Anti-Infective Drugs Advisory Committee Meeting

Raxibacumab for Treatment of Inhalational Anthrax

November 2, 2012

Introduction

Sally Bolmer, PhD

Senior Vice President
Development and Regulatory Affairs
Human Genome Sciences

Limitations of Current Treatment

- Antibiotics
  - Ineffective against toxemia
  - Ineffective against resistant strains
- Vaccine
  - Requires time for immunity to build
  - Requires multiple injections

Raxibacumab Antitoxin

- Delivers antitoxin antibody
  - Neutralizing activity similar to natural immune response
- Immediate protection
  - Faster than vaccines
  - Does not interfere with development of natural immunity
- Mechanism of action different from antibiotics
  - Effective as monotherapy
  - Effective in combination with antibiotics

Agenda

Development History	Sally Bolmer, PhD
Public Health Need	Dan Hanfling, MD
Mechanism of Action Efficacy Nonclinical Safety	Thi-Sau Migone, PhD
Nonclinical and Clinical PK	Alfred Corey
Human Safety	Brian Porter, MD, PhD, MPH
Benefit/Risk	Dan Hanfling, MD

Development Program

Raxibacumab Development

- Demonstrate effectiveness in animals under the Animal Rule
- Translate animal exposure to human dosing
- Establish human safety profile
- Evaluate efficacy and safety in combination with antibiotics

Animal Rule

- Provide path for approval when adequate and well-controlled human efficacy studies are not ethical or feasible
  - Effectiveness demonstrated in animals
  - Safety evaluated in humans

Intended Use of the Animal Rule

- Not required under the Animal Rule
  - Added benefit over existing treatments
  - Toxic agent to be without a proven treatment
- Need for a wide range of therapeutic options
  - Anthrax given as the example

Meets Efficacy Criteria of Animal Rule

1. Known cause of disease; mechanism of treatment
   - B. anthracis toxicity studied and published
   - Raxibacumab mechanism of action demonstrated
2. Efficacy demonstrated in 2 animal species
   - Statistically significant survival benefit in both species
3. Animal study endpoint clearly related to benefit in humans
   - Survival
4. Pharmacokinetics and pharmacodynamics well understood in animals and humans
   - Translate effective exposure in animals to recommended doses in human

Plan for post-marketing study in humans

Development History

HGS identified antitoxin antibody	Dec 2001
FDA Animal Rule finalized	May 2002
Project Bioshield	Jul 2004
BLA filed	May 2009
Advisory Committee	Oct 2009

Additional Information Requested in Complete Response Letter

1. Histopathology examination of surviving animals
   - No CNS findings in raxibacumab-treated survivors
2. Evaluation of potential added benefit of raxibacumab + antibiotic versus antibiotic alone
   - Higher survival with combination group
3. Confirmation of validity of PK assays
   - Samples retested with modified assay
   - Original results reliable

Efficacy Studies

Characterization	Therapeutic Treatment: Monotherapy	Therapeutic Treatment: + Antibiotics	Therapeutic Treatment: Prophylaxis
615	Pivotal 682	Pilot 723	Pre/Post 288
685	Pivotal 724	Efficacy of Combination 781	Post; Time 358
Rabbits		Efficacy of Combination 789	Post; Dose 371
Monkeys			Pre-EP 290
			Rechallenge 374

Efficacy Studies

Therapeutic Treatment

Characterization	Monotherapy	+ Antibiotics	Prophylaxis
615	Pivotal 682	Pilot 723	Pre/Post 288
685	Pivotal 724	Efficacy of Combination 781	Post; Time 358
Rabbits	Efficacy and Histopathology 1103	Efficacy of Combination 789	Post; Dose 371
		Added Benefit 1141	Pre-EP 290
			Rechallenge 374

Human Safety and PK

- Safety
  - Over 400 subjects treated
    - 326 subjects with 40 mg/kg and manufacturing process for licensure
  - Single and repeat dose
  - In combination with antibiotic
- PK
  - Comparable levels with 40 mg/kg dose
    - Healthy humans
    - Healthy and anthrax-infected rabbits and monkeys

Inhalational Anthrax Public Health Need

Dan Hanfling, MD
Special Advisor for Emergency Preparedness and Response
Inova Health System

Clinical Professor of Emergency Medicine
George Washington University

CN-016

2001 Anthrax Attacks

- 5 deaths
- 11 inhalation anthrax infections
- 11 cutaneous anthrax infections
- 32,000 treated with prophylactic antibiotics

Anthrax as a Bioterrorism Weapon

- Highly lethal
- Easy to manufacture
- Easy to weaponize
- Easy to spread in the air over a large area
- Dangerous for a long time

Anthrax Bioterrorism

- Significant bioterrorism risk
- DHS modeling
  - 3.3 million exposed
    - 266,700 infected
- WHO analysis
  - 5 million exposed
    - 250,000 infected
    - 100,000 deaths
- OTA estimate
  - 100 kg of aerosolized anthrax released over Washington, DC
  - 130,000 – 3 million deaths

High Mortality Rates Despite Antibiotics

- US mortality: 90% during 20th century
- In 2001, mortality was 45% with antibiotic-susceptible *B. anthracis*
- Higher mortality expected with multi-drug resistant *B. anthracis*

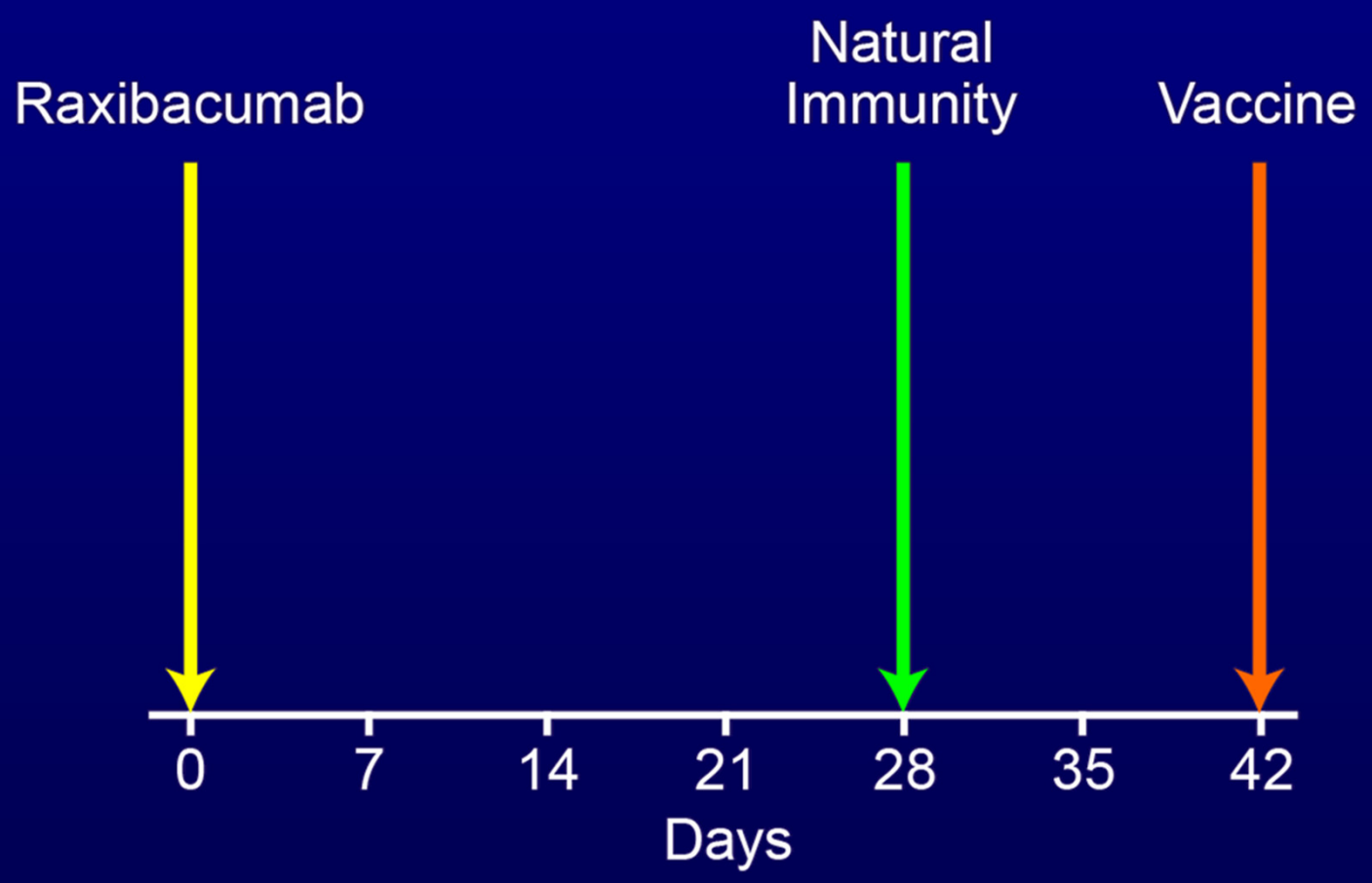
Holty et. al. *Ann Int Med* 2006;144;270-280.

Post-Infection Immunity

- All survivors in 2001 developed antitoxin antibodies by Day 28
- Rapid progression occurs before immune response can develop
- Need intensive treatment until immunity develops

Quinn et. al. *JID* 2004;190;1228-1236.

Comparison of Time Until Effective Antitoxin Levels



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Anthrax Toxin

- Central driver of disease pathogenesis causing morbidity and mortality
- Antitoxin should be beneficial
  - At all stages of infection when toxin is present

Tetanus Infection: Antibiotics + Antitoxin

- Post-exposure prophylaxis
  - Vaccination if patient's immune status is negative or unknown
  - Vaccine induces antitoxin antibody
- Treatment of infection
  - Antibiotics and antitoxin

Bleck T. Tetanus. In Mandell's Principles and Practice ID 6th Edition 2005;2817-2822.

Conclusions

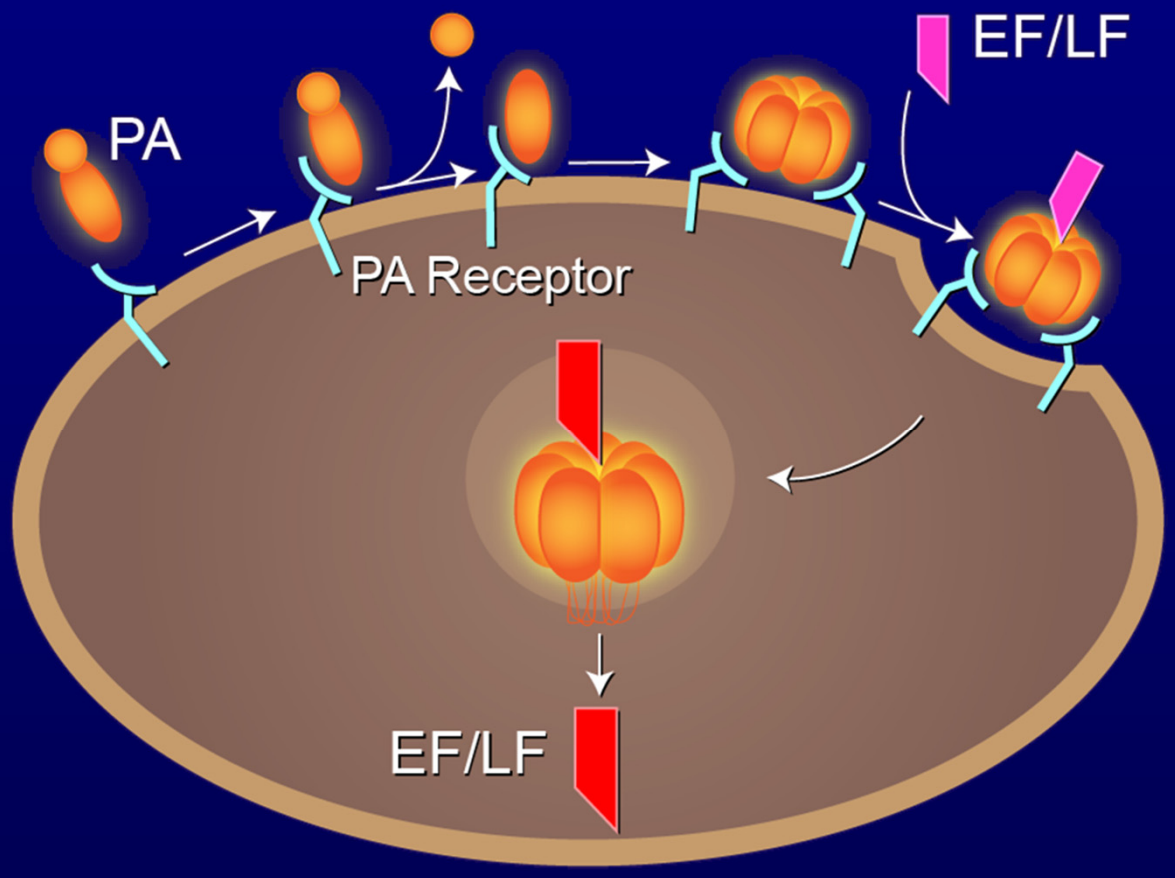
- Anthrax bioterrorism is a serious threat
- High mortality rates persist
- Prolonged intensive care
- Anthrax toxin mediates pathogenesis
- Anthrax antitoxin needed

Mechanism of Action

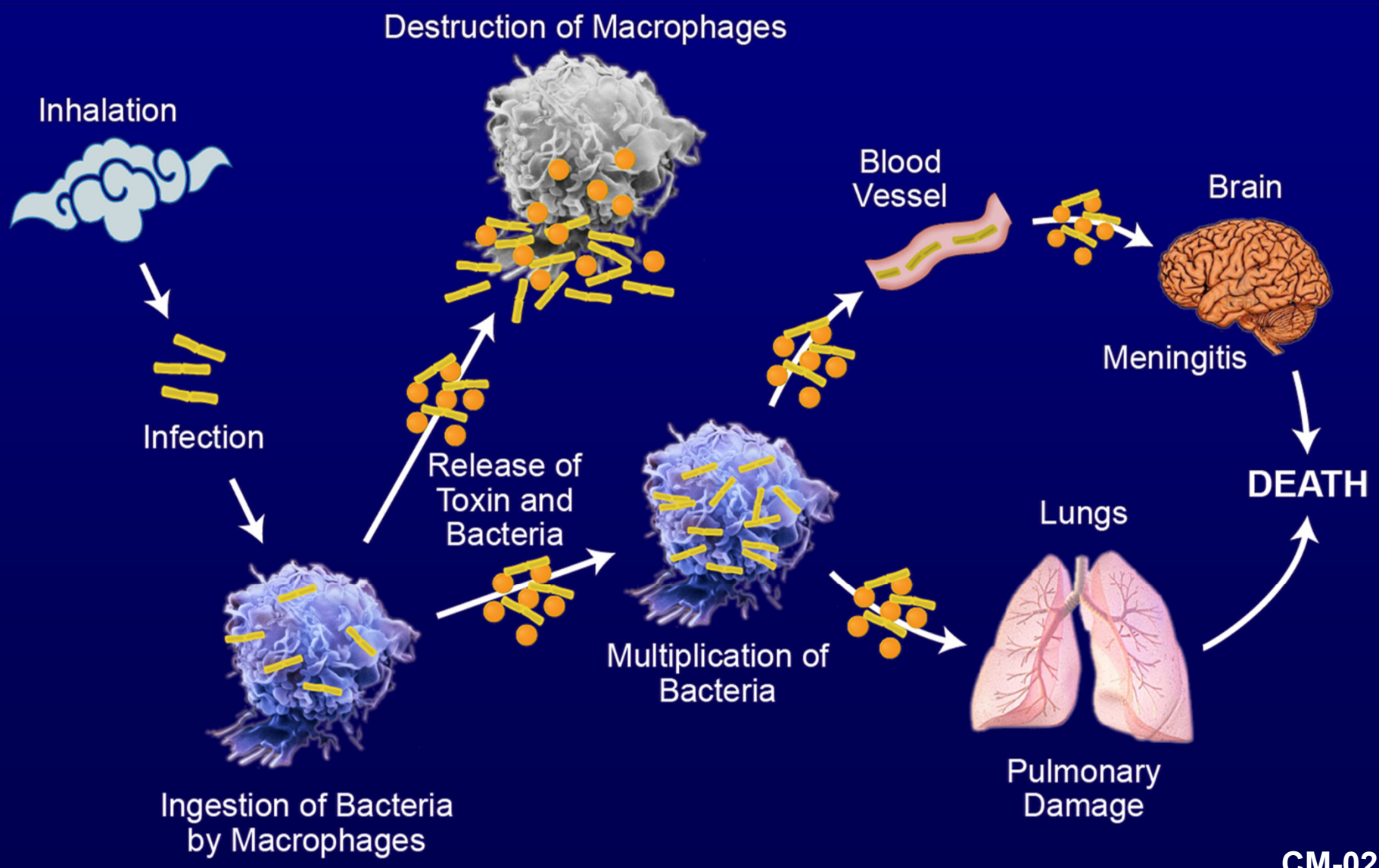
Thi-Sau Migone, PhD

Vice President, Research
Human Genome Sciences

Cellular Entry of Anthrax Toxin



Mechanism of Anthrax Pathogenesis



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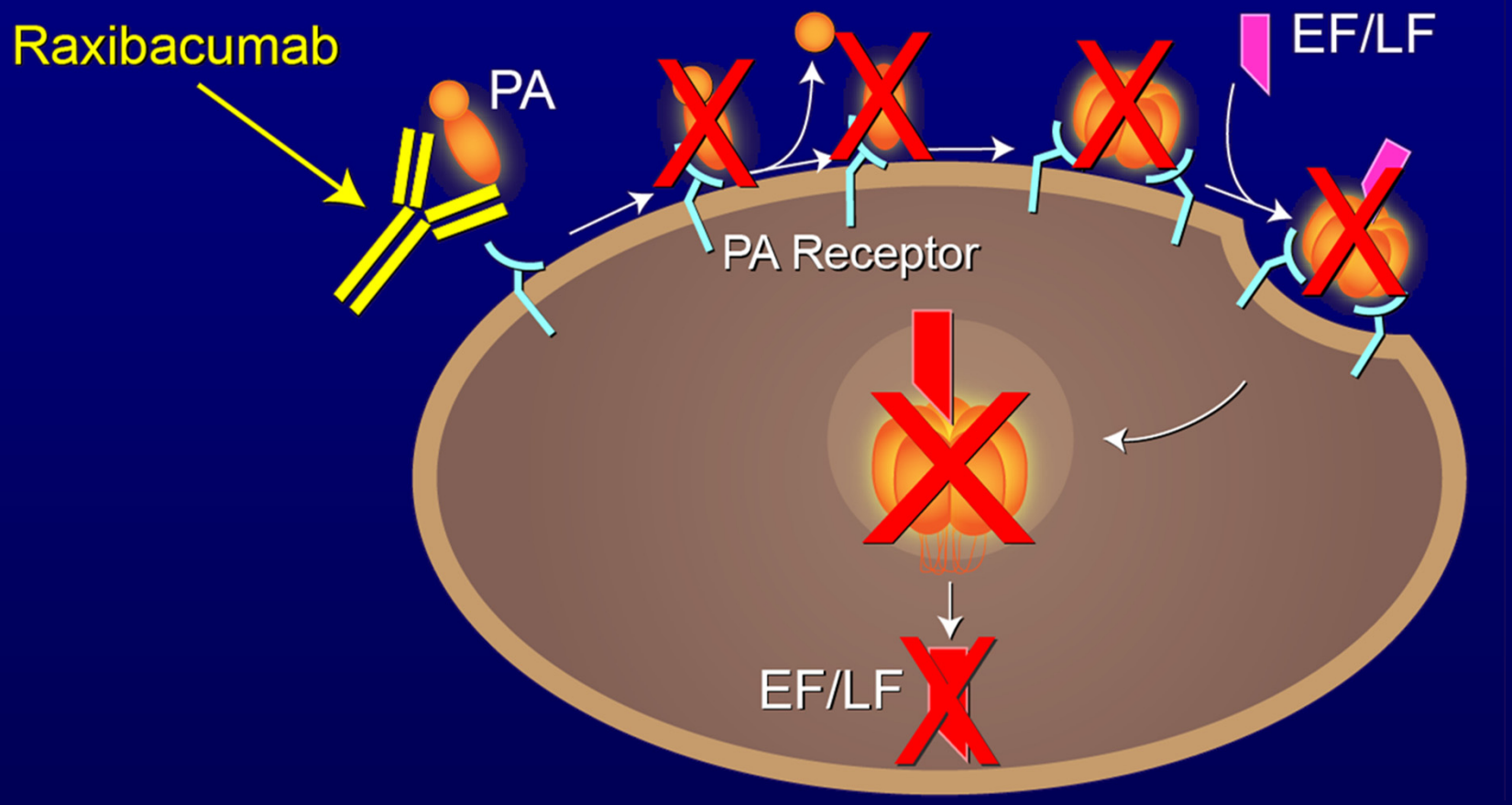
Mechanism of Action



Raxibacumab Antitoxin Activity

- Potent and specific binding
  - High affinity: Kd=2.78 nM
- Epitope conserved among all known strains
  - Recognized by antibodies that are raised naturally during infection and by vaccination
  - Required for receptor binding
  - Ames, Sterne and Vollum

Antibiotic-Resistant Strains

- Mechanism of action is independent of antibiotics
  - Expected to be effective against PA produced by all 14 known antibiotic-resistant strains
    - Epitope is conserved

Animal Models

- Established models
  - Demonstrate efficacy
- Common pathophysiology and natural history
  - Disease course
  - Organ involvement
  - High mortality
- Characterization studies identified triggers for intervention
  - Detectable PA is contemporaneous with onset of bacteremia

Characteristics of Disease across Species

	NZW Rabbits	Cynomolgus Monkeys	Humans
Challenge	*B. anthracis* (Ames)	*B. anthracis* (Ames)	*B. anthracis* (Ames)
Pathogenic factors	PA, LF, EF	PA, LF, EF	PA, LF, EF
Route	Inhalation	Inhalation	Inhalation
Exposure	100-200 x LD_{50}	200 x LD_{50}	Variable; <200 x LD_{50}
Host susceptibility	Lethal (100%)	Lethal (95-100%)	Lethal
Trigger for intervention	PA (=bacteremia); increased temp	PA (=bacteremia)	Bacteremia; symptoms
Natural Hx of disease			
Onset (PA/bacteremia)	24 h	36 h	4-6 days
Time to death	2-3.5 days	3.5-5 days	8-12 days
Manifestations	fever, mediastinal widening, pleural effusions, meningitis; bacteria in visceral organs and brain	fever, mediastinal widening, pleural effusions, meningitis; bacteria in visceral organs and brain, lethargy, weakness, anorexia	fever, mediastinal widening, pleural effusions, meningitis; bacteria in visceral organs and brain, cough, malaise, myalgia
Development of toxin-neutralizing antibodies	14-28 days	14-28 days	15-28 days

CM-033

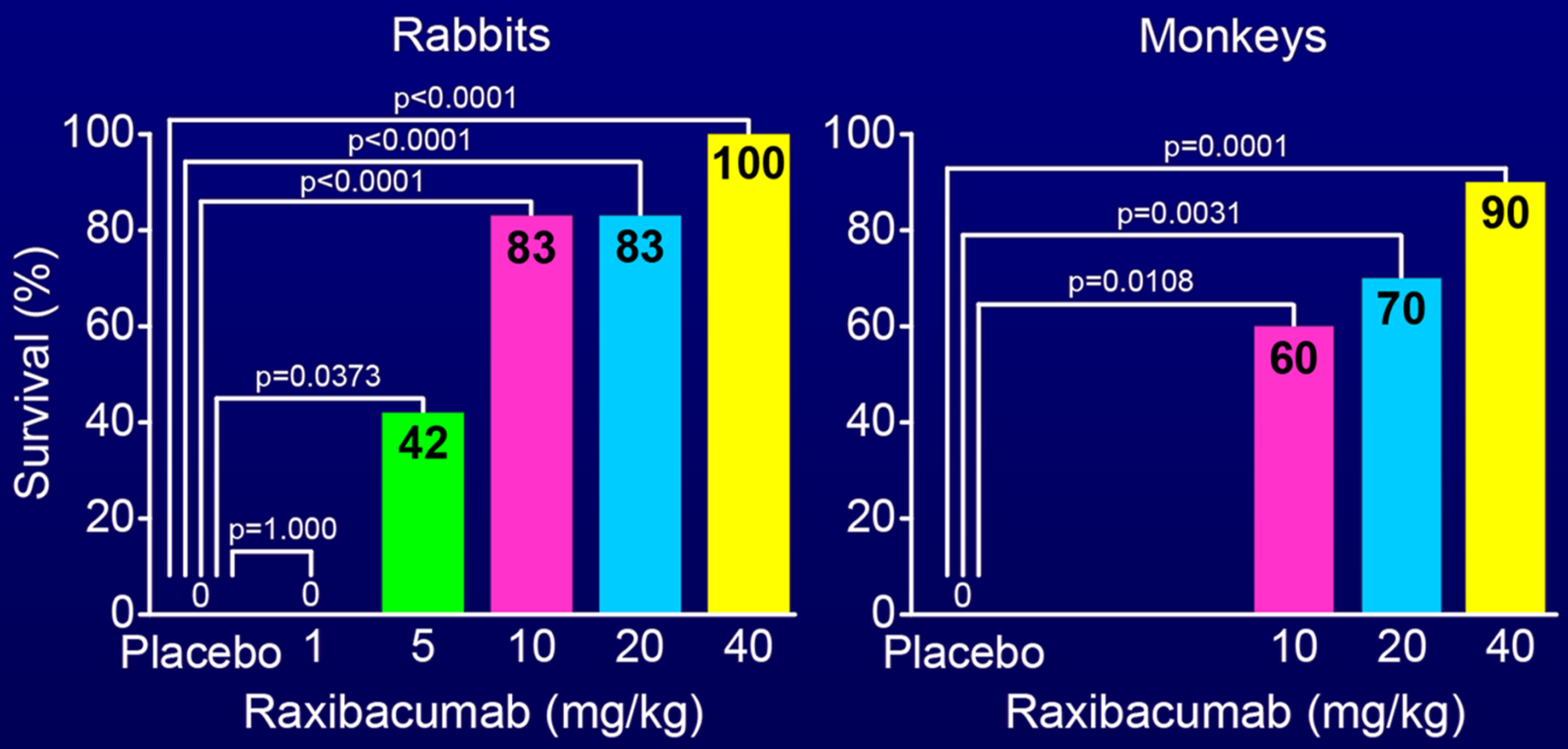
Dose and Time Ranging Studies

Dose-Ranging Studies: Study Design

- NZW rabbits and cynomolgus monkeys
- Anthrax spore challenge: 100 x LD_{50}
- Raxibacumab administered to be at C_{max} at time of exposure
- Endpoint
  - Survival at 14 days post challenge in rabbits
  - Survival at 28 days post challenge in monkeys

Dose-Ranging Efficacy Studies

Survival Rate: Dose Dependence



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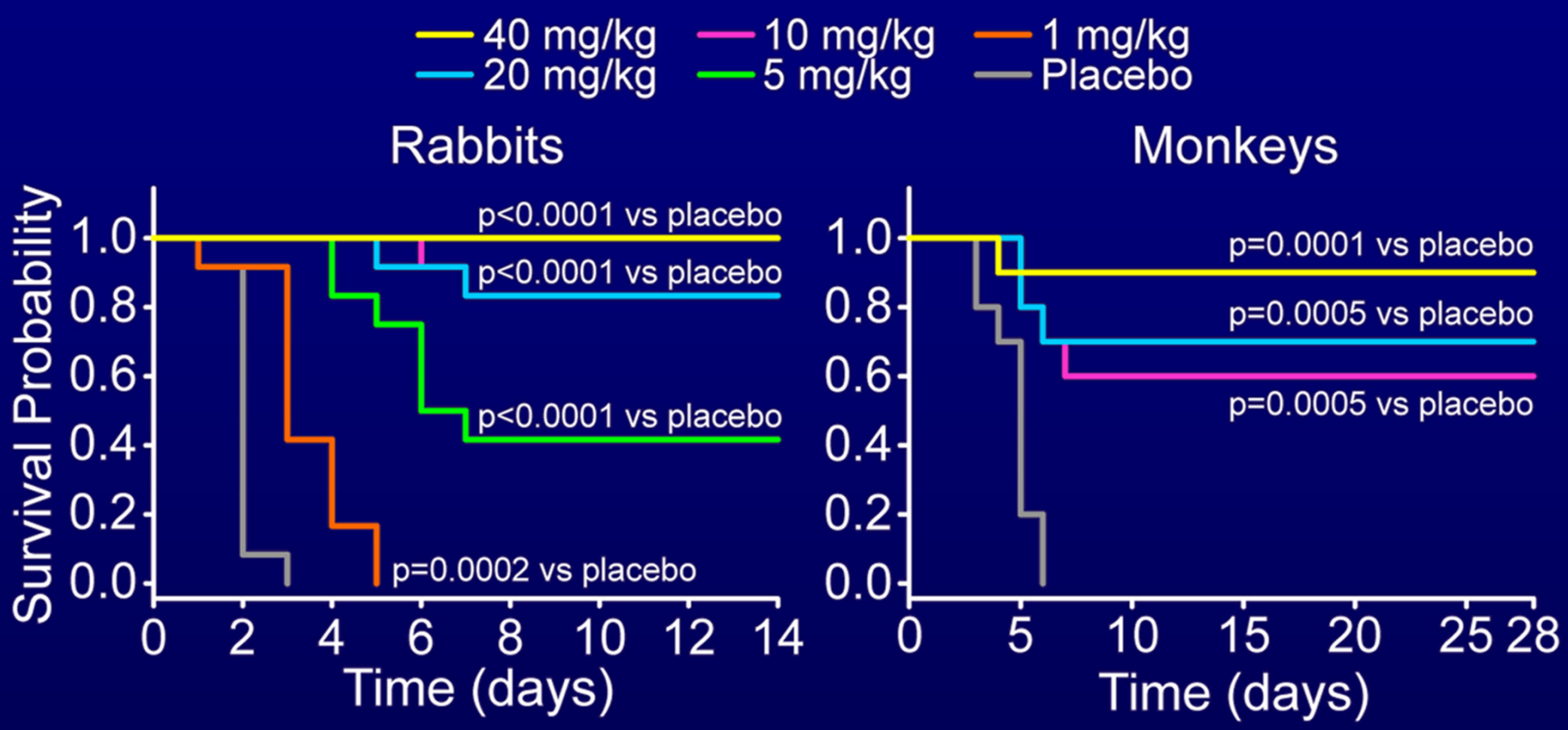
Dose-Ranging Efficacy Studies

Survival Time



CM-037

Rechallenge Study in Monkeys

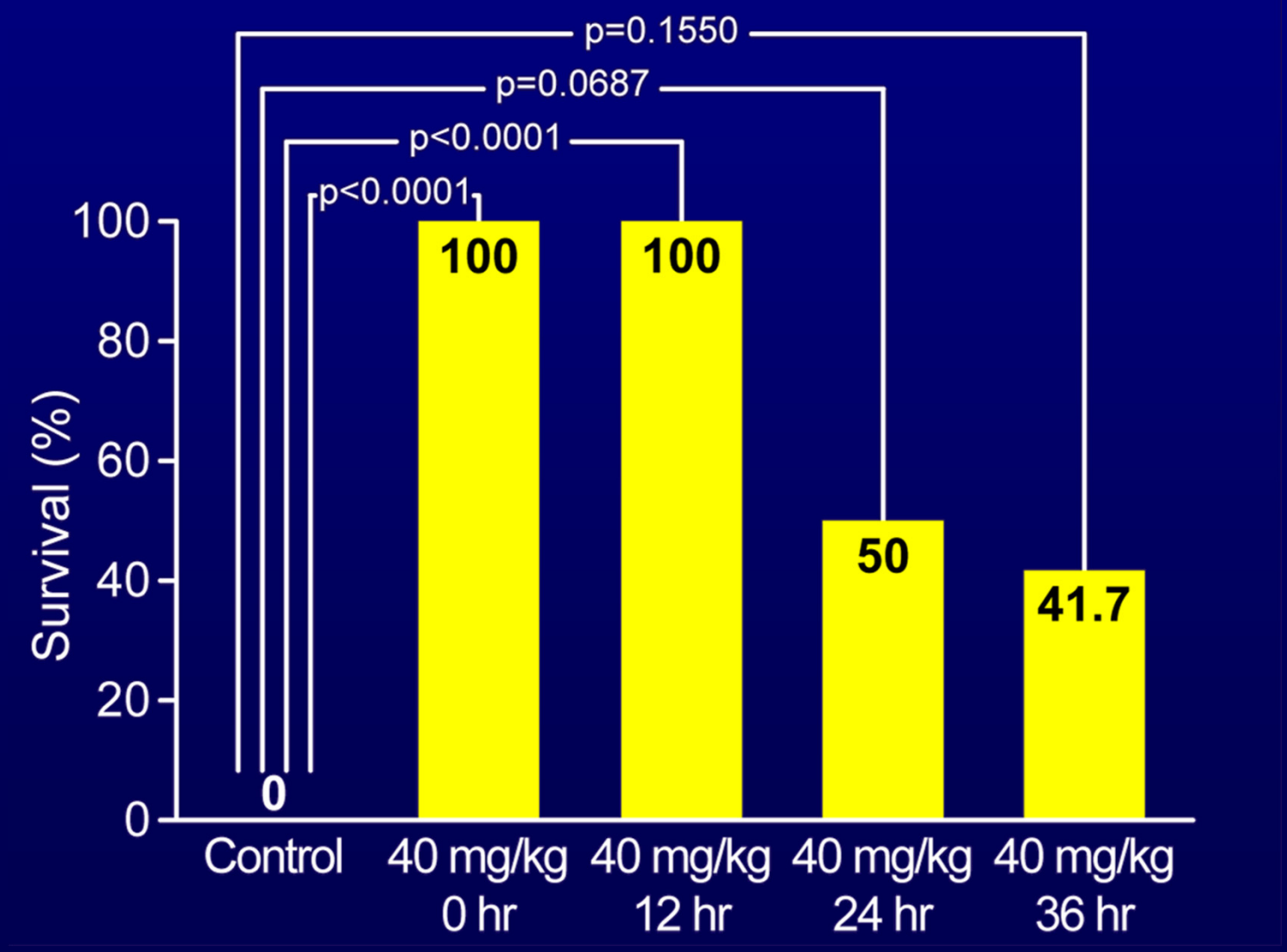
- N=21
- Rechallenged with anthrax spores at 11 months
- 100% survival
- All animals had developed a durable immune response

Time-Ranging Rabbit Study: Study Design

- NZW rabbits
- Anthrax spore challenge: 100 x LD_{50}
- Raxibacumab 40 mg/kg IV
  - At 0, 12, 24 or 36 hours post-challenge
- Endpoint: 14-day survival

Time-Ranging Rabbit Efficacy Studies

Survival Rate: Time Dependence



CM-040

Dose and Time-Ranging Studies: Summary

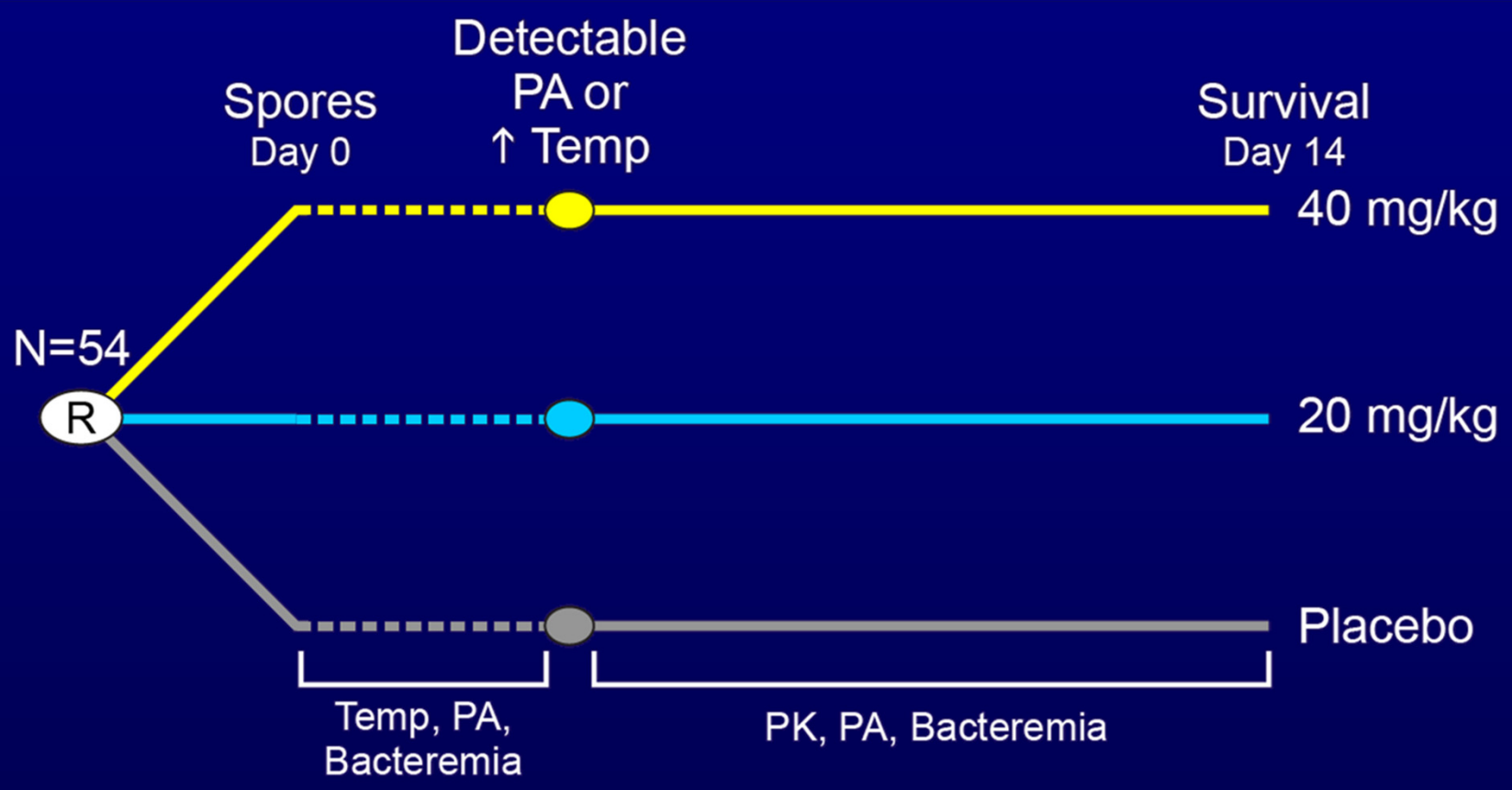
- Survival benefit
  - Statistically significant
  - Consistent across species
- Dose dependent
- Time dependent
- Does not interfere with natural immunity
  - Durable immunity after one year

Efficacy
Therapeutic Treatment

Demonstration of Efficacy

- Increased survival
- No interference with antibiotics
  - Higher survival outcome with combination
- Does not block natural immunity

Pivotal Rabbit Efficacy Study



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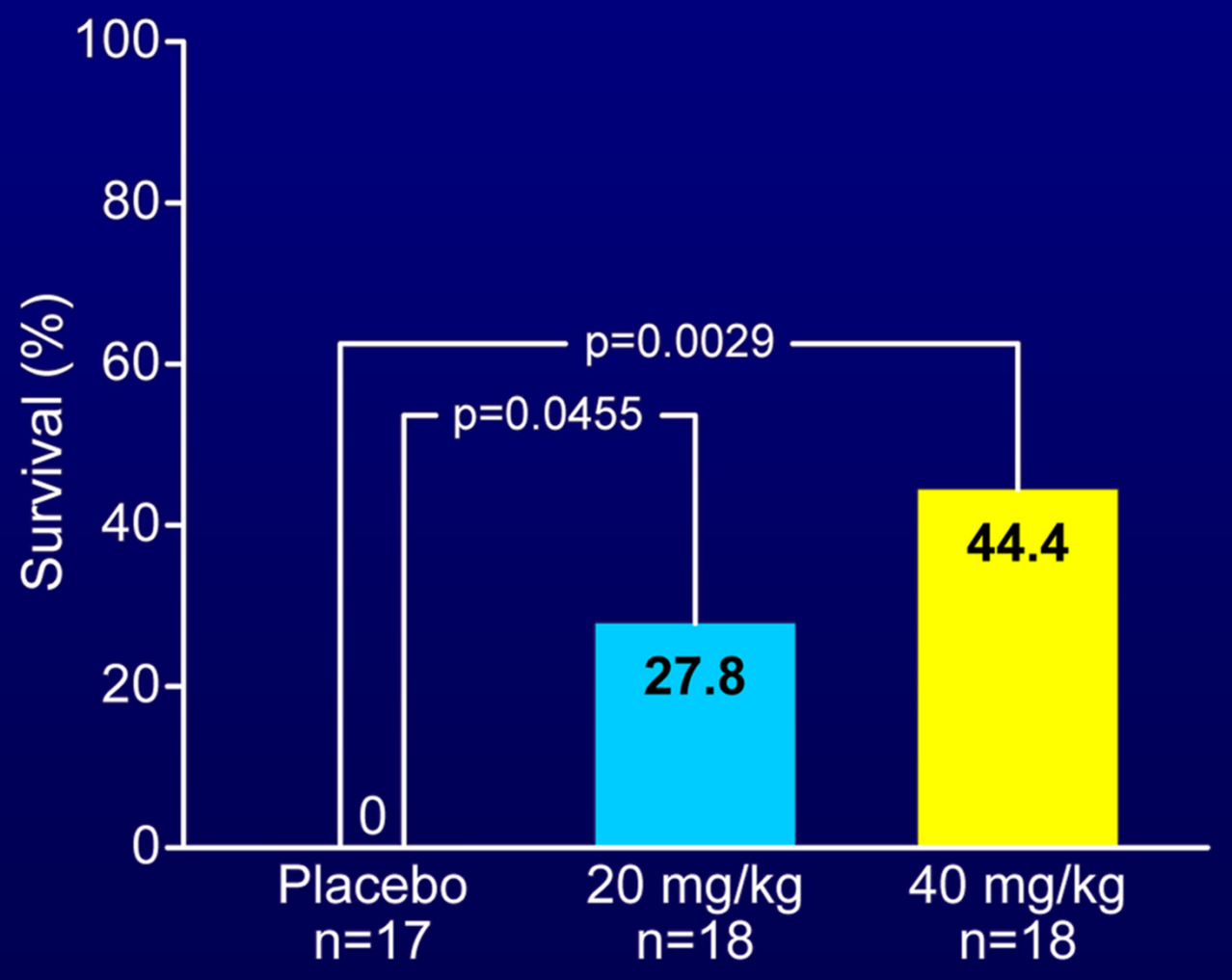
Pivotal Rabbit Efficacy Study

Primary Endpoint: Day 14 Survival



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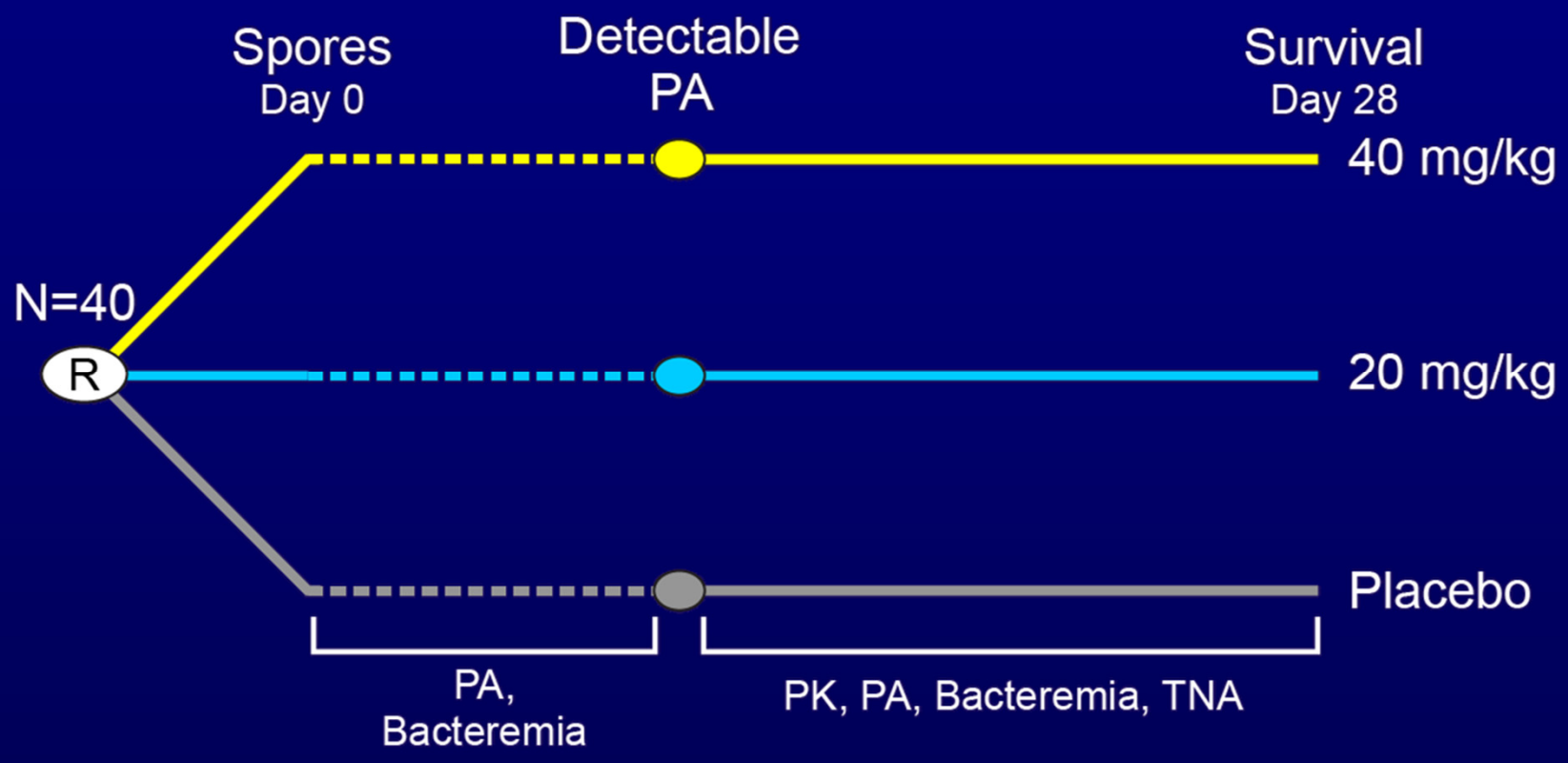
Pivotal Monkey Efficacy Study



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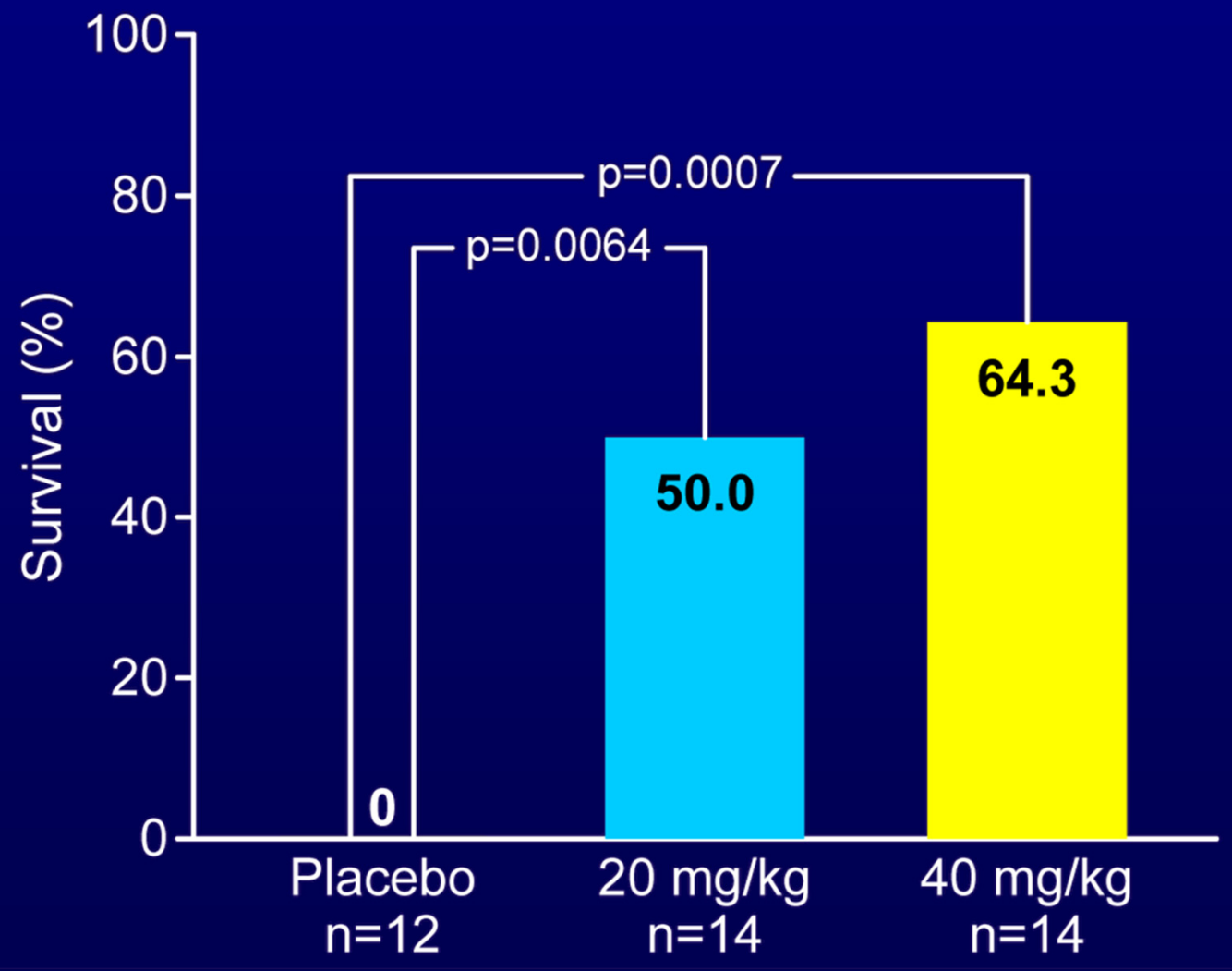
Pivotal Monkey Efficacy Study

Primary Endpoint: Day 28 Survival



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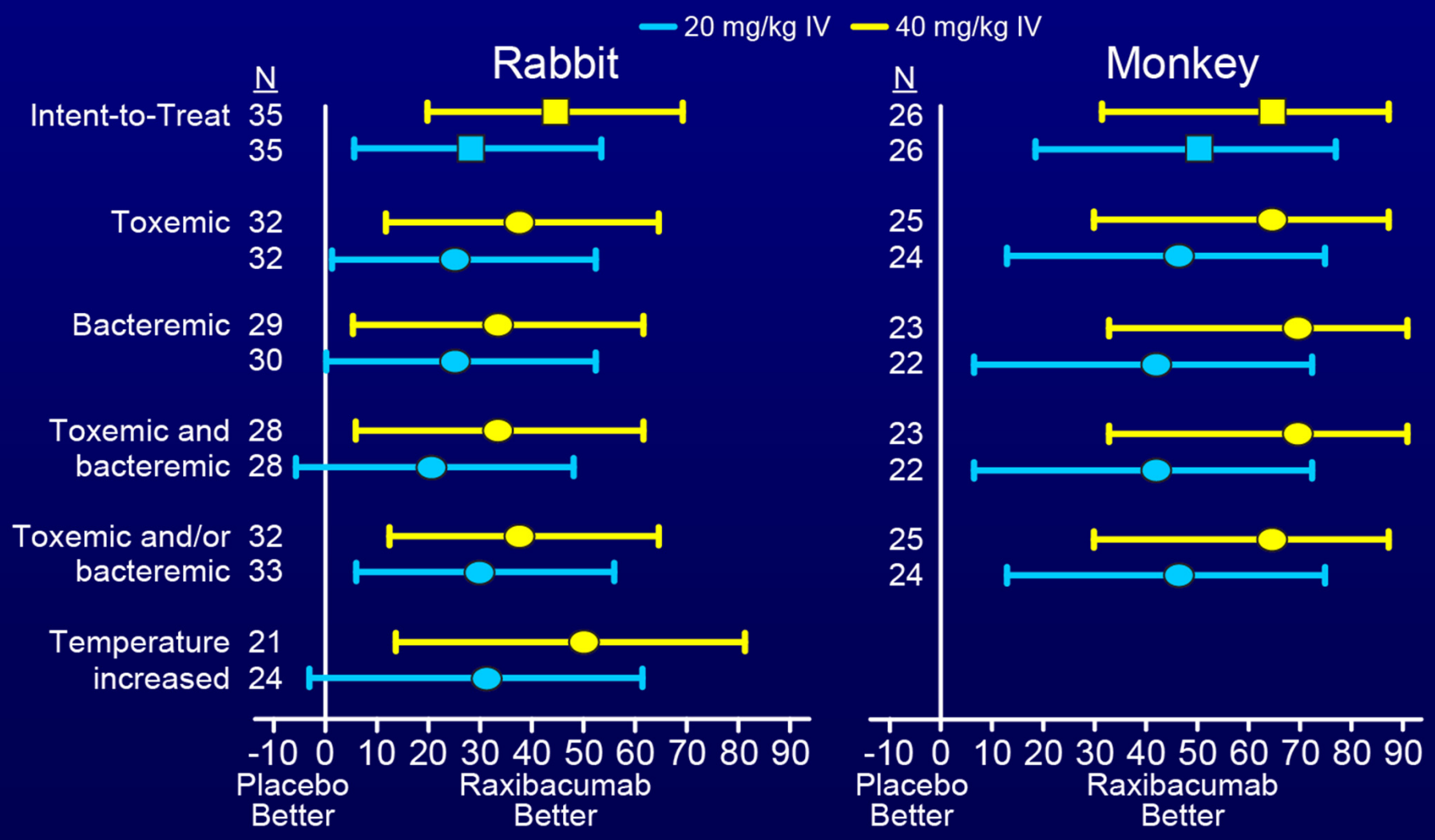
Pivotal Efficacy Studies

Survival Improvement by Pre-Specified Subgroups



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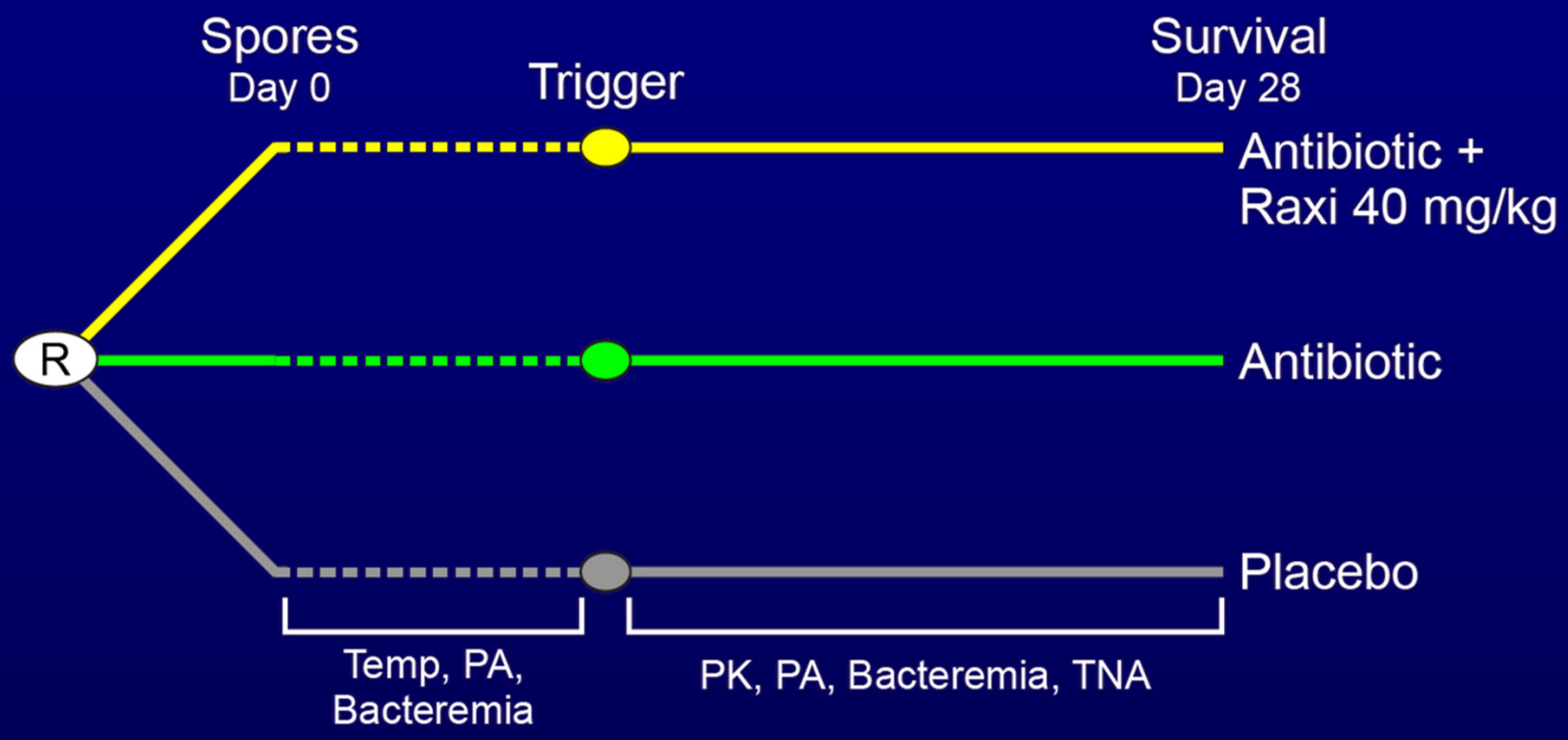
Pivotal Efficacy Studies: Summary

- Survival benefit
  - Statistically significant
  - Clinically relevant
  - Consistent across species
  - Numerically greater with 40 mg/kg
- Efficacy demonstrated in animals bacteremic at time of treatment

Raxibacumab/Antibiotic Combination Efficacy Studies

- Study design requirements
  - Raxibacumab and antibiotic administered at onset of symptoms
  - Antibiotic
    - Human equivalent exposure
    - Sterilize bacterial cultures
  - Superiority of combination arm to placebo
    - Not superiority or non-inferiority between active treatment groups

Raxibacumab/Antibiotic Combination Efficacy Studies: Study Design



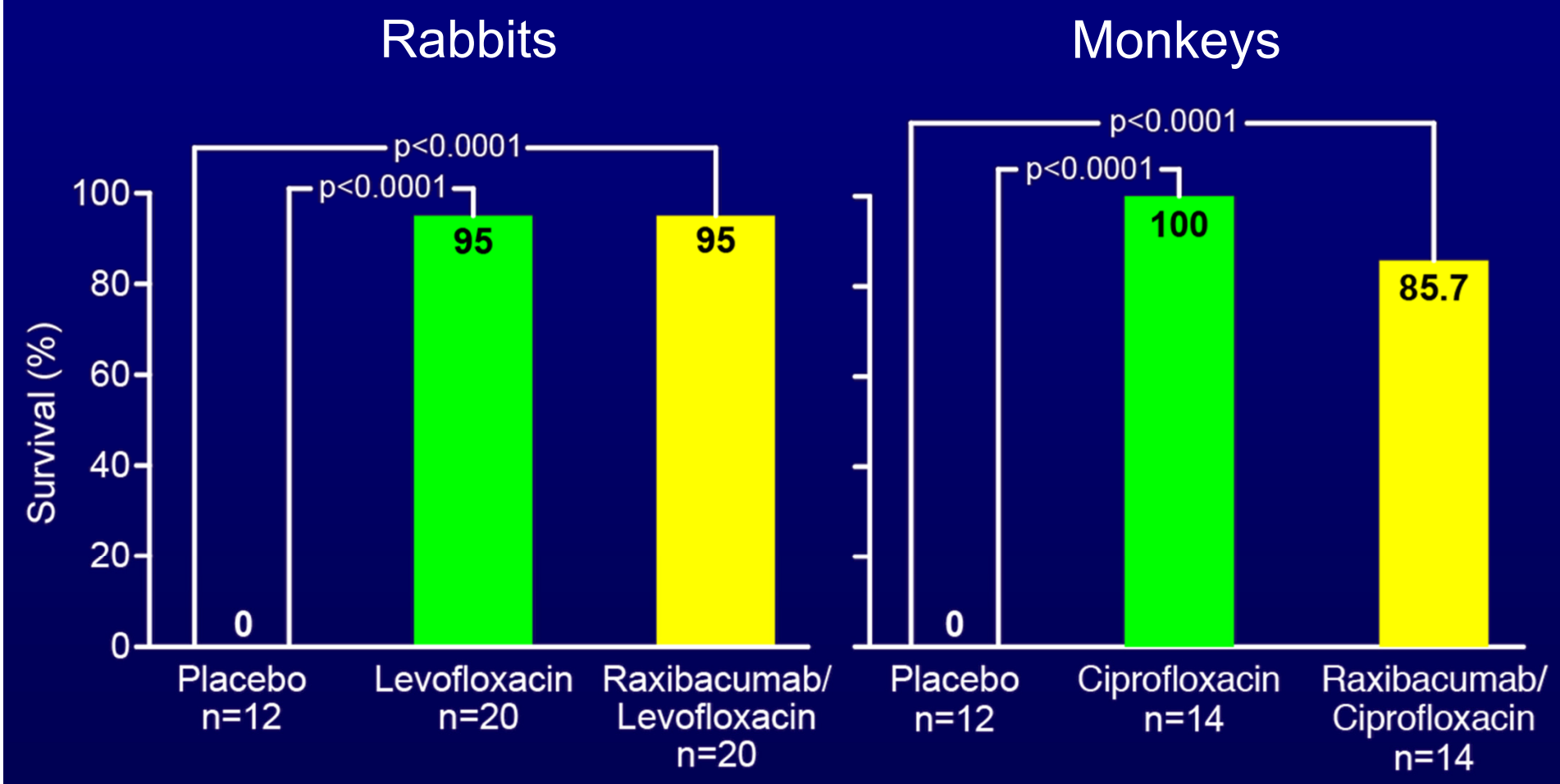
CF-051

Triggers and Antibiotic Regimen

	N	Trigger	Antibiotic
Rabbits	52	Detectable PA or increased temperature	Levo 50 mg/kg x 3 days
Monkeys	40	Detectable PA	Cipro 75 mg bid x 3 days

Antibiotic Combination Studies

Primary Endpoint: Survival at Day 28



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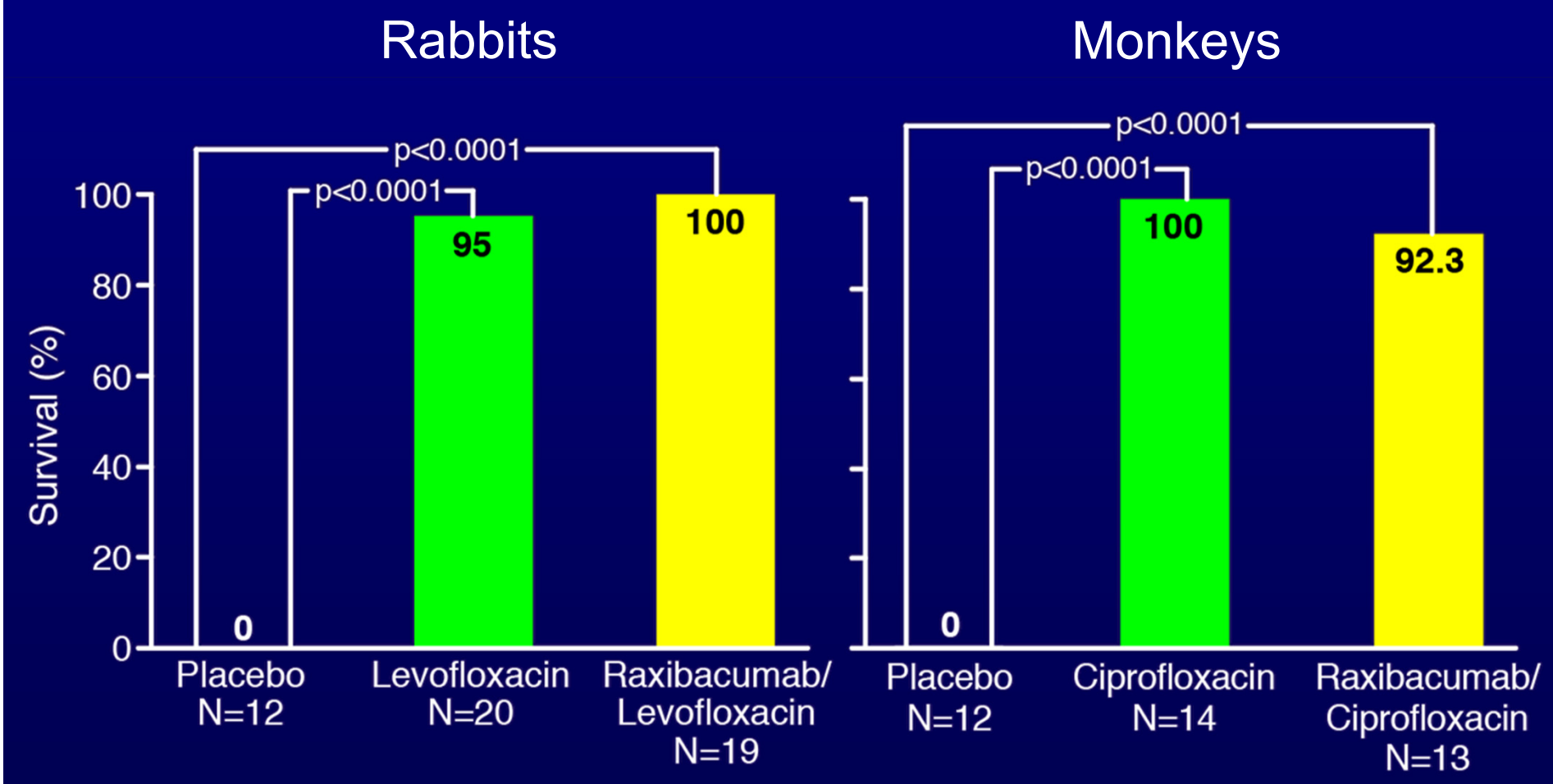
Antibiotic Combination Studies

Survival Rate: Anthrax Deaths



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Added Benefit Efficacy Study Goals

- Evaluate potential added benefit
  - Levofloxacin + raxibacumab vs levofloxacin
- Equivalent human antibiotic exposure
- Survival rate with antibiotics alone similar to that in 2001 anthrax attacks: ~55%
  - Treat late in the course of infection
  - Balance number of animals alive to be treated with suboptimal survival rate with antibiotics

Added Benefit Study Protocol

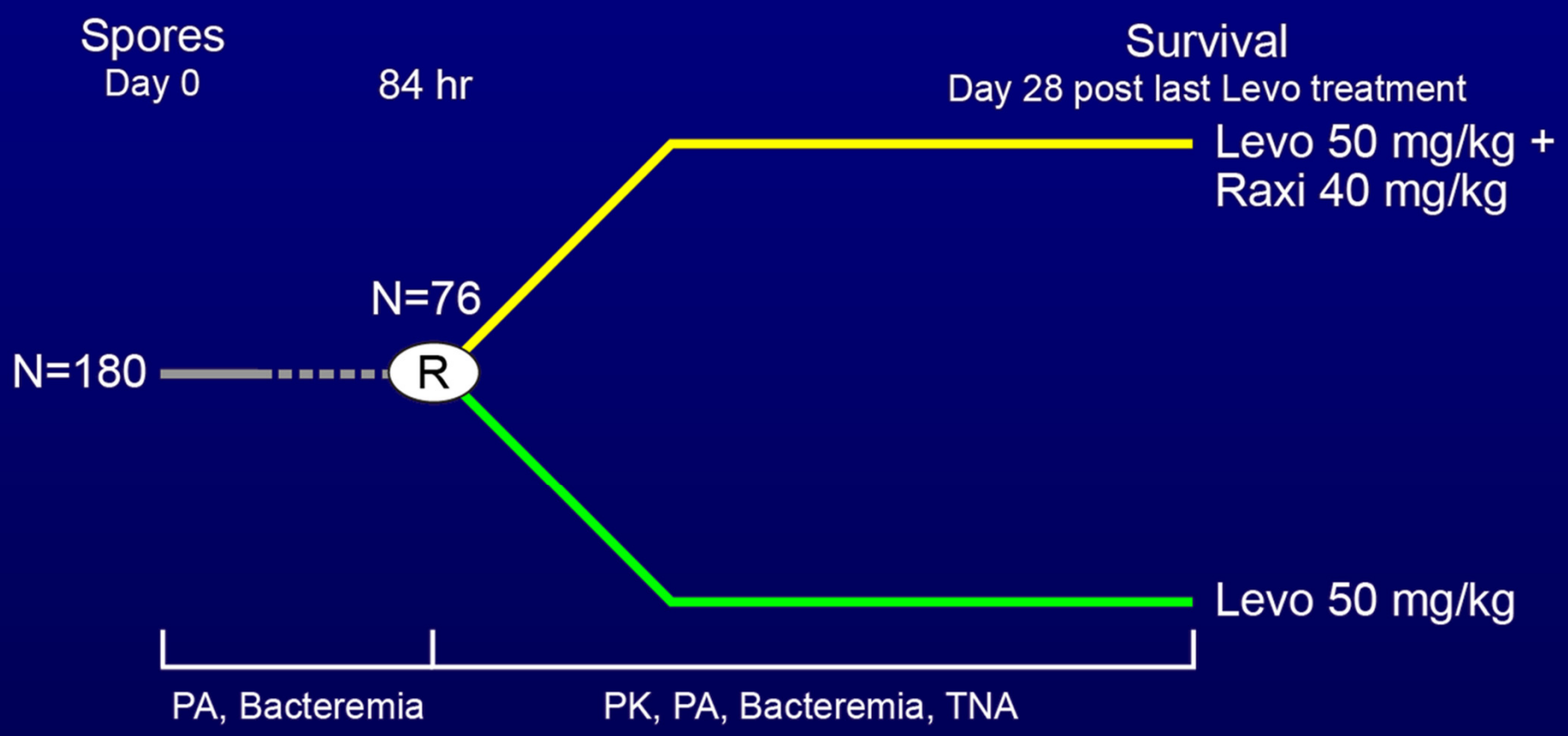
- Treatment late in the course of disease: 84 hours
  - 35-50% survive to be randomized for treatment
- Higher survival outcome for combination therapy
- Study not powered for statistical significance
  - 52% power to detect a 25% difference
  - 13% power to detect a 10% difference
- Special Protocol Assessment

Sample Size for 80% Power

Absolute Improvement in Survival	Number of Animals Treated per Group	Number of Animals To Be Spore Challenged*
10%	388	1838
12.5%	249	1180
15%	173	820
17.5%	127	602
20%	97	460

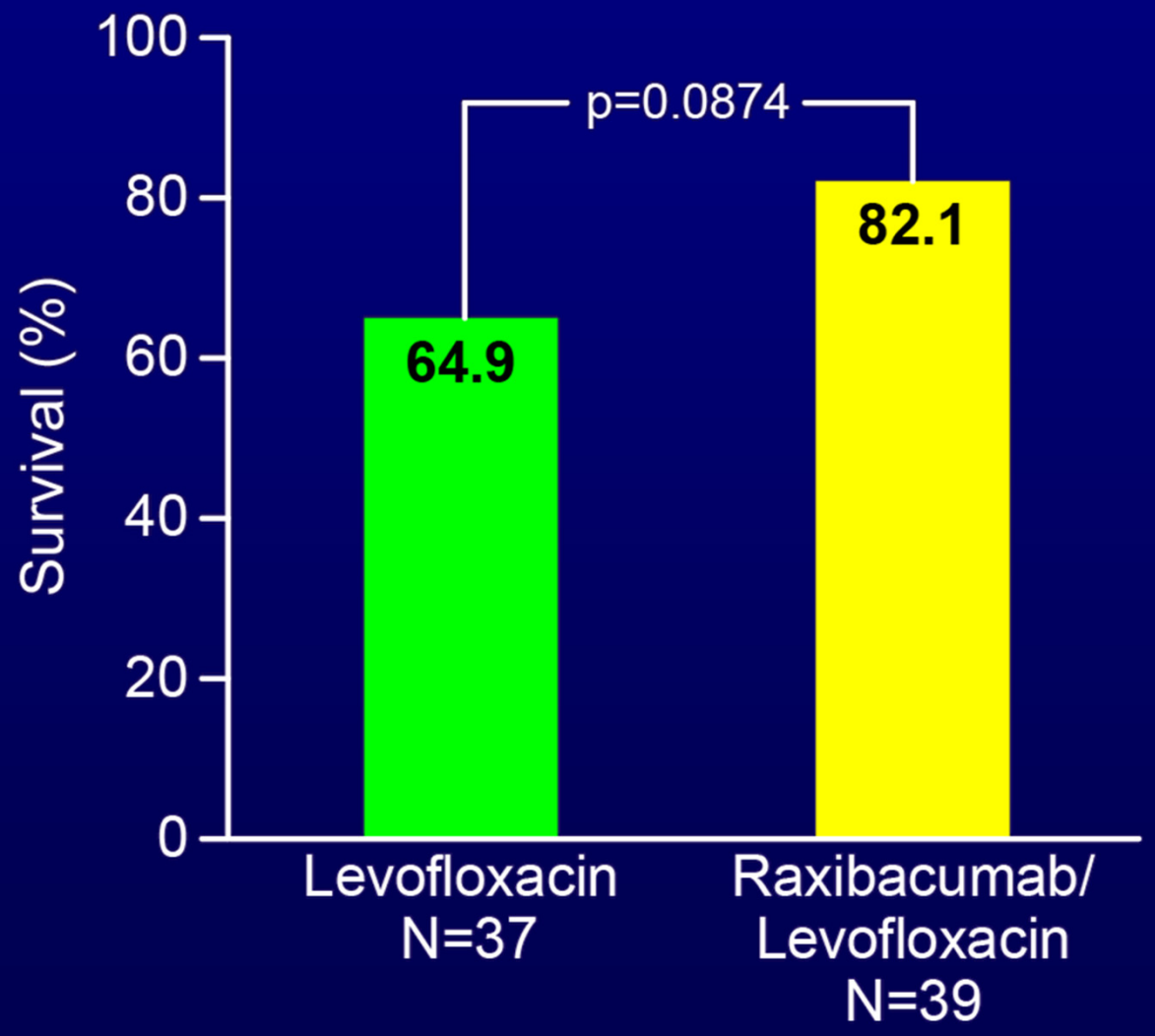
* Assuming 2 treatment groups and 42% animals alive to be treated at 84 hours.

Added Benefit Study



Added Benefit Efficacy Study

Primary Endpoint: Day 28 after Levo



% Difference
Levo/Raxi vs Levo
(95% CI)

17.2 (-2.4, 36.7)

CF-059

Toxin Neutralizing Antibody (TNA) Titers

Study	Species	Treatment	TNA Titer (Median)	
			Baseline	28 Days
1103-G923704	Rabbits	Raxi	0	1878
781-G923701	Rabbits	Raxi + Levo	0	469
		Levo	0	1978
1141-CG920871	Rabbits	Raxi + Levo	0	4519
		Levo	0	3835
724-G005829	Monkeys	Raxi (20 mg/kg)	0	4459
		Raxi (40 mg/kg)	0	8076
789-G923702	Monkeys	Raxi + Cipro	0	3746
		Cipro	0	5585

Efficacy Summary

- Survival benefit compared with placebo
  - Monotherapy and in combination with antibiotics
  - Statistically significant
  - Clinically relevant
  - Consistent across species
- No interference with antibiotic efficacy
  - Higher survival outcome in added benefit study
- No interference with natural immunity

Nonclinical Safety

Safety in Toxicology Studies

- PA is not an endogenous target
- GLP repeat-dose study in healthy monkeys
  - No toxicity
  - No immunogenicity
- GLP embryo-fetal study in healthy rabbits
  - No adverse maternal or fetal findings
  - Low level of immunogenicity did not compromise exposure

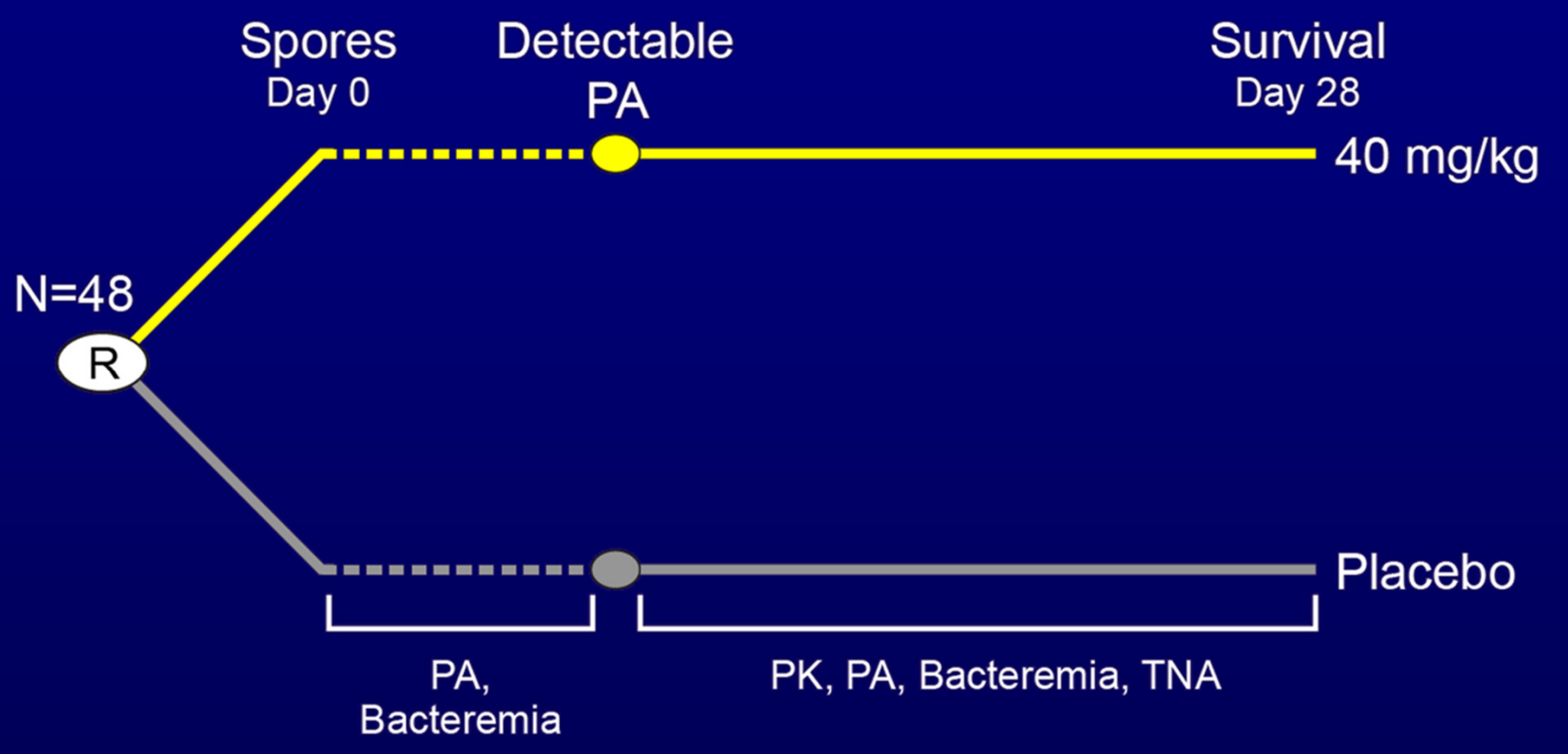
Evaluation of Histopathology: Submitted in Original BLA

- Gross necropsy to confirm death due to anthrax
- Histopathology
  - Non-survivors
    - Lesions and cause of death consistent with anthrax
  - Survivors
    - No adverse clinical observations
    - No histopathology performed

Observations in Non-survivors: Submitted in Original BLA

- Placebo
  - Visible bacteria, hemorrhage and inflammation in all organs
- Raxibacumab monotherapy
  - Less bacteria and inflammation in visceral organs
  - More bacteria and pathology in brain

Survivor Histopathology Study



CF-066

Survivor Histopathology Study

- Survival rates replicated those of pivotal trial
  - 45.8% raxibacumab; 0% placebo
- Non-survivors
  - Placebo
    - More frequent/severe lesions in visceral organs, less in brain
  - Raxibacumab monotherapy
    - More frequent/severe lesions in brain, less in visceral organs
    - Similar staining for raxibacumab and endogenous IgG
- Survivors
  - No adverse clinical sequelae
  - No bacteria or inflammation in the brain

Histopathology in Added Benefit Study

- Non-survivors
  - Levofloxacin alone
    - More frequent/severe lesions in all organs, including the brain
  - Raxibacumab/levofloxacin
    - Less frequent/severe lesions in all organs
    - No lesions in the brain
- Survivors
  - No adverse clinical sequelae
  - No lesions in any organs

Nonclinical Safety Conclusions

- No adverse effects of raxibacumab
  - No drug-related brain findings (repeat dose toxicology)
  - Does not cross blood-brain barrier (biodistribution)
  - No binding to brain (tissue cross-reactivity)
- Raxibacumab does not exacerbate disease
  - Increases survival
  - No clinical sequelae or histopathologic signs in survivors
  - Antibiotic combination studies show protection of both brain and visceral organs

Pharmacokinetics and Translation to Human Dosing

Al Corey

Senior Pharmacokineticist
Human Genome Sciences

CP-070

Nonclinical Pharmacology

- Linear and predictable PK across species
- C_{max} is similar
  - Rabbits and monkeys
  - Healthy and anthrax-infected animals
  - Survivors and non-survivors
- Concomitant administration with antibiotics does not alter PK of either drug
- Reaches target organs, except the brain

Raxibacumab PK in Healthy and Anthrax-Infected Rabbits (40 mg/kg IV single dose)

Parameter	Healthy	Monotherapy, Disease Onset	With Levofloxacin, Disease Onset	With Levofloxacin, Added Benefit
C_{max} (µg/mL)	1104	919	928	1114
CL (mL/day/kg)	7	12	9	9
$t_{1/2,z}$ (day)	6.9	4.0	4.5	4.7
$AUC_{0-\infty}$ (µg•day/mL)	6072	3424	4361	4590
V_{ss} (mL/kg)	63	64	59	56

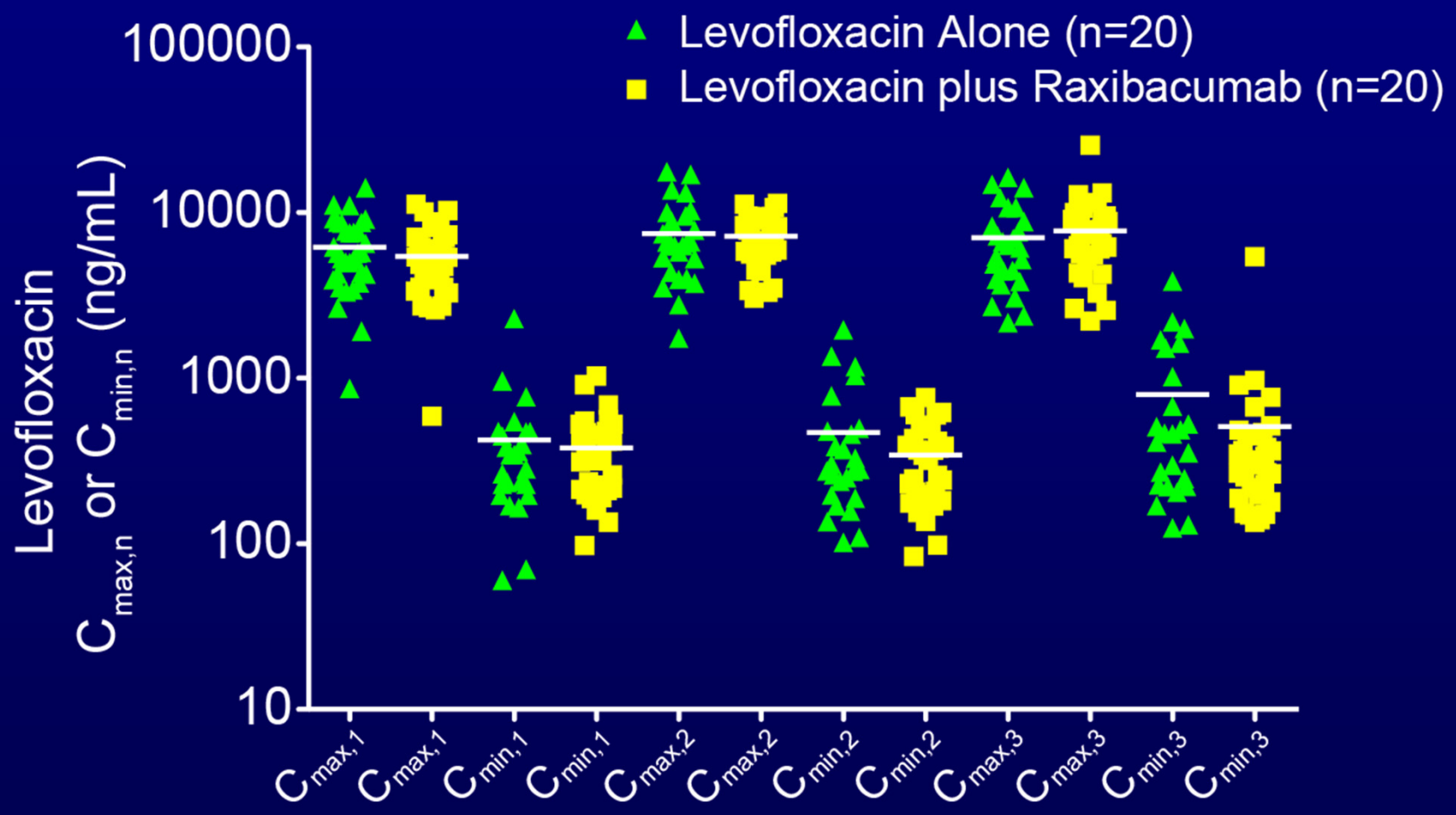
CP-072

Raxibacumab PK in Healthy and Anthrax-Infected Monkeys (40 mg/kg IV single dose)

Parameter	Healthy	Monotherapy, Disease Onset	With Ciprofloxacin, Disease Onset
C_{max} (µg/mL)	1046	990	1067
CL (mL/day/kg)	5	7	4
$t_{1/2,z}$ (day)	11.8	10.1	16
$AUC_{0-\infty}$ (µg•day/mL)	8120	6491	10782
V_{ss} (mL/kg)	78	83	83

CP-073

Levofloxacin PK with and without Raxibacumab in Rabbits



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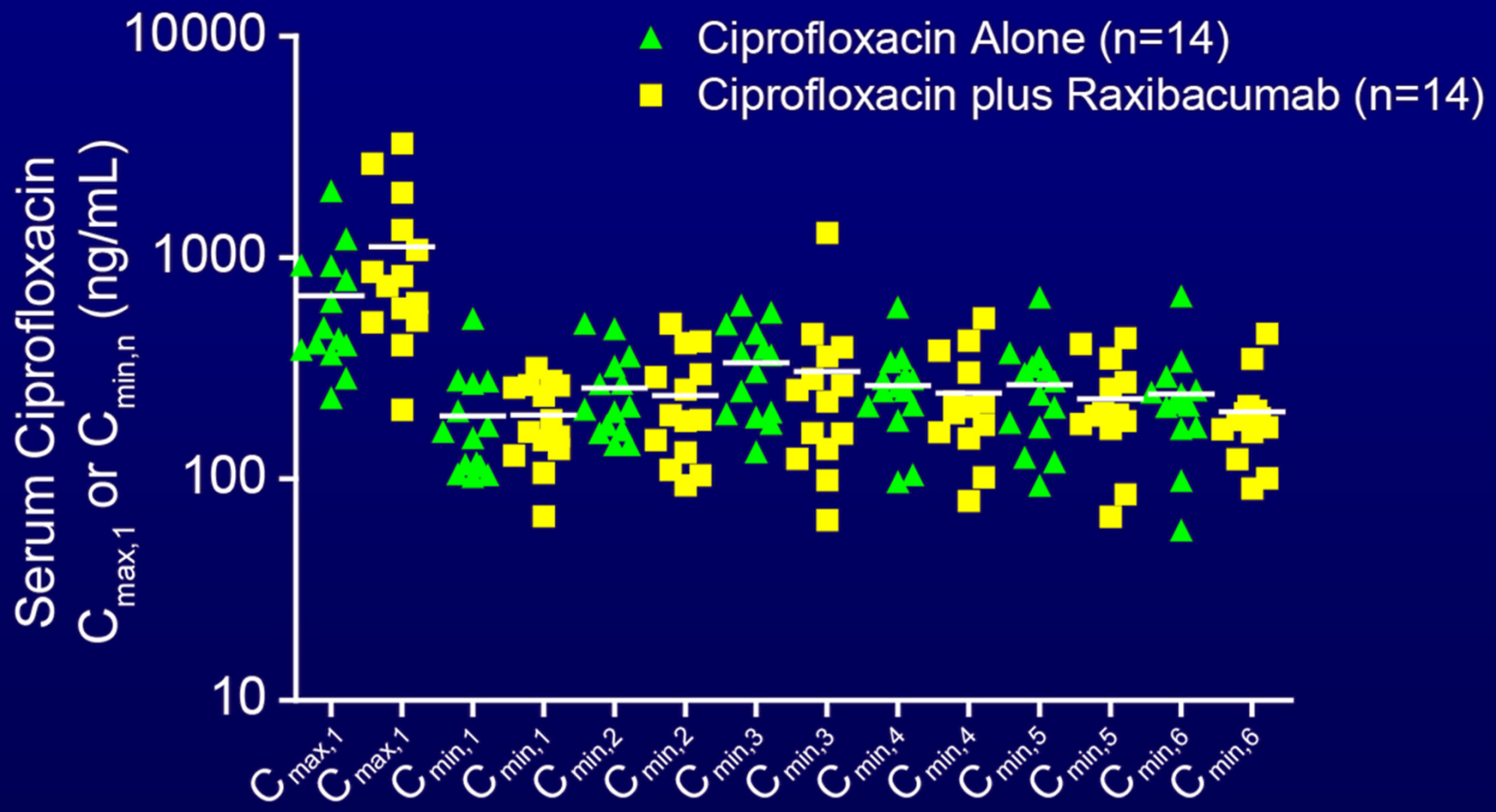
Ciprofloxacin PK with and without Raxibacumab in Monkeys



CP-075

CNS Exposure to Raxibacumab

- Raxibacumab cannot cross intact blood-brain barrier
- Raxibacumab only found in the brain when endogenous IgG was present
- Cerebrospinal fluid levels
  - Generally not detectable in survivors
  - <2% of plasma level for non-survivors

PA Kinetics

- PA levels correlate with bacteremia
- Consistent rise-plateau-rise pattern
- Death associated with highest PA levels
- Faster progression to high PA levels associated with death
- PA levels decline after treatment in surviving animals
  - $t_{1/2} \approx 10$ hours

Pharmacologic Approach to Dosing

- Raxibacumab exposure does not differ between survivors and non-survivors
- Neutralization of PA
  - Immediate, high raxibacumab concentration
- Protection against toxemia needed until natural anti-PA can develop
  - Sustained exposure

C_{max} Across Species

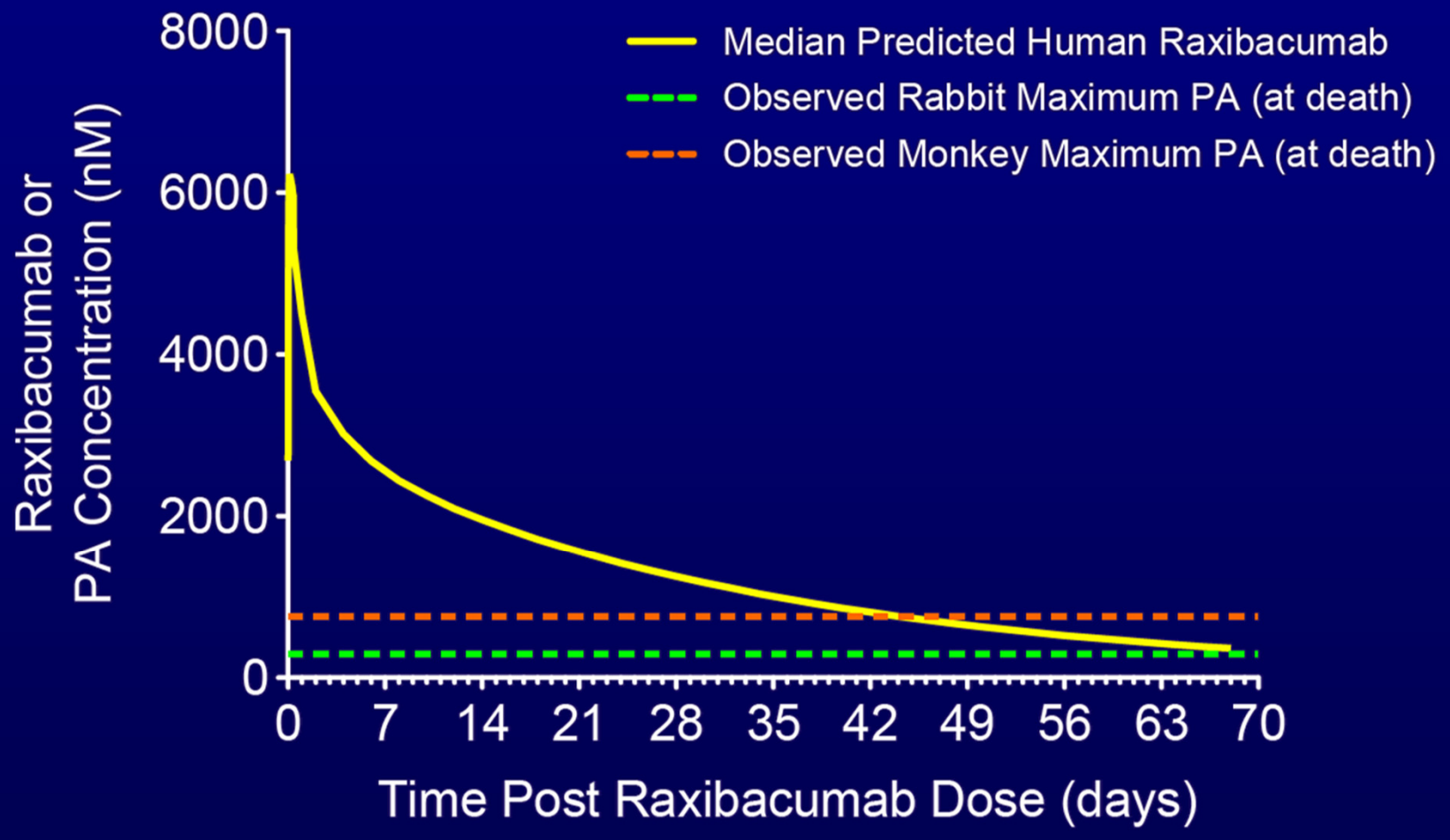
Species	Study	Mean ± SD (µg/mL)
Rabbit	Healthy	1104 ± 76
	Embryo-fetal (healthy)	1022 ± 46
	Monotherapy, disease onset	919 ± 124
	With levofloxacin, disease onset	928 ± 106
	With levofloxacin, delayed tx	1114 ± 138
Monkey	Healthy	1046 ± 12
	Toxicology (healthy)	1089 ± 113
	Monotherapy, disease onset	990 ± 170
	With ciprofloxacin, disease onset	1067 ± 158
Human	PAM-NH01	1042 ± 88
	C1064	988 ± 220
	C1069	979 ± 148
	C1063 (Pop PK)	960 ± 164

Minimum Raxibacumab Exposures

	Mean $t_{1/2,z}$ (days)	Lowest C_{max} (µg/mL)	Lowest $AUC_{0-\infty}$ (µg·day/mL)
Surviving rabbits	4.8	405	1411
Surviving monkeys	10.1	385	2499
Healthy humans	22.4	589	8720
Humans with anthrax*	13.9	589	5129

* Predicted data for anthrax-infected humans, assuming raxibacumab clearance increase matches largest increase observed in animals.

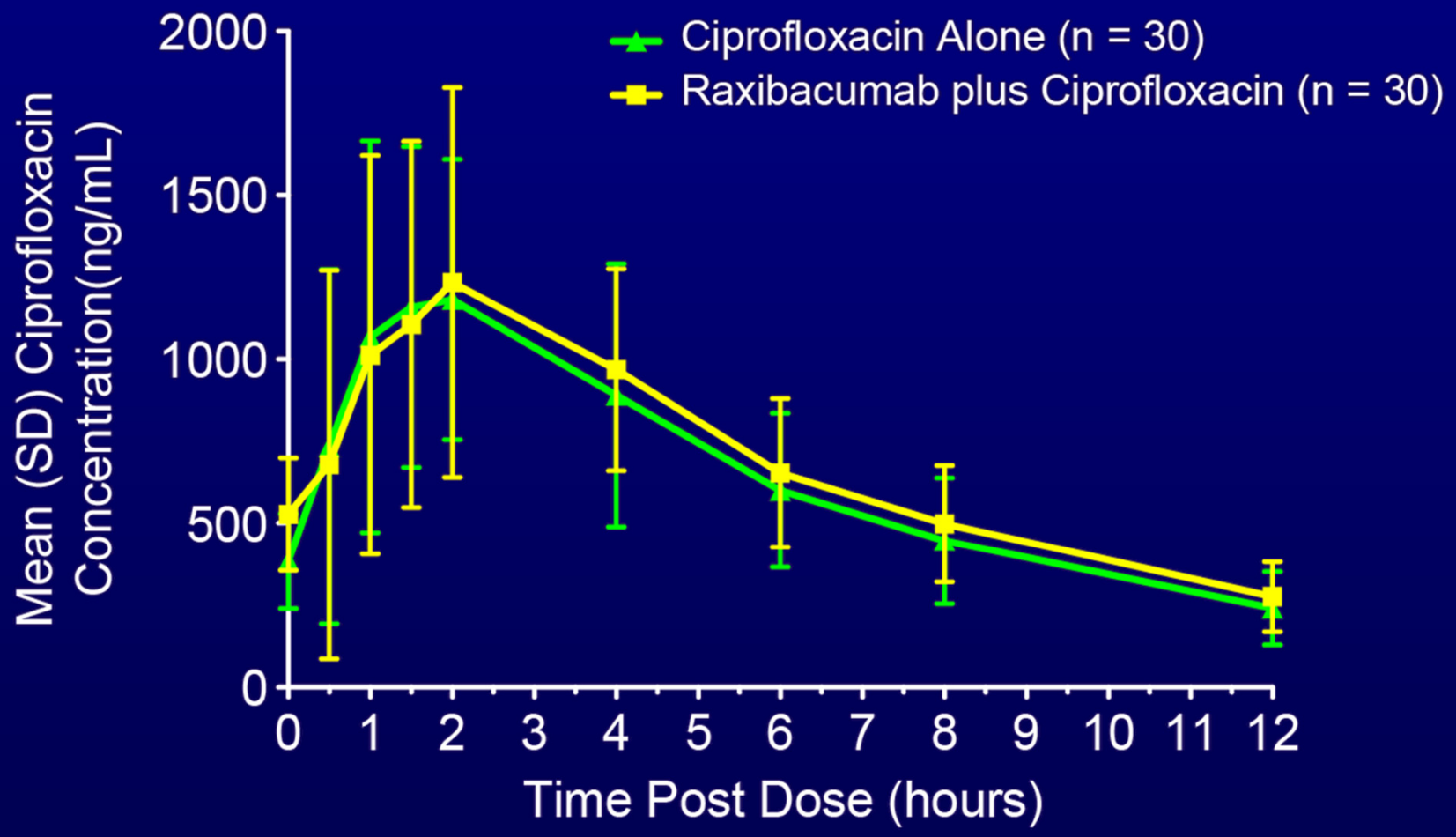
Raxibacumab Concentration-Time Profile Relative to the Highest PA Concentrations



CP-081

Human Raxibacumab/Ciprofloxacin Combination Safety Study C1064

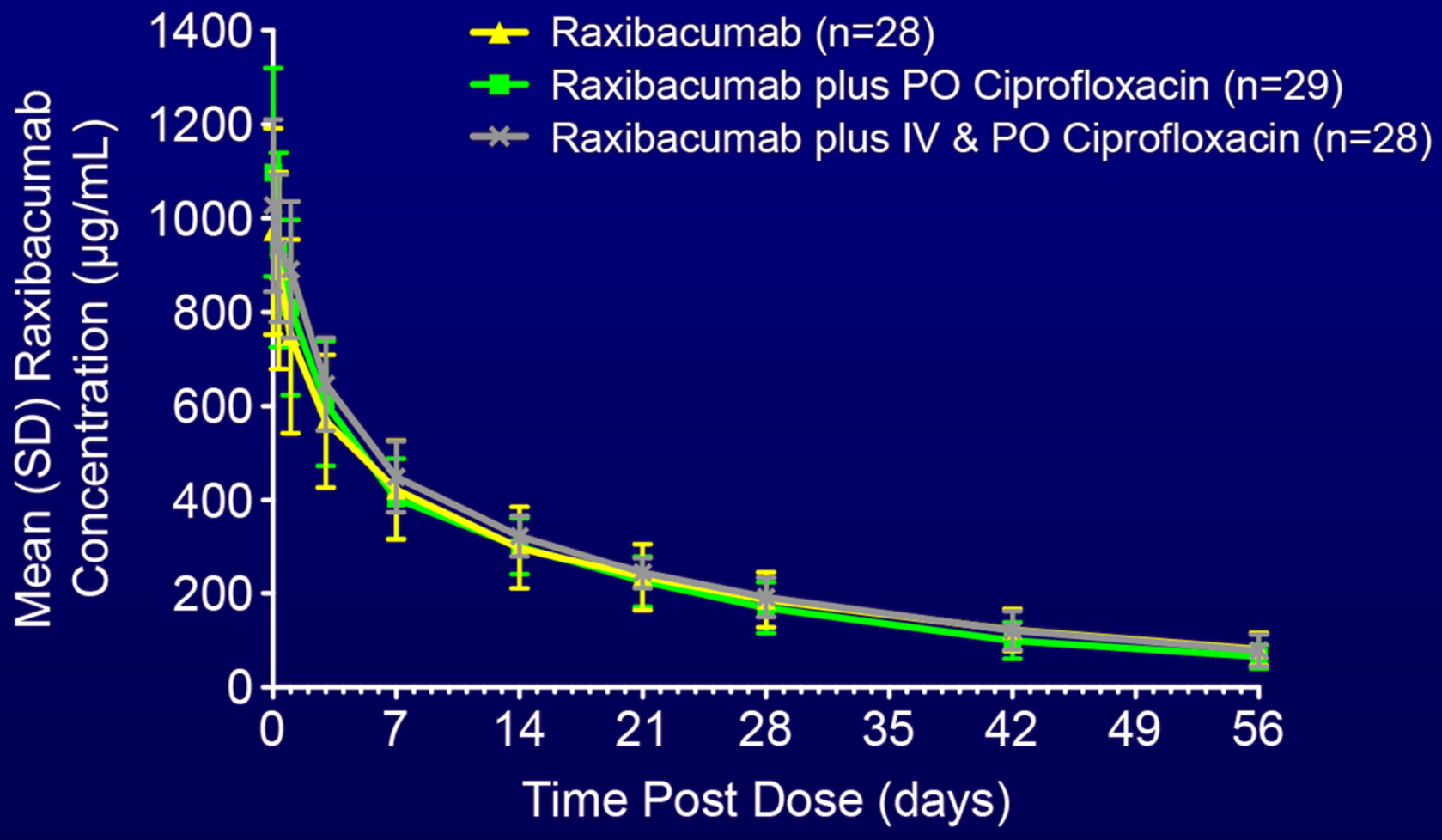
Ciprofloxacin PK with Raxibacumab



CP-082

Human Raxibacumab/Ciprofloxacin Combination Safety Study C1064

Raxibacumab PK with Ciprofloxacin



CP-083

Covariate Effects on PK

- PK not affected by
  - Age
  - Sex
  - Race
- Weight affects PK
  - Impact mitigated by mg/kg dosing
  - Has implications for pediatric dosing

Pediatric Dose Rationale

- No pediatric studies conducted or requested
  - Not ethical
  - Not required for an orphan drug
- FDA requested PK simulations to guide selection of pediatric dose
  - Multiple scenarios simulated by HGS and FDA
  - Some simulations suggested need for higher dose for younger subjects
- Higher dosing proposed for pediatric subjects

Pediatric Dose Recommendation

- Proposed pediatric doses
  - 80 mg/kg if ≤15 kg
  - 60 mg/kg if >15 to ≤50 kg
  - 40 mg/kg if >50 kg
- Data to support safety
  - 40 mg/kg x 2 in adults
  - 120 mg/kg in animals

PK Conclusions

- Raxibacumab PK translatable across species
- Antitoxin levels
  - Immediate
    - C_{max} ensures virtually complete PA binding
  - Durable
    - Long half-life ensures protection until natural immunity develops
- No PK interactions with antibiotics

Human Safety

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Clinical Research
Human Genome Sciences

Human Safety Studies

Study	Design	Population	n
PAM-NH01	Placebo-controlled, dose-ranging, IM, IV	Placebo Raxibacumab	25 80
C1063	Placebo-controlled, single & repeat dose	Placebo Raxibacumab	80 (single) 217 (repeat) 23
C1064	Combination with ciprofloxacin	Raxibacumab Raxibacumab + ciprofloxacin	28 58
C1069	Repeat dose after ≥4 months	Raxibacumab	20

Demographics

	Placebo (n=105)	Raxibacumab (n=406)
Age – mean (range) (yrs)	40.4 (18-78)	39.0 (18-88)
Males (%)	61.0	50.0
Race/Ethnicity (%)		
White	72.4	65.0
Black	22.9	26.8
Asian/Pacific Islander	5.7	6.4
American Indian	0	0.5
Hispanic	8.6	13.1
Weight – mean (range) (kg)	78 (48-120)	78 (45-164)

Safety Population

Population	Subjects (n)	
	Placebo	Raxibacumab
Primary Safety*	80	326
Dose-ranging	25	80
Total Safety	105	406

* Subjects who received 40 mg/kg from commercial manufacturing process.

Total Safety Population

Deaths and Serious Adverse Events

Study Agent (Subjects, %)	Event	Latency	Investigator Attribution
Deaths			
Placebo (1/105, 1.0%)	Motor vehicle accident	25	Not related
SAEs			
Raxibacumab (3/406, 0.7%)	Severe cholecystitis	10	Poss. related
	Severe asthma*	56	Not related
	Moderate pyelonephritis*	56	Not related
	Schizophrenia	0	Not related

* Same subject.

Total Safety Population

Dosing Interruptions Due to AEs

Study Agent (Subjects, %)	Event*	Investigator Attribution
Placebo (1/105, 1.0%)	Moderate skin infection	Not related
Raxibacumab (4/406, 1.0%)	Mild urticaria	Related
	Mild urticaria	Related
	Mild clonus	Related
	Moderate dyspnea	Not related

* None of these events were SAEs.

Primary Safety Population

Adverse Events

	Placebo (n=80) %	Raxibacumab 40 mg/kg (n=326) %
AE	47.5	49.7
Severe AE	2.5	1.8
Serious AE	1.3	0.6
Death	1.3	0

Primary Safety Population

Common Adverse Events (≥ 5 subjects)

	Placebo (n=80) %	Raxibacumab (n=326) %
Headache	10.0	9.5
Upper respiratory infection	5.0	4.9
Nausea	3.8	2.5
Pain in extremity	1.3	2.1
Pruritus	0	2.1
Diarrhea	2.5	1.8
Rash	1.3	1.8
Abdominal pain	2.5	1.5
Sinusitis	1.3	1.5
Joint sprain	0	1.5
Somnolence	0	1.5
Cough	3.8	1.5

Total Safety Population

Rash

	Placebo		Raxibacumab	
	n/N	%	n/N	%
Without diphenhydramine prophylaxis				
PAM-NH01	0/25	0	0/80	0
C1064	–	–	6/25	24.0
With diphenhydramine prophylaxis				
C1064*	–	–	2/63	3.2
C1069	–	–	0/20	0
C1063	2/80	2.5	6/240	2.5

* Protocol was amended during trial to initiate prophylaxis.

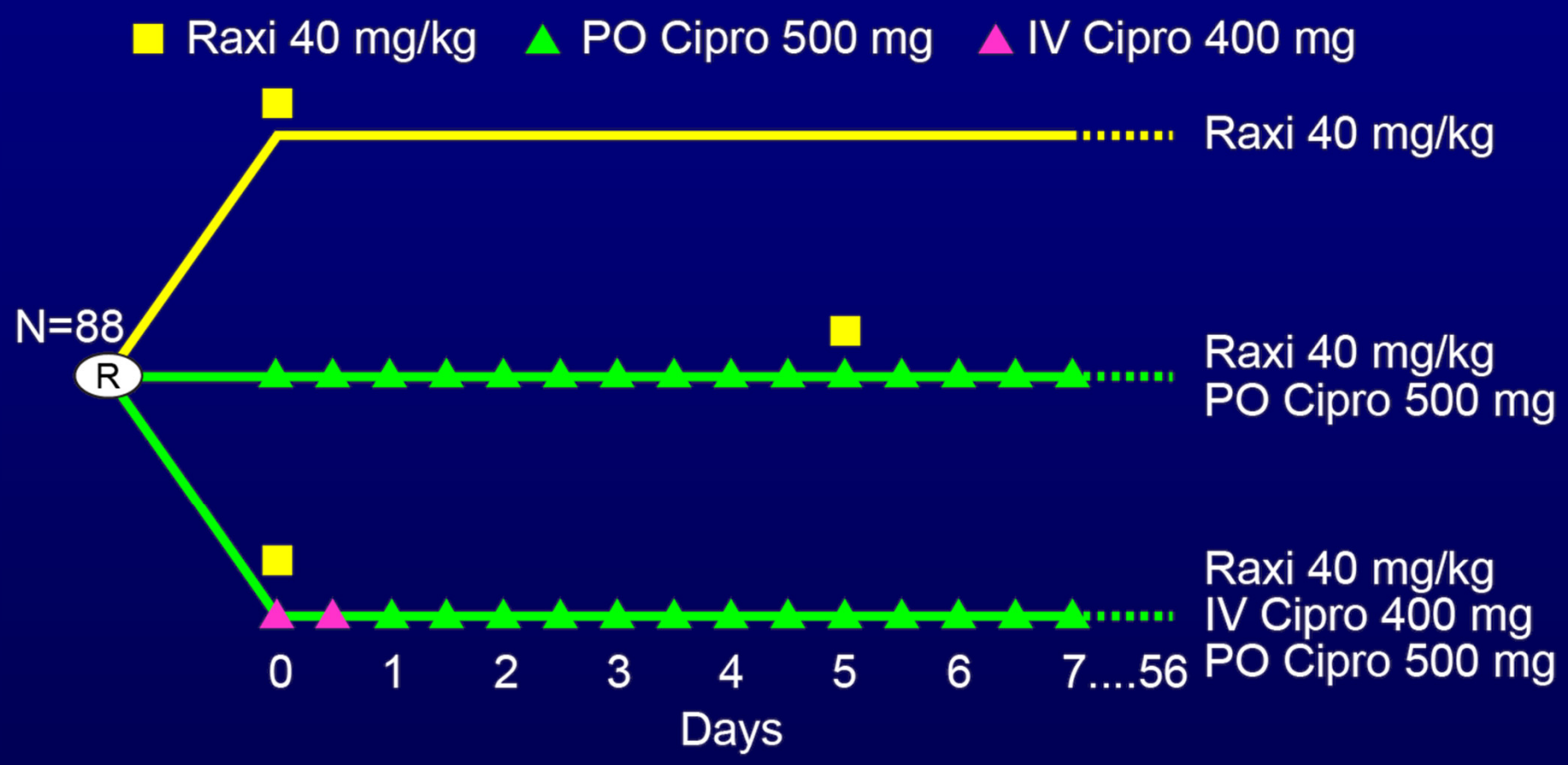
Primary Safety Population

Immunogenicity

- No raxibacumab immunogenicity observed
  - Single dose (n=310)
  - Repeat dose
    - After 14 days (n=23)
    - After 4 months (n=20)
  - Measured by a sensitive assay (LOD 100 ng/mL)

Raxibacumab/Ciprofloxacin Safety Study C1064

Raxibacumab/Cipro Combination Study



CS-098

Raxibacumab/Ciprofloxacin Safety Study C1064

Adverse Events: Combination Study

	Raxibacumab (n=28) %	Raxibacumab + PO Cipro (n=32*) %	Raxibacumab + IV/PO Cipro (n=28) %
AE	67.9	56.3	53.6
Severe AE	0	6.3	3.6
Serious AE	0	3.1	0

* 2 subjects withdrew voluntarily prior to receiving raxibacumab.

Raxibacumab Safety Profile

- Safety profile similar to placebo
  - Low incidence of mild to moderate rashes managed/prevented by oral diphenhydramine
  - No hypersensitivity/anaphylactoid reactions
- No safety signal or patterns of AEs emerged with repeat dosing
- No immunogenicity with single or repeat dosing
- No safety signal or patterns of AEs emerged following co-administration with fluoroquinolone

Benefit/Risk

Dan Hanfling, MD
Special Advisor for Emergency Preparedness and Response
Inova Health System

Clinical Professor of Emergency Medicine
George Washington University

Raxibacumab as Medical Countermeasure

- Immediate protection against anthrax toxin
- Potential to diminish healthcare system impact
- Directly addresses pathogenesis
- Single dose durably inhibits anthrax toxin
- Allows natural immunity to develop

Proposed Indication and Use

- Raxibacumab is indicated for the treatment of patients with inhalational anthrax due to *B. anthracis.*
- Recommendations for use
  - Initiate treatment when a diagnosis of inhalational anthrax is suspected or confirmed
  - Use in combination with antibiotics that cross the blood-brain barrier
  - Premedicate with diphenhydramine

Practicing Physician Perspective

- Potent anthrax antitoxin
- Demonstrated survival benefit
- Safe and well tolerated
  - Alone and in combination with antibiotics
- Favorable benefit/risk profile

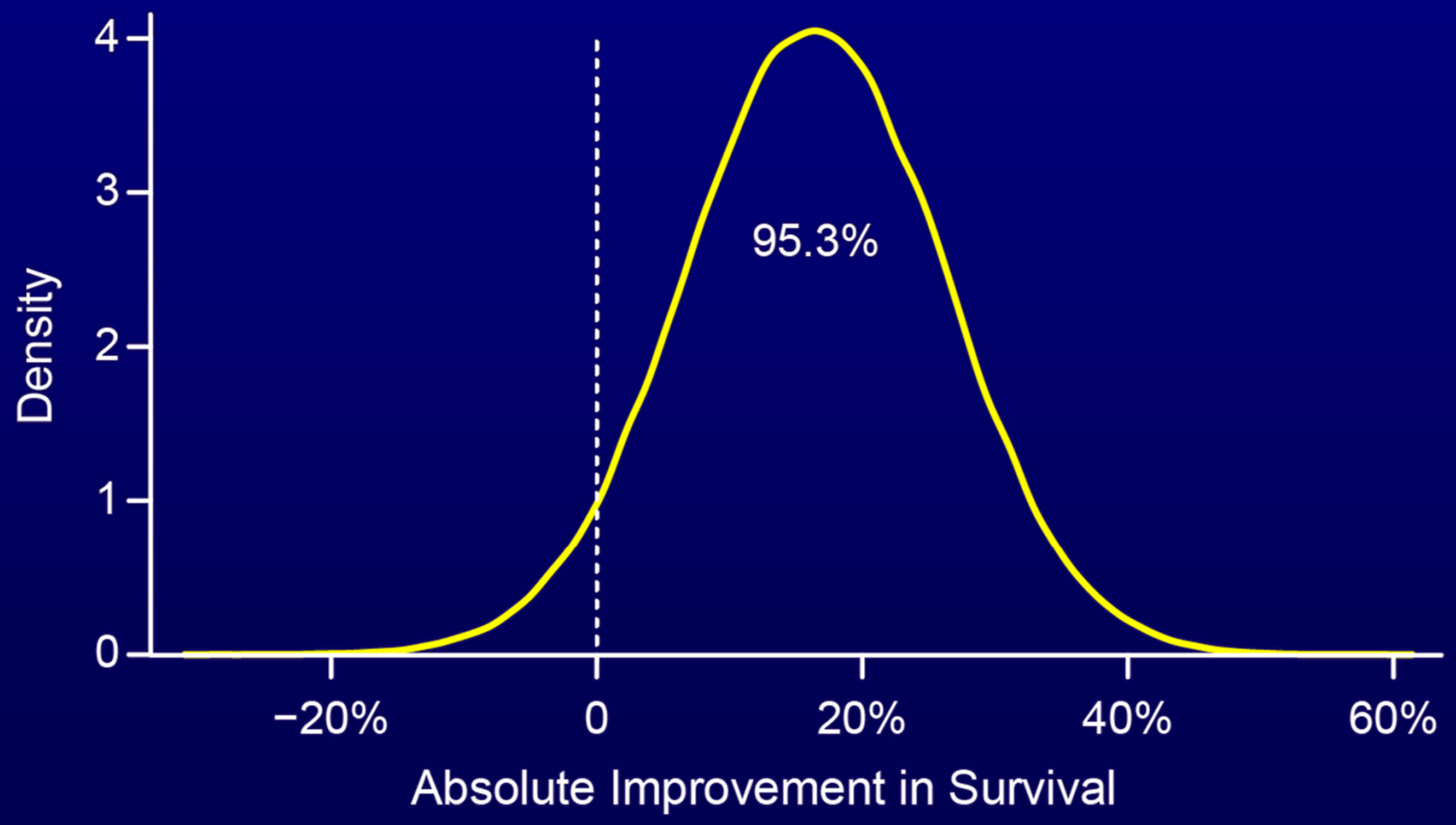
Available to Answer Questions

- HGS
  - Erik Pulkstenis, PhD — Statistician
- University of North Carolina
  - Gary Koch, PhD — Statistician
- Battelle Biomedical Research Center
  - Gabriel Meister, PhD — Study Director
  - Daniel Sanford, PhD — Study Director
  - Daphne Vasconcelos, DVM — Pathologist

Backup Slides

Added Benefit Efficacy Study

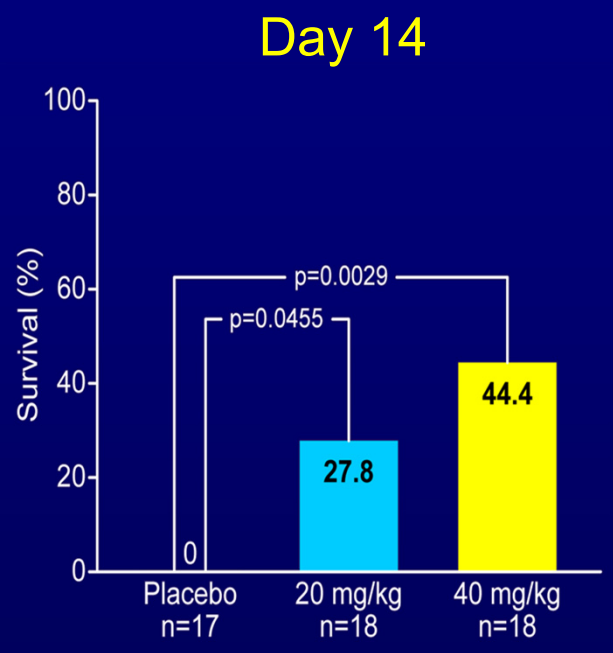
Probability Distribution of Treatment Effect



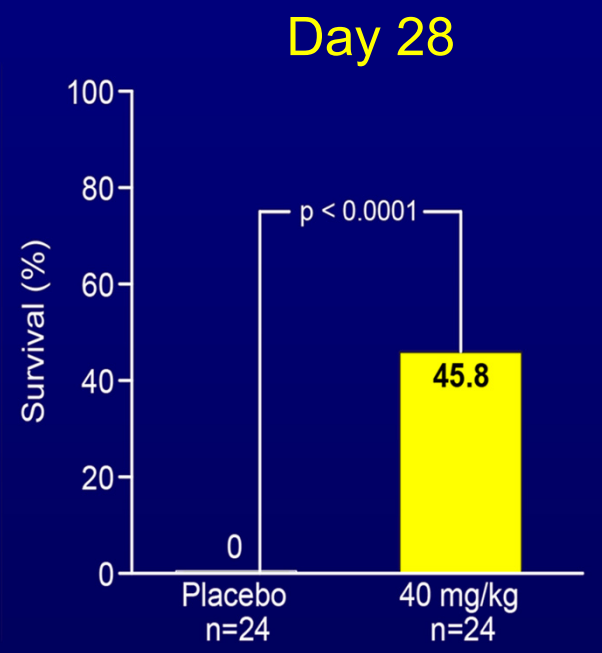
ST-045

Raxibacumab Monotherapy Studies

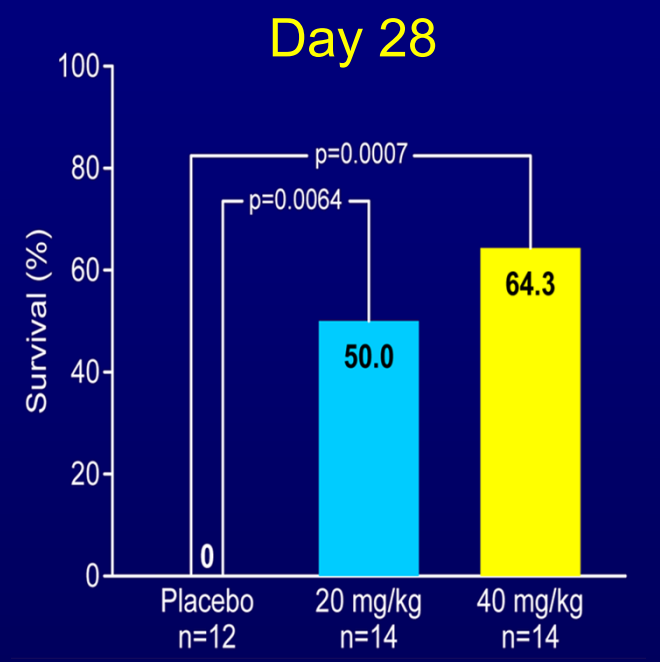
Survival at Primary End Points



Rabbit Pivotal Efficacy Study



Survivor Histopathology Study



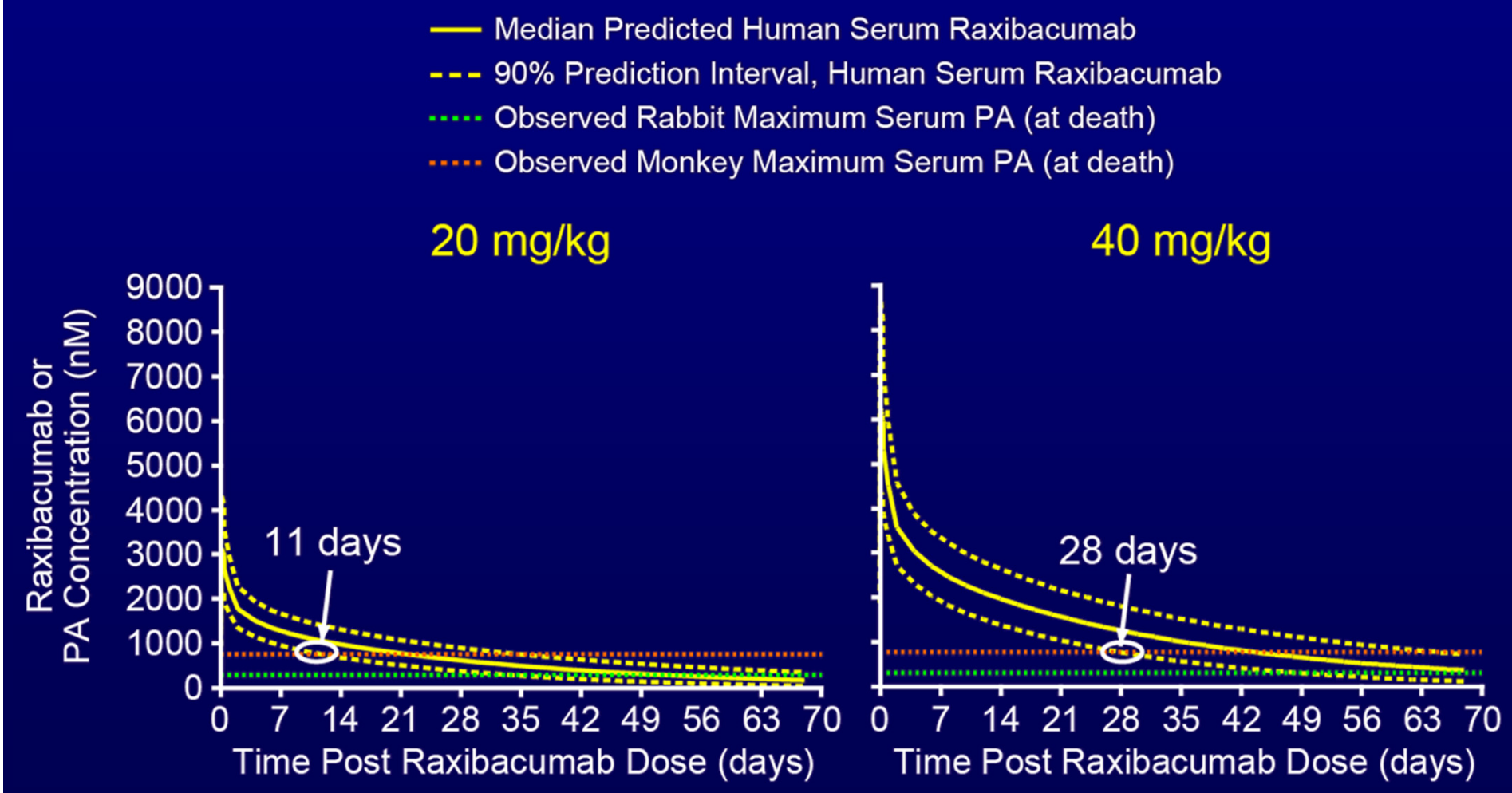
Monkey Pivotal Efficacy Study

ME-092

Statistical Significance Achievable with 80% Power by Study Design

Absolute Improvement in Survival	Number of Animals Treated / Spore Challenged	Two-Sided Statistical Significance Level
10%	76 / 180	0.71
15%	76 / 180	0.57
20%	76 / 180	0.35
25%	76 / 180	0.16

Human Exposure for Efficacy



PK-066

Raxibacumab Protects Against Lethal Toxin (PA + LF) in Rats

Treatment (Excess to PA)	Deaths	Time To Mortality (Minutes)
IgG control (10)	5/5	63
Raxibacumab (0.25)	5/5	77
Raxibacumab (0.5)	5/5	223
Raxibacumab (1)	0/5	>1440
Raxibacumab (10)	0/5	>1440

PK-044

Added Benefit Efficacy Study

PA and Raxibacumab Levels at Time of Death

Rabbit No.	Time of Death† (h)	PA (nM)	Raxibacumab (nM)
L29367	9.7	3	6992
L33730	19.3	138	5265
L33735	96.6	2	1210
L33747	9.6	7	6386
L34809	58.7	2	2353
L34818	3.4	38	10325
L34829	12.4	83	5405

†Post treatment.

Characterization Studies
Median Time to Event

Time (hours)	Rabbits	Monkeys
PA detected	24.0	36.0
Bacteremia (culture)	24.0	36.0
Temperature increase	26.7	47.5
First positive CRP	34.0	42.0
Death	70.5	96.3

Vial Contents

- 50 mg/mL raxibacumab

- 0.13 mg/mL citric acid
- 2.8 mg/mL sodium citrate
- 10 mg/mL sucrose
- 18 mg/mL glycine
- 0.2 mg/mL polysorbate 80, pH 6.5

- Each vial contains 34 mL

Diagnostic Criteria for Inhalation Anthrax: Clinical Factors

Clinical Presentation Consistent with Inhalation Anthrax:

- ≥5 symptoms
- Fever
- Tachycardia

- Signs
  - Fever (low grade: mean T, 38° C)
  - Tachycardia

- Symptoms
  - Fever
  - Sweats (often drenching)
  - Fatigue
  - Cough
  - Chest discomfort, pleuritic pain
  - Nausea/vomiting
  - Headache
  - Dyspnea
  - Myalgias
  - Abdominal pain
  - Confusion

Howell JM, Mayer TA, Hanfling D, et al. Screening for inhalational anthrax due to bioterrorism: evaluating proposed screening protocols. *Clin Infect Dis.* 2004 Dec 15;39(12):1842-7.

Looking at the 11 Inhalational Anthrax Cases

- Mean number of symptoms: 7.0 (range 2-10)
  - Survivors: 8.5
  - Non-survivors: 5.5
- Mean days from symptoms to antibiotic Tx: 5.1
  - Survivors: 4.7
  - Non-survivors: 5.8
- 10 had abnormal CXR
  - 4 initially interpreted as normal
- 7 patients had fever (T > 37.8ºC)
  - Mean presenting temperature: 38 ºC
- 10 presented with tachycardia (HR >100 bpm)
  - Mean: 116 (range 79-152 bpm)
- 8/8 were culture positive prior to antibiotics
  - Median time to positive culture: 18 hours

Primary Safety Population

Hematology

	Placebo (n=80) %	Raxibacumab (n=326) %
Leukocytosis		
≥2 Grade Shift	1.3	0.6
Grade 3-4	1.3	0.3
Leukopenia		
≥2 Grade Shift	0	0.3
Grade 3-4	0	0
Lymphopenia		
≥2 Grade Shift	0	0.3
Grade 3-4	0	0
Neutropenia		
≥2 Grade Shift	1.3	0.6
Grade 3-4	0	0.3
Prothrombin time		
≥2 Grade Shift	0	0.9
Grade 3-4	0	0.9

Primary Safety Population

Serum Electrolytes

	Placebo (n=80) %	Raxibacumab (n=326) %
Hyperkalemia		
≥2 Grade Shift	0	0.6
Grade 3-4	0	0.3
Hypercalcemia		
≥2 Grade Shift	0	0.3
Grade 3-4	0	0
Hypophosphatemia		
≥2 Grade Shift	1.3	1.5
Grade 3-4	0	0

Primary Safety Population

Other Serum Chemistries

	Placebo (n=80) %	Raxibacumab (n=326) %
Amylase		
≥2 Grade Shift	3.8	1.5
Grade 3-4	0	0.3
ALT		
≥2 Grade Shift	0	0.6
Grade 3-4	0	0.3
Hyperglycemia		
≥2 Grade Shift	0	0.9
Grade 3-4	0	0
Hypoglycemia		
≥2 Grade Shift	2.5	1.8
Grade 3-4	0	0

Primary Safety Population

Urinalysis

	Placebo (n=80) %	Raxibacumab (n=326) %
Proteinuria		
≥2 Grade Shift	3.8	3.3
Grade 3-4	0	0
Hematuria		
≥2 Grade Shift	5.0	5.9
Grade 3-4	0	0