018 Health Care Conference

June 6, 2018

Forward-looking Statements

This presentation contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995 regarding, among other things, development plans, regulatory activities, anticipated milestones, product candidate benefits, competitive position, business strategies, objectives of management, potential growth opportunities, potential market size, possible or assumed future results of operations, projected costs and use of proceeds. 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: uncertainties inherent in the initiation and completion of preclinical studies and clinical trials and clinical development of the Company's product candidates, including adverse results in our clinical development processes; whether results from one clinical trial will be predictive of the results of future trials; decisions made by the U.S. Food and Drug Administration and other regulatory authorities with respect to the development and commercialization of our products; availability of funding sufficient for the Company's foreseeable and unforeseeable operating expenses and capital expenditure requirements; our ability to obtain, maintain and enforce intellectual property and other proprietary rights for our product candidates; our ability to implement our strategic plans; and other factors discussed in the "Risk Factors" section of the Company's Annual Report on Form 10-K filed with the Securities and Exchange Commission on April 2, 2018, and risks described in other filings the Company may make with the Securities and Exchange Commission 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.

Building the Next Great Antibacterials Company

Differentiated pipeline addresses unmet needs

SPR994 Oral Carbapenem

SPR741 SPR206 IV Potentiators

SPR720 NTM Program

Significant Near-Term Catalysts

4 Major near-term clinical catalysts, including the start of a Phase 3 trial for SPR994

Multi-billion Commercial Opportunity

Focus on unmet needs in and out of hospital drive significant opportunity

Strong Team & Track Record

Teflaro (ceftaroline fosamil) for injection 600 mg • 400 mg

Dalvance (dalbavancin) for injection

SIVEXTRO (tedizolid phosphate)

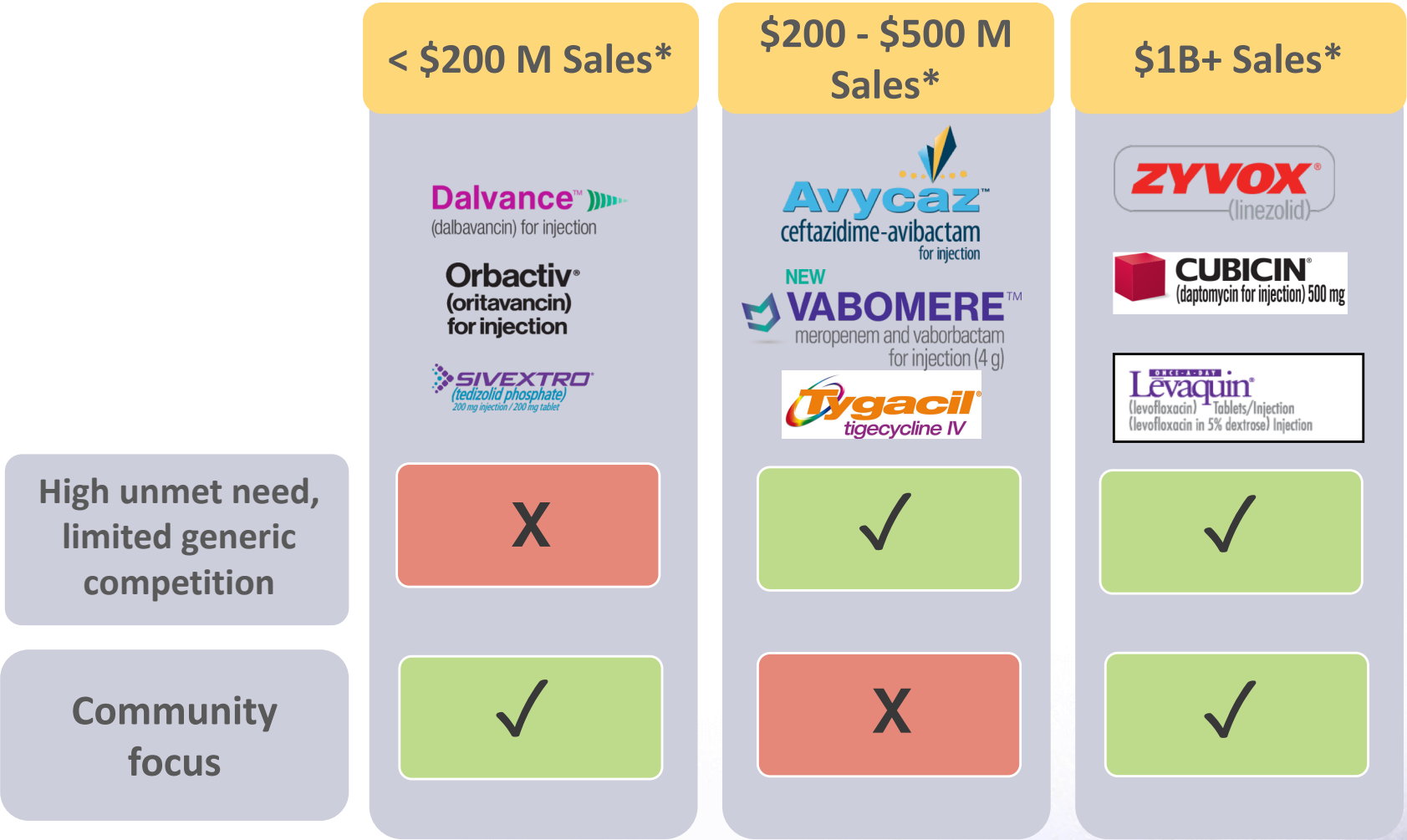
ZERBAXA ceftolozane / tazobactam

Levaquin (levofloxacin) Tablets/Injection (levofloxacin in 5% dextrose) Injection

Avycaz ceftazidime-avibactam for injection

SPERO THERAPEUTICS

Blockbuster Anti-infectives Share Common Attributes



*Estimated Peak Year Worldwide Sales

The Right Business Model is Key to Building a Successful Anti-infective Company

Spero's Vision and Commitment

- Anchor pipeline around products that can support commercial scale
- Develop products with differentiation from generics
- Meet patient needs outside of hospital
- Complementary products in pipeline to leverage sales force

SPERO THERAPEUTICS

Spero Therapeutics: Complementary, Novel Programs

Clinical Value Drivers for Spero

Oral Gram-negative

SPR994: Oral Carbapenem

Could be first new oral therapy for cUTI in 21 years

IV Gram-negative

SPR741 and SPR206: IV Potentiator Platform

Address major unmet needs in hospital setting

CARB-X

NIH

Oral Rare Orphan Disease

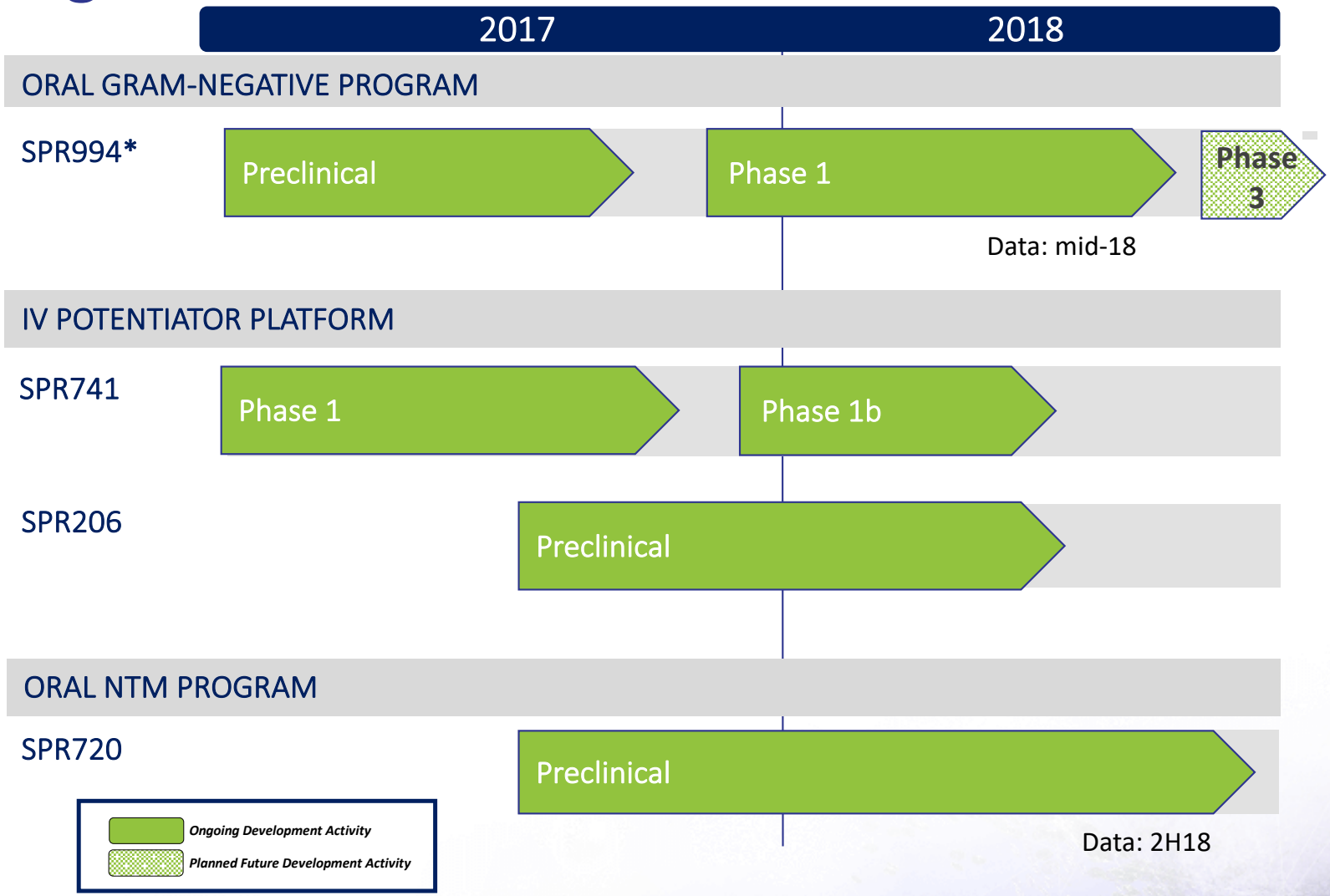
SPR720: Oral Non-Tuberculous Mycobacterial Disease

Long-term therapy for orphan disease

NIH

SPERO THERAPEUTICS

Ongoing and Anticipated Development Activities through 2018



- Our ability to progress SPR994 to a pivotal Phase 3 cUTI clinical trial is subject to a pre-Phase 3 meeting with the FDA to confirm no additional clinical trials or preclinical studies are required prior to initiating a Phase 3 clinical trial. Following our discussions with the FDA, we expect to initiate a pivotal Phase 3 clinical trial of SPR994 for the treatment of cUTI around year-end 2018 in support of a new drug applications (NDA).

As of June 6, 2018

SPERO THERAPEUTICS

SPERO THERAPEUTICS

First Oral Carbapenem: SPR994

SPR994 Offers an Oral Option to Address Gram-Negative Fluoroquinolone Resistance

Quinolones are most widely used agents for UTI*

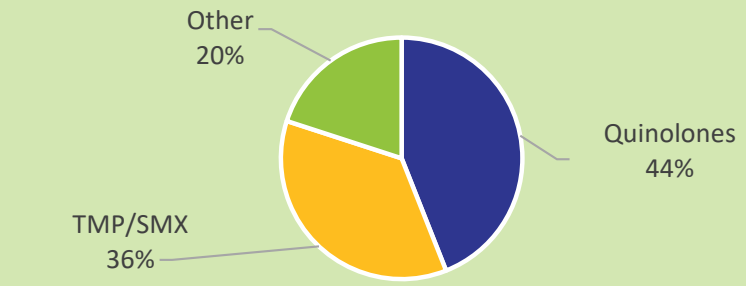
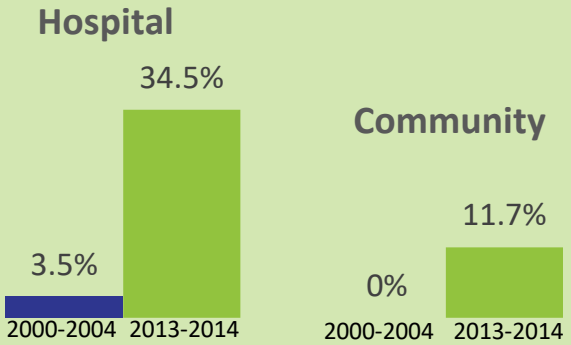


*chart reflects 2016 data

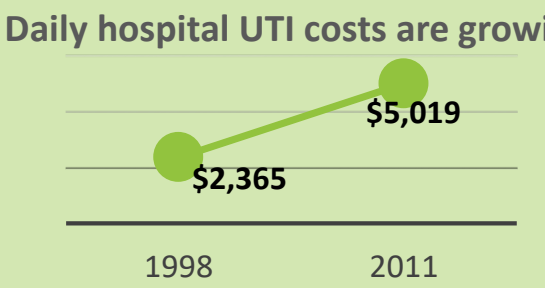
Quinolone Resistance to *E. coli* in United States



Hospitalizations due to UTI are growing

76% Increase in hospitalizations 1999-2011

Hospital UTIs cost healthcare system $2.8 B



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.

SPR994: Novel Oral Carbapenem

- First ***oral*** carbapenem in adults; potency similar to IV carbapenems
- ***~1,200 subjects dosed in human studies*** supporting PK and efficacy; 3,500 patient post-marketing study and 8 years on market in Japan
- High drug serum levels and urine concentrations at the site of infection; high bioavailability
- ***Two completed pilot Phase 2 studies*** in cUTI
- Granted FDA Qualified Infectious Disease Product (QIDP) designation; expedited review and additional market exclusivity
- IP through 2038

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Extensive Clinical Dataset Supports Safety and Tolerability

SPR994

~1,200 subjects dosed in clinical and pharmacologic studies with SPR994 API
741 adult subjects dosed

Safety and tolerability consistent with approved oral antibiotics

- No significant adverse events reported
- Diarrhea most common reported AE
  - No statistically significant difference between tebipenem and oral cephalosporin control in Phase 3
  - GI AE rates in uncontrolled studies consistent with other oral antibiotics
  - In clinical bacterial flora study: No fecal *C. difficile* bacteria or toxin detected (up to 200 mg dosing for 7 days)

Pilot cUTI studies conducted in Japanese adults

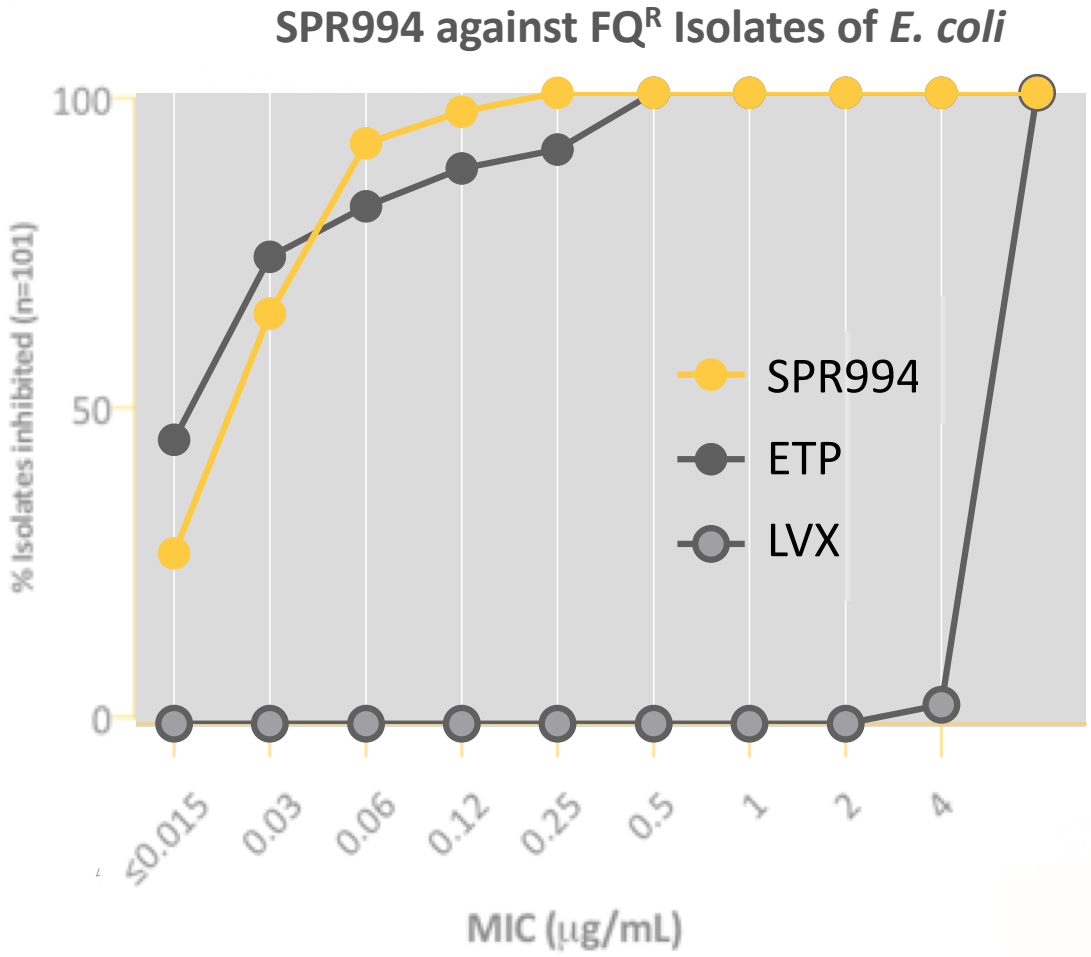
~ 3,500 patient post-marketing study

8 years of post-approval use in Japan

SPR994 API marketed in Japan since 2009 for use in common pediatric infections including pneumonia, otitis media and sinusitis

Data on file

SPR994 Activity Comparable to IV Carbapenems

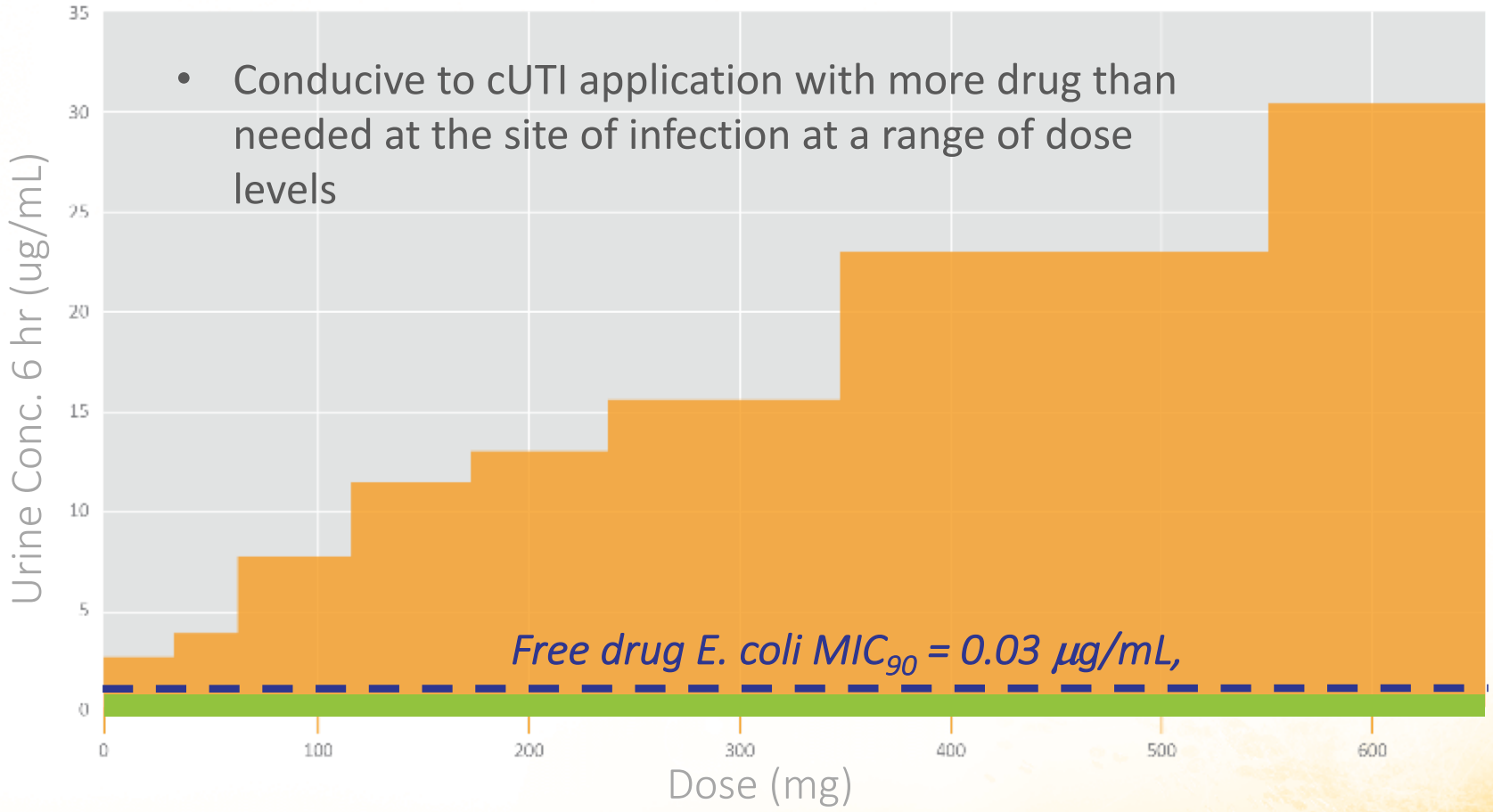


Result (µg/mL)	SPR994 (tebipenem)	Ertapenem (ETP)
MIC_{90}	0.06	0.25
MIC_{50}	0.03	0.03
Range	≤0.015-0.25	≤0.015-0.5

JMI Laboratories, 2017
Data on file
FQR: Fluoroquinolone resistant
LVX: Levofloxacin

High Urinary Levels of SPR994 Achieved in Healthy Human Volunteers

Single Ascending Dose (Immediate-release Tablet) Calculated Urine Levels



Calculated from %urinary excretion (0-24hr) values reported in Meiji Publication: Nakashima et al. *Japanese Journal of Chemotherapy*, Volume 57 S-1, March 2009.

JMI Laboratories, 2017

SPR994 Clinical Development Plan

	PLANNED TRIAL DESIGN	PLANNED TRIAL SIZE	PURPOSE
Phase 1 PK Study	SAD/MAD/PK in NHVs	~50 subjects	Justify dose and schedule of administration of Spero formulation for Phase 3
Single Phase 3 Pivotal Study cUTI (FPI 2018)	Double-blind/ double-dummy, single 1:1 randomization vs comparator; 10% NI margin	1,100 patients	Designed to satisfy requirements for US & EU approval

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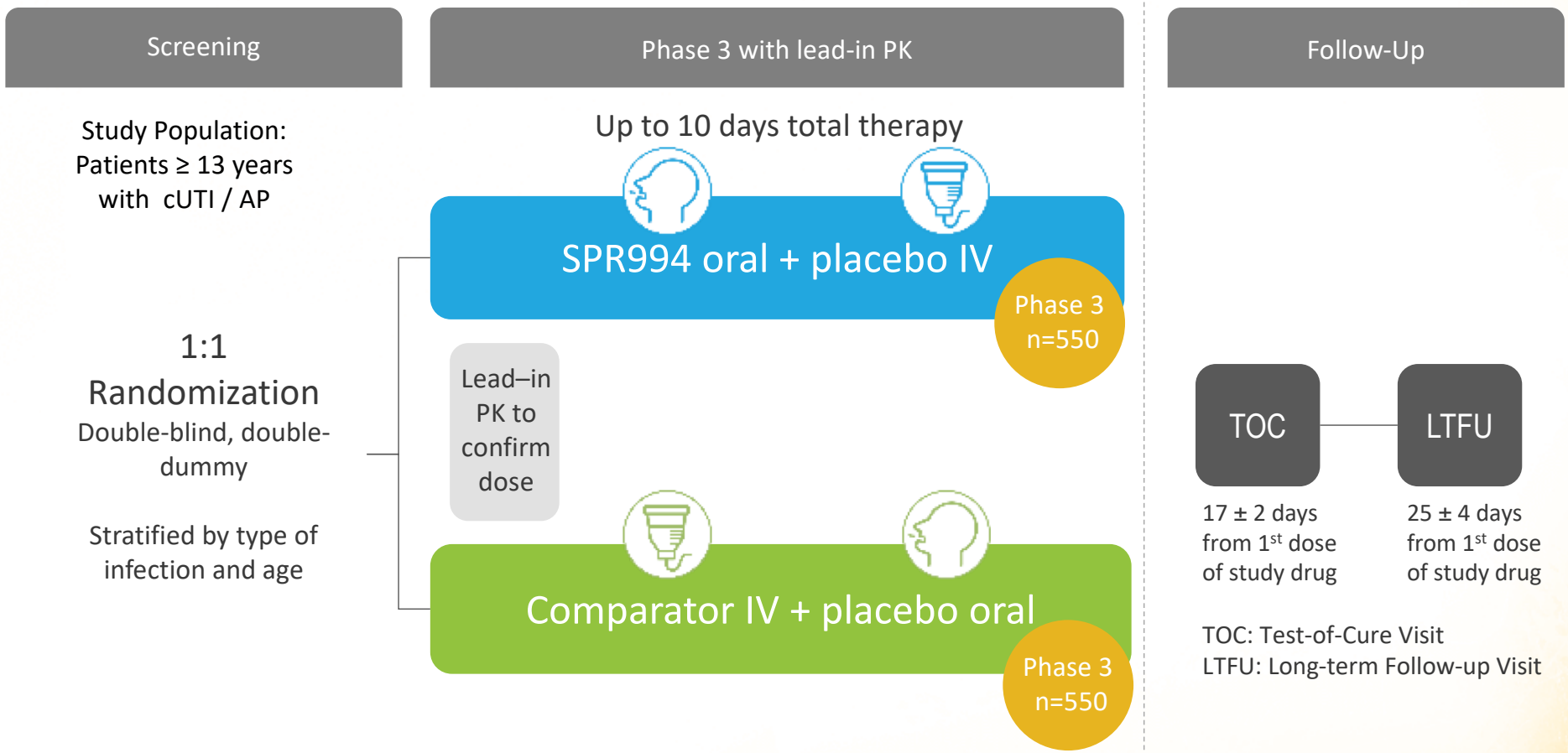
As of June 6, 2018. Our ability to progress SPR994 to a pivotal Phase 3 cUTI clinical trial is subject to a pre-Phase 3 meeting with the FDA to confirm no additional clinical trials or preclinical studies are required prior to initiating a Phase 3 clinical trial.

Planned SPR994 Phase 3 Design with PK Lead-in

Phase 3 design supports key value proposition for SPR994: Clinical equivalency of oral regimen versus IV



* **Masked individual and composite PK data will be reviewed by an IDMC after enrolling the first 50 and 100 patients to confirm the SPR994 dose. Efficacy and safety will remain blinded**.

Primary Endpoint: Microbiological response and Clinical Response at TOC (micro-ITT). Resolution of symptoms of cUTI present at screening and no new symptoms of cUTI, and reduction of baseline bacterial pathogens to fewer than 10^4 CFU/mL on urine culture.

Secondary Endpoints: 1. PK parameters (Vd, Cmax, AUC, T>MIC) in SPR994 recipients compared to PK parameters reported from Phase 1 studies in normal healthy volunteers; 2) Population PK in SPR994 based on sparse sampling; 3) Clinical response at EOT, TOC, and LTFU visits (micro-ITT, CE, and ME); 4) Microbiological response at TOC and LTFU (micro-ITT and ME) by Overall, Baseline pathogen, Stratified infection category, Country/Region; 5) Time to resolution of cUTI and AP; 6) Time to clinical cure (resolution of symptoms of cUTI present at randomization); 7) Time to microbiological success (reduction of the baseline bacterial pathogen(s) to fewer than 104 CFU/mL on urine culture obtained daily during the treatment period; 8) Time to defervescence; 9) Time to urine sterility; 10) Rate of relapse, recurrence and superinfection at LTFU; 11) Rates of AE incidence

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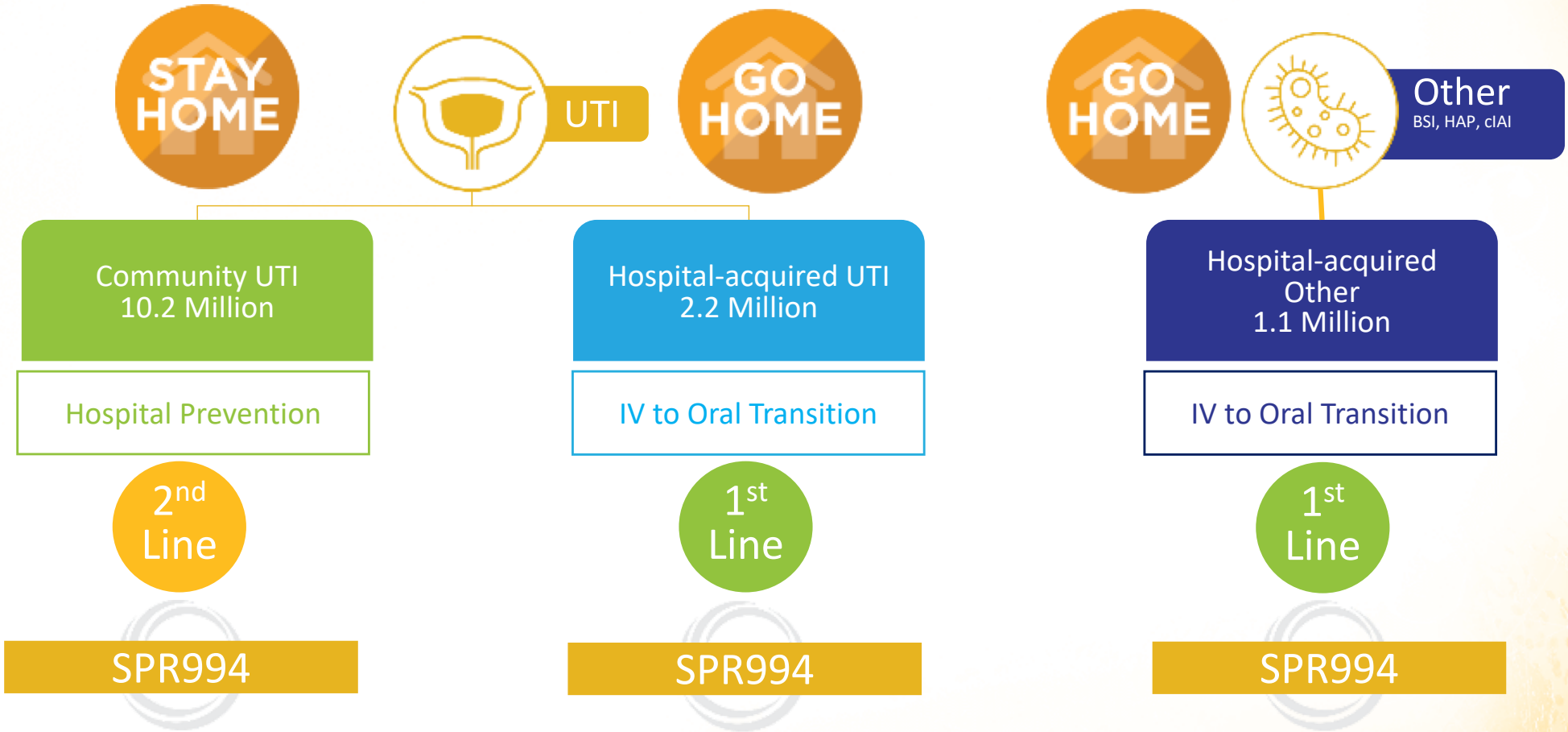
SPR994 Has Differentiated Profile vs Current and Future Oral Agents for cUTI

	Broad Spectrum	High Bioavailability
SPR994	+++	+++
Quinolones	+	+++
TMP/SMX	+	++
Nitrofurantoin	+	++
Sulopenem*	+++	+
Omadacycline	+	+
C-Scape	++	+++

*No public disclosure on prodrug moving forward. Data is based on the most advanced clinical prodrug Pf-00398899 and data in table reflects that prodrug. Other prodrugs exist with bioavailability between 15-39%.

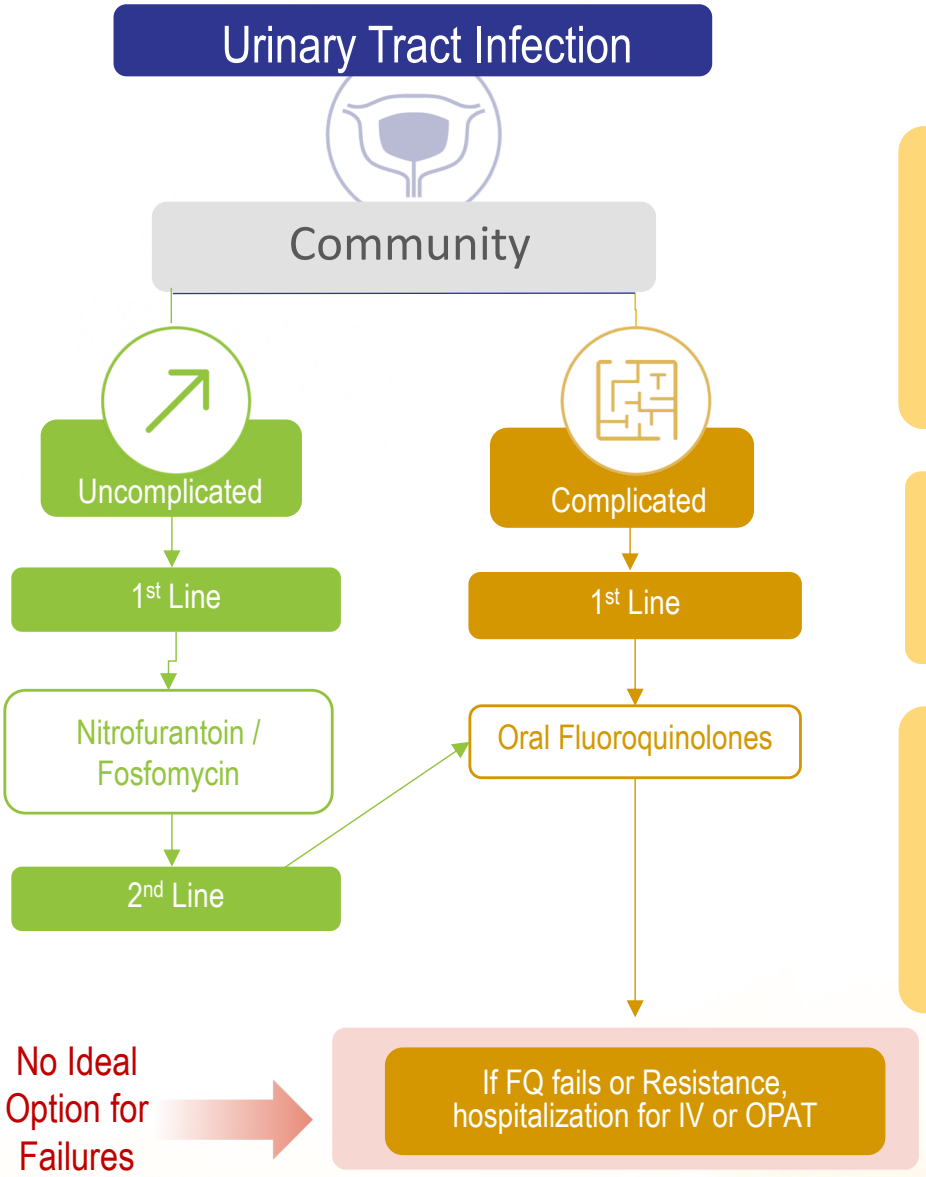
SPR994 Could Enable Patients in Community & Hospital to Avoid or Shorten Hospitalization



Clinical profile and development plan supports significant U.S. market opportunity

Management estimate derived primarily from QuintilesIMS market assessment (August 2017)
Other Hospital: BSI (Bloodstream Infections), HAP/VAP (Hospital Acquired Pneumoniae, Ventilator Acquired Pneumoniae), cIAI (Complicated Intra-abdominal Infections)

SPR994 Addresses Unmet Need in the Community



65-year-old
woman presents to doctor's office

Symptoms

- Burning when urinates
- Frequent and persistent urge to urinate
- Cloudy urine
- Urine sample in office shows sign of blood

History

- Previous history of UTI in last 30 days and prescribed levofloxacin

Options

- Send to ER for dose of IV therapy and send home on levofloxacin. **Why not?**
- Hospitalize – **Why not?**
- SPR994

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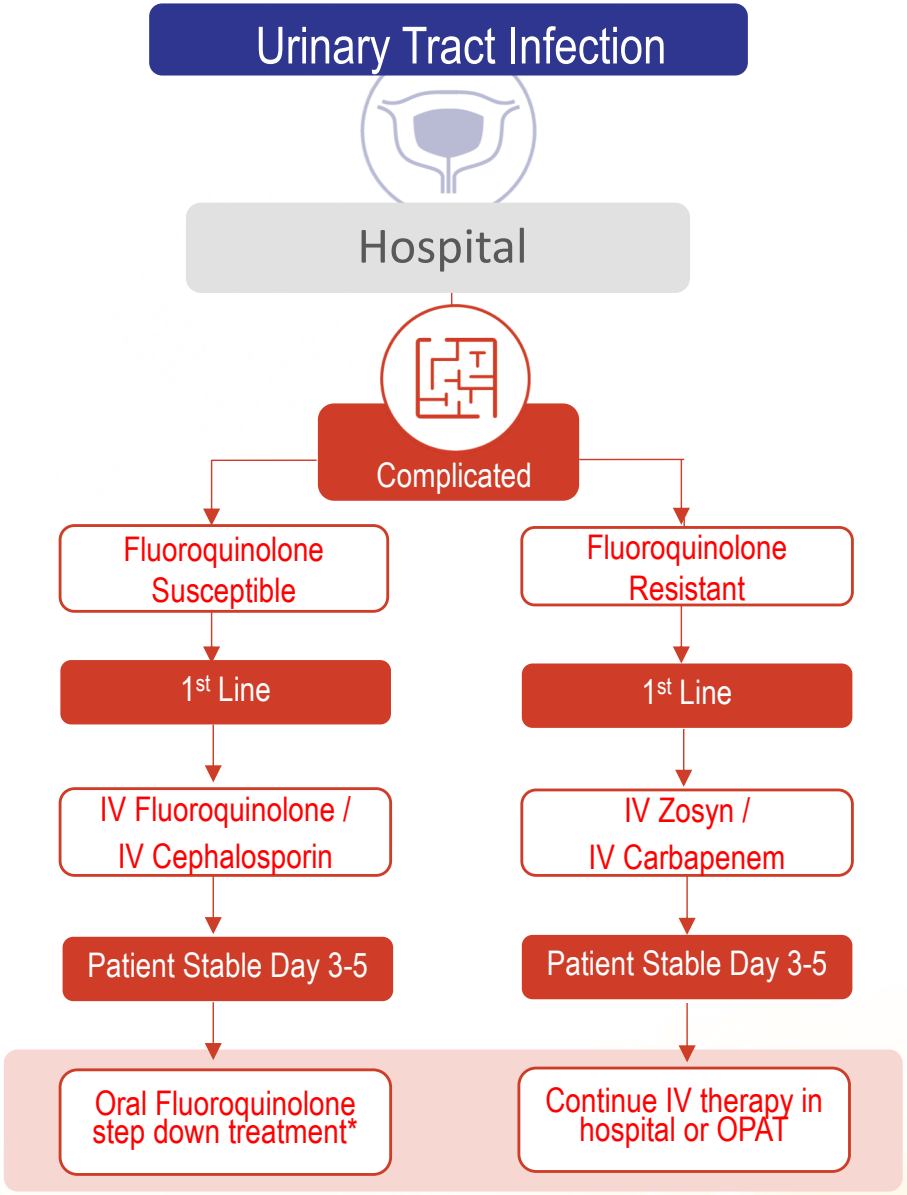
SPR994 Addresses Unmet Need in Hospital cUTI



No Ideal Option for Failures

70-year-old man hospitalized for hip replacement surgery

Symptoms
- Fever

History
- Has catheter
- Started on IV carbapenem
- Day 3 is stable and ready for discharge

Options
- Discharge on levofloxacin – **Why not?**
- Discharge on IV therapy – **Why not?**
- SPR994

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* Oral fluoroquinolone step down treatment may not be an option for certain populations where risk outweighs benefit

SPR994: Multi-Billion Market Opportunity
U.S. Market Segment Summary

Market Segment	Total Patients	FQ-R	Addressable Market	LOT	SPR994 Peak Year Market Share
Community UTI FQ-Resistant	**10.2M**	**7%**	**714K**	5.5 DAYS	**32%-40%**
Hospital UTI FQ-Resistant	**2.2M**	**37%**	**814K**	7 DAYS	**47%-48%**
Hospital "Other" FQ-Resistant *(BSI, HAP, cIAI)*	**1.1M**	**37%**	**407K**	7 DAYS	**24%-40%**

Community

714K Patients × 5.5 days × $348/day at Peak = $1.4 Billion US Market Opportunity

Hospital

1.2M Patients × 7 days × $348/day at Peak = $2.9 Billion US Market Opportunity

EU Multiplier 60% of US Sales

RoW (excluding Asia & EU) Multiplier 5% of US Sales

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Source: Estimates derived primarily from QuintilesIMS market assessment (August 2017)
FQ: Fluoroquinolone

SPR994: Differentiated Antibiotic for a Large, Unmet Need

- ✓ Innovative oral carbapenem
- ✓ Safe and tolerable drug backed by a dataset of ~1200 subjects
- ✓ High urine concentration levels at the site of infection support utility in cUTI
- ✓ Rapid development plan with single pivotal Phase 3 trial initiation in cUTI planned by year-end 2018
- ✓ Robust clinical profile and development plan
- ✓ Multi-billion U.S. market opportunity

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Potentiator Platform: SPR741 & SPR206

Potentiators Allow Entry of Antibiotics Into Gram-Negative Bacteria

The major reasons for a low hit rate for Gram-negative development:

- Low permeability barrier of two-membrane cell envelopes of Gram-negative bacteria
- Insufficient chemical diversity of compound libraries to probe this barrier

Potentiator Platform Has Potential to Treat Most Threatening Pathogens in the Hospital

WHO Priority Pathogens

WHO PRIORITY PATHOGENS LIST FOR R&D OF NEW ANTIBIOTICS

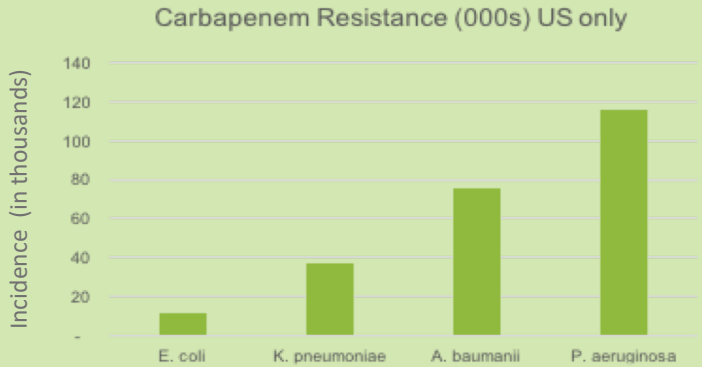
Priority 1: CRITICAL#

Acinetobacter baumannii, carbapenem-resistant

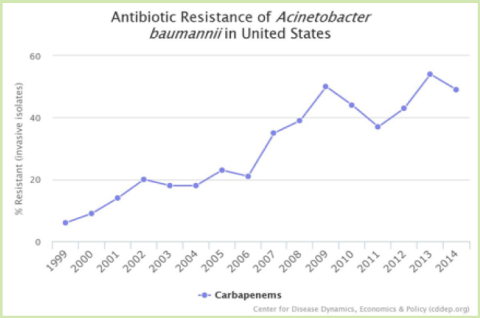
Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

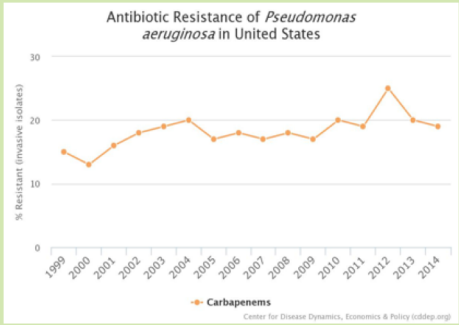
Carbapenem resistance to KP, PA & AB is significant problem for hospitalized patients



Carbapenem Resistant *Acinetobacter* in US exceeding 50%



Carbapenem Resistant Pseudomonas in US reaching 20%



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QuintilesIMS NDTI and MIDAS Database; Quintiles/IMS Market Assessment 2017.

Potentiator Platform Addresses IV MDR Gram-Negative Hospital Market

	SPR741+partner	SPR206 single agent
WHO Priority Pathogens		
Potency Against ESBLs	✓	✓
Potency Against CRE	✓	✓
Potency Against *P. aeruginosa*		✓
Potency Against *A. baumannii*		✓
MOA		
Expands coverage of partner agents	✓	✓
Single agent activity		✓

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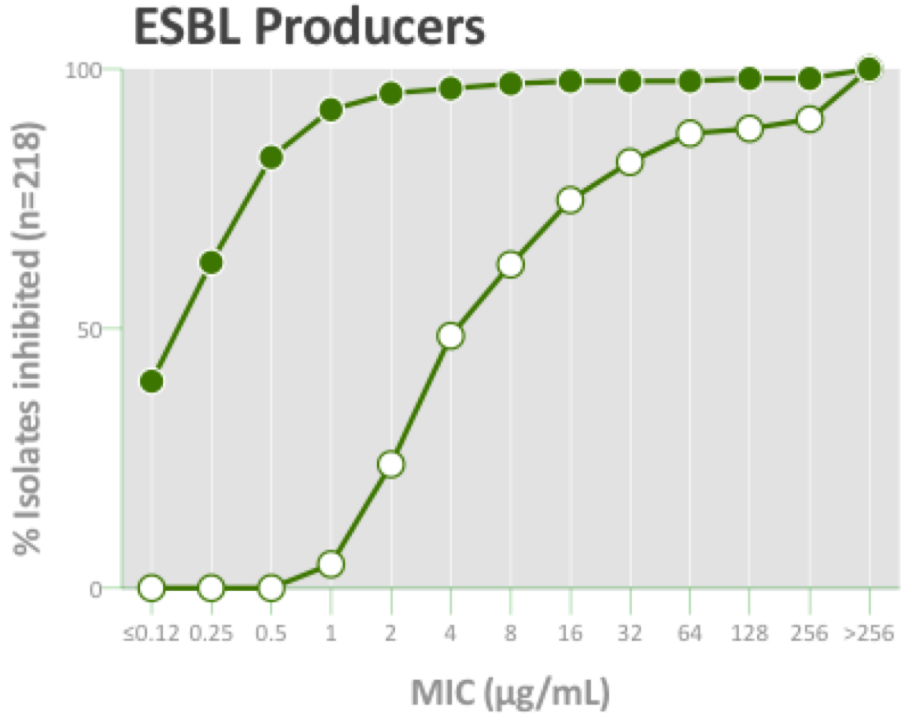
SPR741 + Partner Expand Potency Against Multidrug Resistant Gram-Negative Pathogens



	MIC_{90} (µg/mL)	% Susceptible
TZP	256	75%
TZP+741	**1**	**98%**

Phase 1b drug-drug interaction trial results

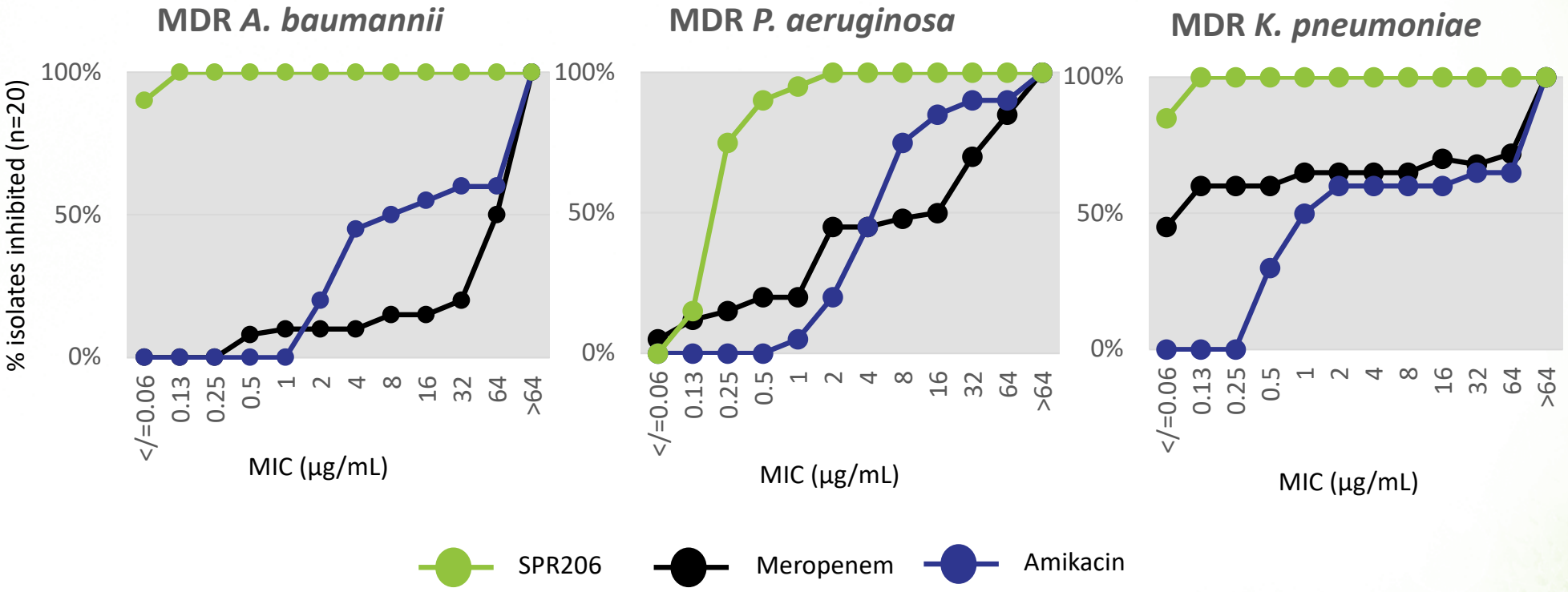
- Administration of b-lactam antibiotics had no impact on PK or tolerability of SPR741

Phase I trial results

- Generally well tolerated at doses up to and including 600 mg every 8 hours for 14 days

TZP: Piperacillin/Tazobactam (Zosyn)
ESBL: Extended Spectrum Beta Lactamase Producing Organism – carry resistance to range of commonly prescribed antibiotics
Breakpoint for TZP: CLSI ≤ 16
JMI Reference Labs, 2017

SPR206 as Single Stand Alone Agent Demonstrates Potency Against MDR & XDR Gram-Negative Pathogens



Results from IND-enabling studies

- Demonstrated potential to achieve wide therapeutic margins in the treatment of serious Gram-negative infections
- Supports advancement into clinical development

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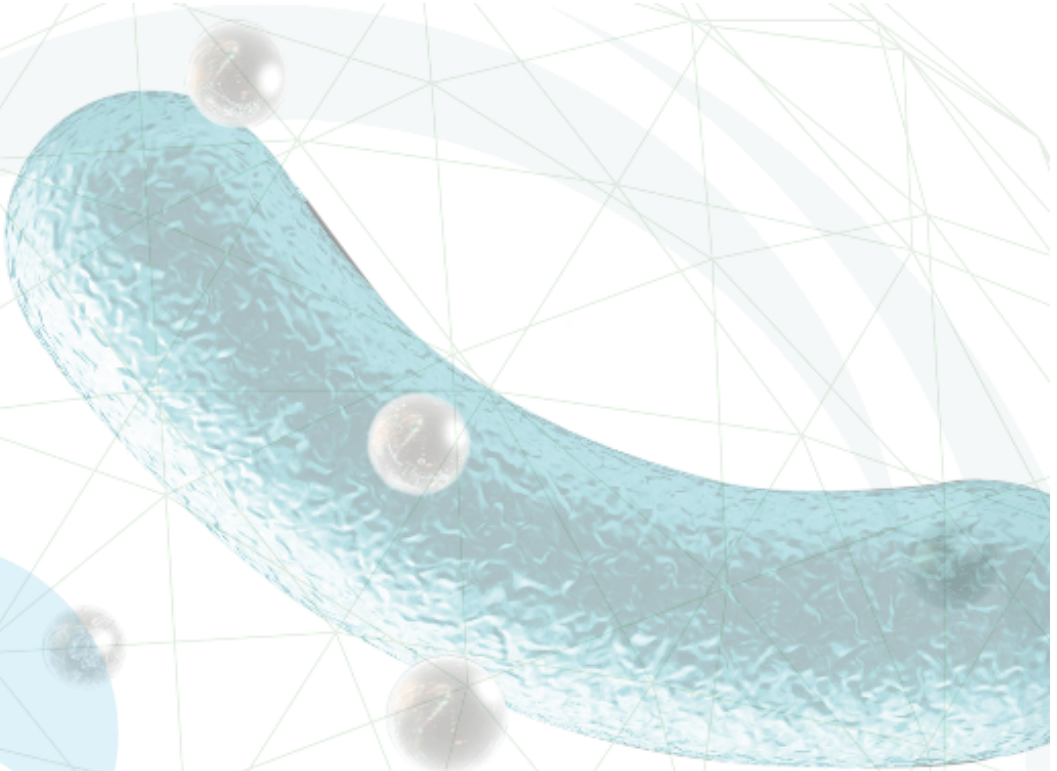

First Novel Oral NTM Treatment: SPR720

Major Unmet Need in NTM Infections

A Growing Market

- 13% annual increase in prevalence predicted YOY in the US
- 6% prevalence annual increase in Europe
- High healthcare costs, high mortality

Unsatisfied Market

- No currently approved agents
- Need for **oral agents**
- Need for **more potent therapies**

Promising Regulatory Incentives

- Orphan designation
- QIDP

Adjemian J, Olivier KN, Seitz AE, Holland SM, Prevots DR. Prevalence of nontuberculous mycobacterial lung disease in U.S. Medicare beneficiaries. Am J Respir Crit Care Med. 2012;185(8):881-886.
Strollo SE, Adjemian J, Adjemian MK, Prevots DR. The burden of pulmonary nontuberculous mycobacterial disease in the United States. Ann Am Thorac Soc. 2015;12(10):1458-1464.

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SPR720: First Novel Oral Candidate to Treat NTM Infections

Novel anti-bacterial mechanism of action with activity against difficult to treat nontuberculous mycobacteria (NTM)

Orally available small molecule

Potent, dose-responsive activity

- Potent activity against most common NTM species (*M. avium, M. abscessus, M. kansasii*)
- Dose-responsive *In vivo* efficacy demonstrated
- IND-enabling activities ongoing

Broad spectrum of activity beyond NTM pathogens

Strong IP position - composition of matter protection to 2032

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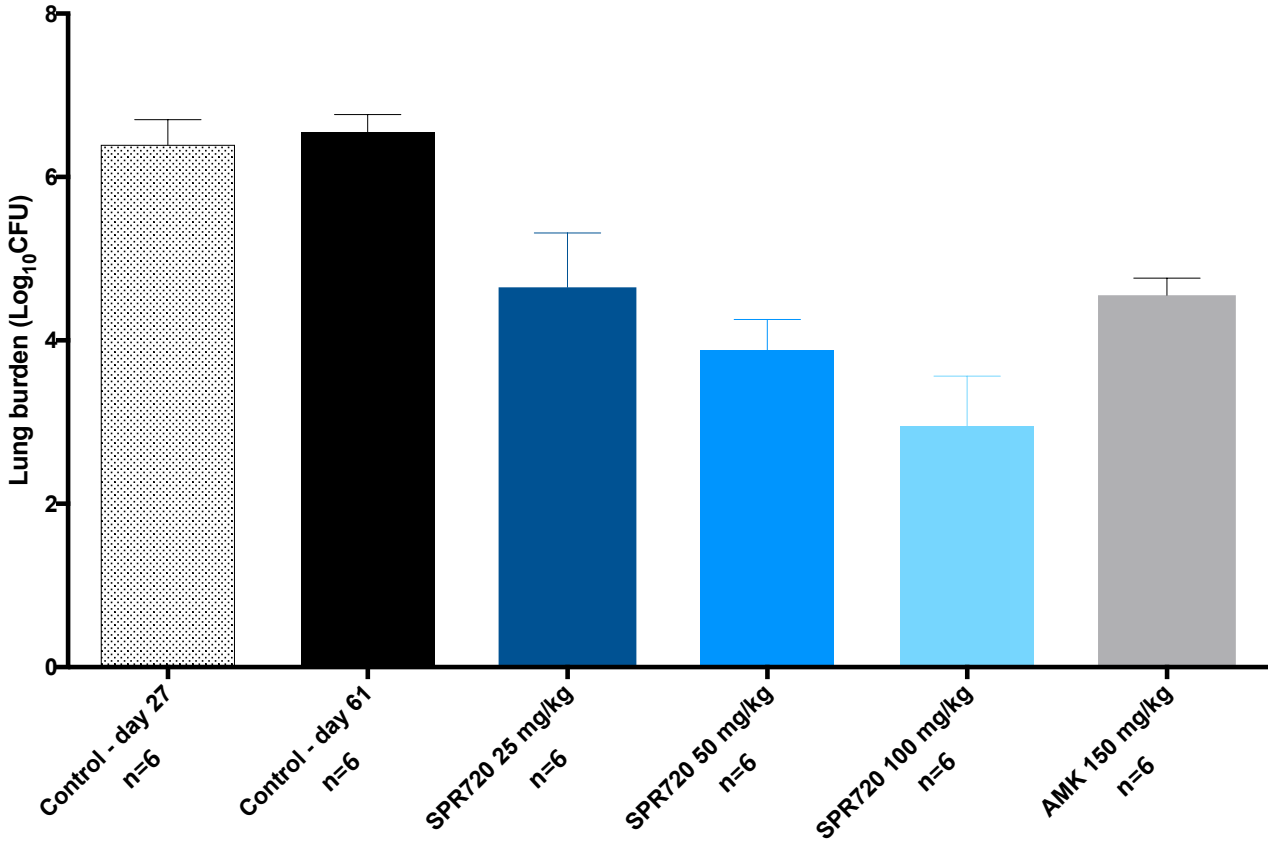
Dose Responsive Efficacy Against Difficult to Treat NTM Pathogens

Lung Infections in Multidrug Resistant *M. abscessus* Strains



Multidrug resistant *M. abscessus* strain infection set for 27 days, dosing in SCID mice days 27 to 61. AMK=Amikacin SQ dosed every 24h. SPR720 dosed every 48h at the doses listed above

Leadership Team

Ankit Mahadevia, MD
Chief Executive Officer

Venture Partner, Atlas Venture; Genentech, McKinsey, Johns Hopkins, PCAST Task Force on Anti-infectives Development

Joel Sendek
Chief Financial Officer

Chief Financial Officer, Forward Pharma
Senior Biotech Analyst at Stifel, Lazard

David Melnick, MD
Chief Medical Officer

Vice President Clinical Development for anti-infectives; Allergan, AstraZeneca

Ian Critchley, PhD
Head of Clinical Microbiology

Vice President, Clinical Microbiology, Allergan; Cerexa, Replidyne

Melissa Stundick, PhD
Head of Strategic Alliances

Chief, Anti-infectives Program, BARDA

Tom Parr, PhD
Chief Scientific Officer

CSO, Fedora Pharma; CSO, Targanta; Microcide, Head of Antibacterials, Eli Lilly; ICAAC Program Committee

Cristina Larkin
Chief Operating Officer

Vice President, Infection, Forest Laboratories; Launched Teflaro, Dalvance and Avycaz

Tim Keutzer
Senior Vice President, Development

Vice President, Program and Portfolio Management, Cubist; Program Leader for Zerbaxa

Troy Lister, PhD
Vice President of Research

Team Leader of Infectious Chemistry, AstraZeneca; Global Discovery Chemistry, Novartis

Susannah Walpole, PhD
Head of Clinical Operations

Head of Therapeutic Operations, ModeRNA, Tetraphase, Sirtris, Shire, TKT

SPERO THERAPEUTICS

Financial Overview

Strong financial position following November IPO

$ in 000's

Income Statement	Three Months Ended March 31, 2018
Grant Revenue	$1,153
R&D Expense	$8,925
G&A Expense	$3,044
Loss from Operations	$(10,816)
Net Loss Attributable to Common Stockholders	$(10,644)

Balance Sheet	As of March 31, 2018
Cash and Cash Equivalents	$75,393

SPERO THERAPEUTICS

Key Investment Highlights

Experienced management team with blue chip investor base

Novel approaches to antibacterial development

Accelerated path to market

Multiple drugs in clinical development

Significant near-term catalysts

Large opportunity in complementary markets

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