

DuraSeal Spine Sealant System (P080013) Adjunct to Sutured Dural Repair to Obtain Watertight Closure During Spine Surgery

Neurological Device Panel of the
Food and Drug Administration
May 14, 2009

Introduction and Product Overview

Theresa McGovern, MS, RAC
Senior Director, Regulatory Affairs
Covidien Surgical Devices
(formerly Confluent Surgical)

Proposed Indication for DuraSeal Spine Sealant Pivotal Study

- Adjunct to sutured dural repair to provide watertight closure during spine surgery

Agenda

| | |
|---|---|
| Introduction and Product Overview | Terry McGovern, MS, RAC Senior Director, Regulatory Affairs Covidien Surgical Devices |
| Clinical Study Design | Xavier Lefebvre, PhD Global Vice President, Clinical Affairs Covidien Surgical Devices |
| Clinical Perspective and Effectiveness Results | Kee D. Kim, MD Associate Professor Department of Neurological Surgery University of California Davis School of Medicine |
| Clinical Study Safety Results | Neill M. Wright, MD Associate Professor Neurological and Orthopedic Surgery Washington University School of Medicine |
| Concluding Remarks | Xavier Lefebvre, PhD |

Covidien and External Experts

Art Driscoll

Vice President, Research and Development
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Jennifer Doyle, MS, CCRA

Director, Clinical Affairs
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President and Chief Biostatistician
Biostatistical Consulting

Brent A. Blumenstein, PhD

Statistical Consultant

Craig van Horne, MD, PhD

Chief, Division of Neurosurgery
Saint Elizabeth's Medical Center

No FDA Approved Treatments Off-Label Treatments Have Shortcomings

- No approved devices for spinal dural sealing
- Off-label therapies
 - Hemostatic agents - to stop bleeding
 - Dural substitutes - to augment dura
 - Adhesive glues - for use as a hemostatic agent
- Off-label therapies have shortcomings
 - Animal or human origins
 - Restrictive storage conditions

Widely Used in Cranial Procedures

- FDA approved in 2005 for cranial procedures
 - Cranial pivotal study (n=111)
 - Cranial post approval study (n=237)
- Indicated for an adjunct to sutured dural repair during cranial surgery
- Identical formulation as Spine Sealant

Significant Real World Use of DuraSeal Sealant

- DuraSeal Cranial and Spinal Sealant available in more than 20 countries
- 177,000 units sold for cranial indication in the United States
- 43,000 total units sold outside the United States

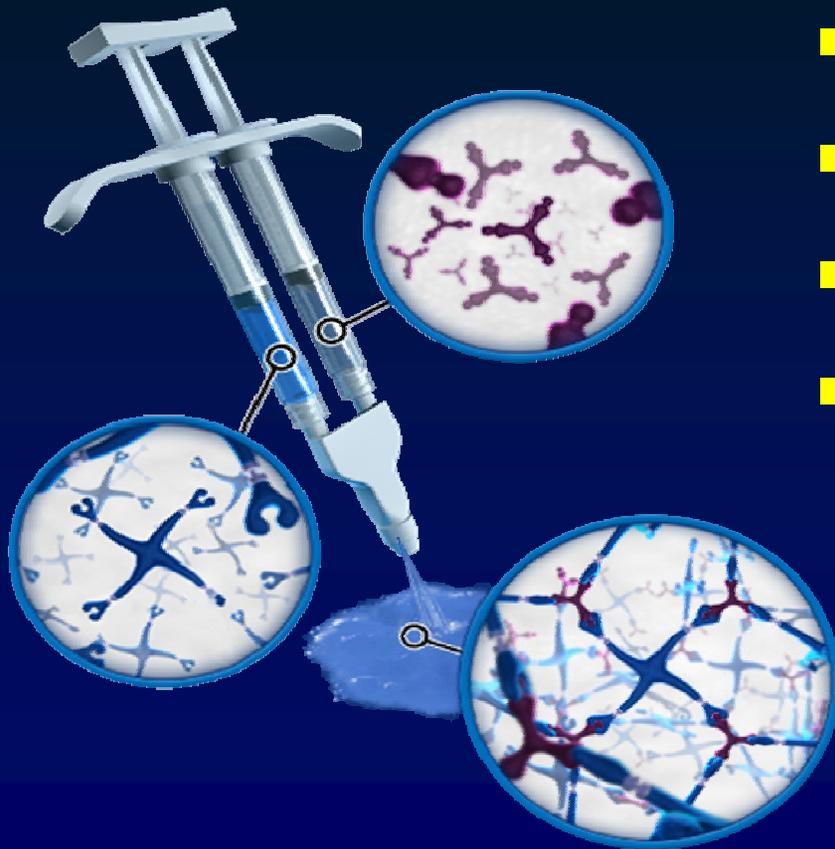
DuraSeal Spine Sealant: Liquids Crosslink to Form an Absorbable Hydrogel in Seconds



DuraSeal Spine Sealant: Liquids Crosslink to Form an Absorbable Hydrogel in Seconds



DuraSeal Spine Sealant: Liquids Crosslink to Form an Absorbable Hydrogel in Seconds



- Easy to apply
- Highly visible
- Seals in seconds
- Bio-absorbs in 4-8 weeks

Preclinical Evaluations: Toxicology/Biocompatibility

- Cytotoxicity
- Sensitization
- Intracutaneous reactivity
- Subchronic toxicity
- Implantation (2 weeks)
- Implantation – subcutaneous (10 days)
- In vitro hemolysis
- Pyrogenicity
- Mutagenicity

Cranial Preclinical Evaluations

- Applicator system testing
- Cranial sealing study
- Cranial parenchymal implant study
- Neurotoxicity study following cranial injection
- Evaluation of DuraSeal persistence following subcutaneous implantation
- Reproductive toxicity/teratology
- Hydrogel appearance under MR and CT imaging

Spine Preclinical Evaluations

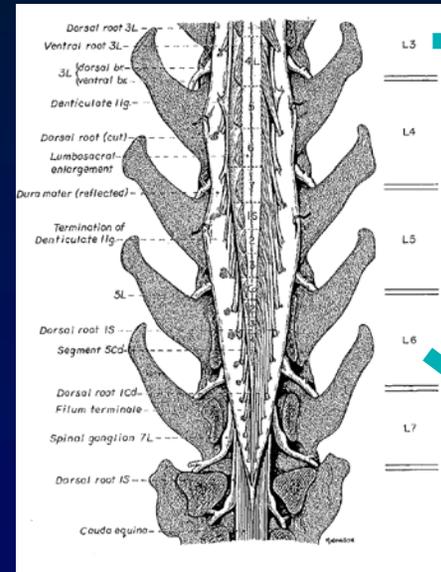
- Canine Lumbar Laminectomy Study
- Canine Cauda Equina Study

Lumbar Laminectomy Study Design

- Two level laminectomy (L3 and L5)
- Dural exposure and treatment (n=12)
 - n=6 control treatment sites (no treatment)
 - n=6 test treatment sites (Duraseal)
- 12 – 14 weeks after treatment
 - n=6 histological evaluation
 - n=6 gross pathological evaluation of scar and adhesion formation

Preclinical Study Included Spinal Cord Application – Well-tolerated in the Spine

- No evidence of neurological lesions
- All sites exhibited similar bone regrowth
- Confirmation of absorption at 12 weeks



Anatomy of the Dog, Evans, 1993



Mid L3 – DuraSeal treated



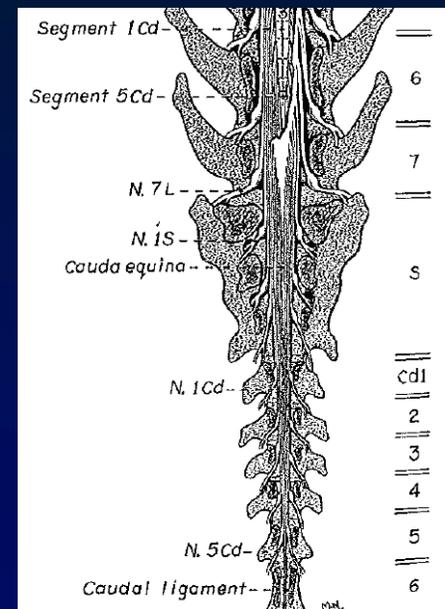
Mid L5 – DuraSeal treated

Cauda Equina Study Design

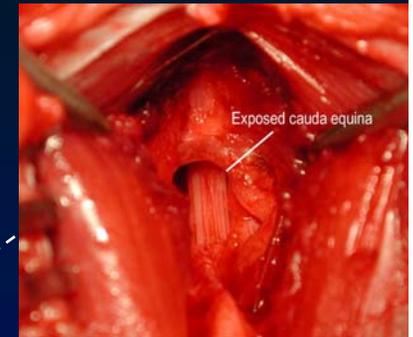
- Partial discectomy through L7 – S1 intervertebral space
- Abrasion of nerve root and cauda equina (n=18)
 - 9 control treatment sites (no treatment)
 - 9 test treatment sites (Duraseal)
- 8 weeks after treatment
 - n=2 (1 test, 1 control) histological evaluation
 - n=16 (8 test, 8 control) gross pathological evaluation of adhesion formation, local tissue response

Cauda Equina Study

- No difference in neurologic findings between DuraSeal and control
- Peridural scar formation was minimal
- DuraSeal sites had better nerve root mobility than control sites
- Results indicated less impingement of spinal canal for DuraSeal



Anatomy of the Dog, Evans, 1993



Treated with DuraSeal

Pre-clinical Studies Provide Objective Evidence that DuraSeal was Safe and Effective for Human Spinal Clinical Studies

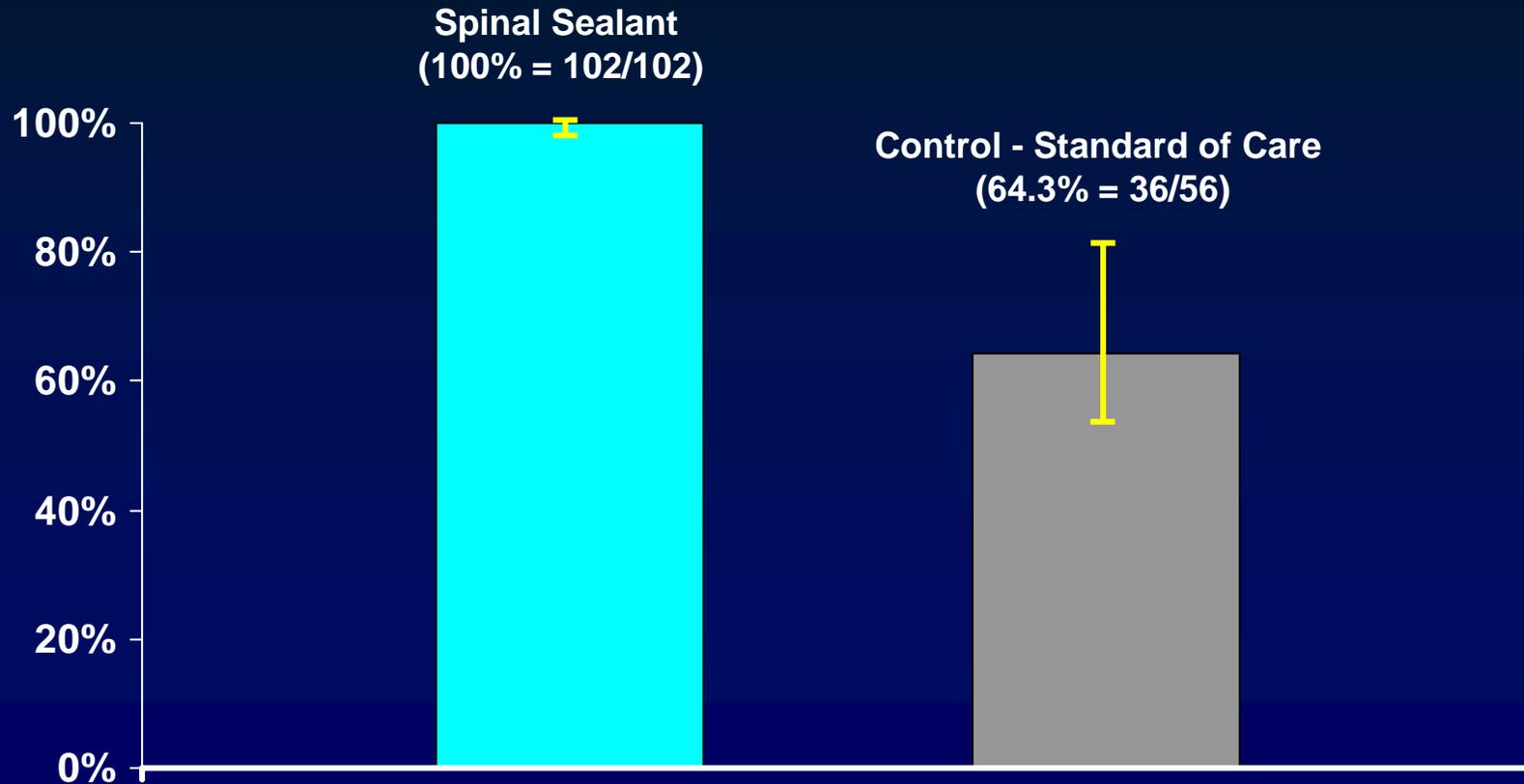
- 7 pre-clinical cranial studies
- 2 pre-clinical spine studies
 - Investigated neural compression
 - No adverse neurological responses
 - No evidence of neurological behavioral problems
 - No evidence of neurological lesions

Study Designed to Test Intra-operative Dural Sealing

- Prospective, multi-center, randomized
 - 2-to-1 randomization
- Primary endpoint – intra-operative sealing
- Comprehensive post-operative safety evaluations
- Consistent with previous studies on devices intended to seal

Primary Effectiveness Endpoint Intra-operative Dural Sealing

$p < 0.001$



p-value based on two-sided Fisher's Exact test testing for a difference between treatments.

Safety of the Spinal Sealant when Applied as an Adjunct to Sutures has been Established

- Adverse events are consistent with a patient population undergoing neurosurgery
- Overall adverse event profile is similar between DuraSeal Spinal Sealant and Control groups
- No statistical difference in serious adverse event rate

Clinical Study Design

Xavier Lefebvre, PhD

Global Vice President, Clinical Affairs

Covidien Surgical Devices

Evaluate Safety and Efficacy of Spine Sealant as Adjunct to Sutured Dural Repair

- Evaluate safety vs control over 90 days
- Evaluate efficacy as measured by an intra-operative watertight seal
- Adjunct to sutured dural repair
- Multi-center, randomization (2-to-1)

Surgical Intra-operative Watertight Endpoint is an Appropriate Endpoint

- Consistent with previous studies on devices intended to seal
 - DuraSeal Cranial Sealant – pivotal study
 - CoSeal Surgical Sealant

Surgical Intra-operative Watertight Endpoint is an Appropriate Endpoint

- Postoperative steroid use
- NSAIDs
- Smoking
- Duration of bed rest
- Degree of physical exertion
- Variation of standard of care between sites
- Patient compliance

Primary Effectiveness Endpoint

- Demonstrate superiority of DuraSeal when compared to standard-of-care in spinal procedures
- Achieve intra-operative watertight dural closure in patients with leakage after primary closure

Details of Control Group

- Real-world practice is to use any and all techniques to ensure a watertight dural closure prior to leaving OR
- Control group treatments permitted
 - Additional sutures
 - Adhesive glue (off-label)
 - Soft tissue patch / graft
- Rescue intervention
 - Adhesive glue (off-label)
 - Absorbable gelatin sponge (off-label)
 - Dural substitute (off-label)
 - Hemostatic agent (off-label)

Key Preoperative Inclusion / Exclusion Criteria

■ Inclusion

- Age 18 to 75 years
- Procedure requires a dural incision
- Class I clean procedure

■ Exclusion

- Active spinal or systemic infection
- Chronic steroid therapy
- Prior surgery in same area
- Prior or planned chemotherapy or radiation

Key Intra-operative Randomization Criteria

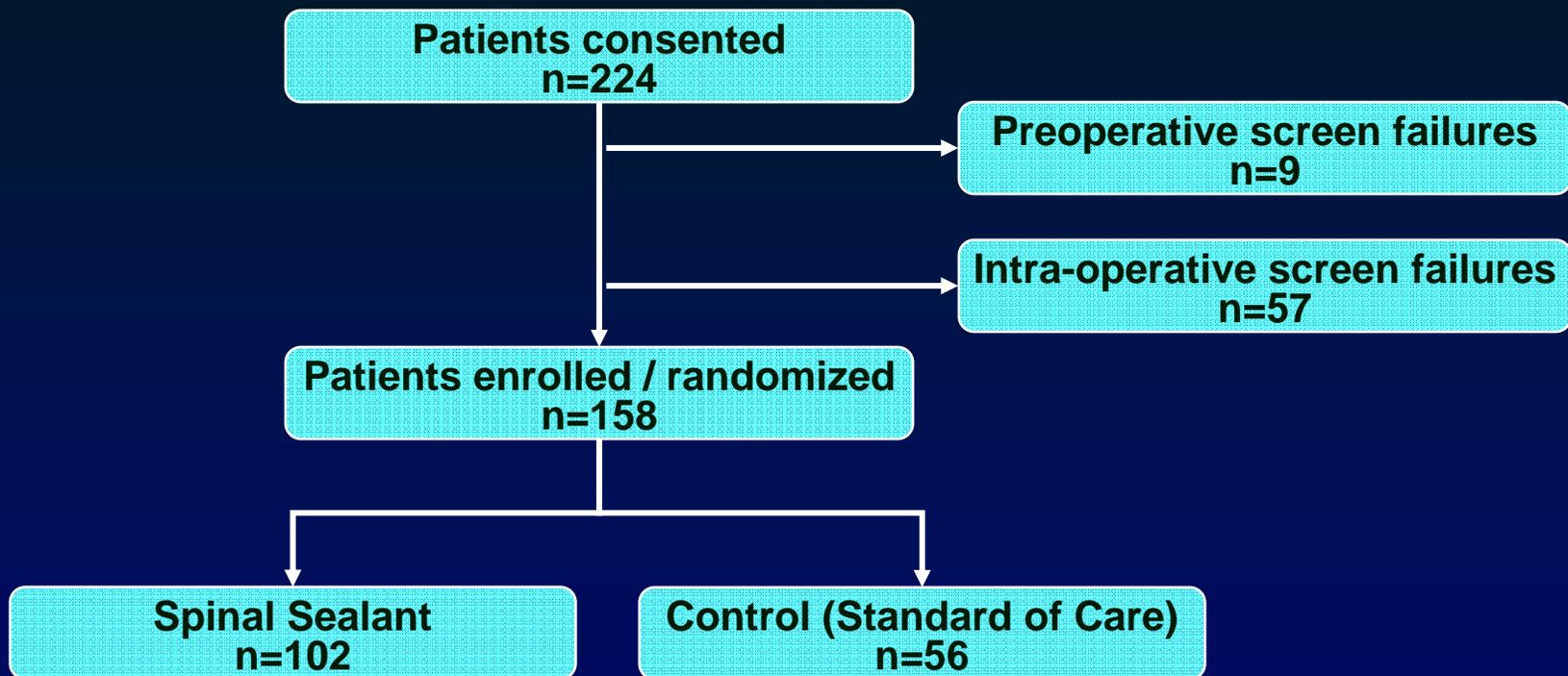
■ Inclusion

- Presence of non-watertight closure
 - Spontaneously
 - Valsalva maneuver at 20-25 cm H₂O

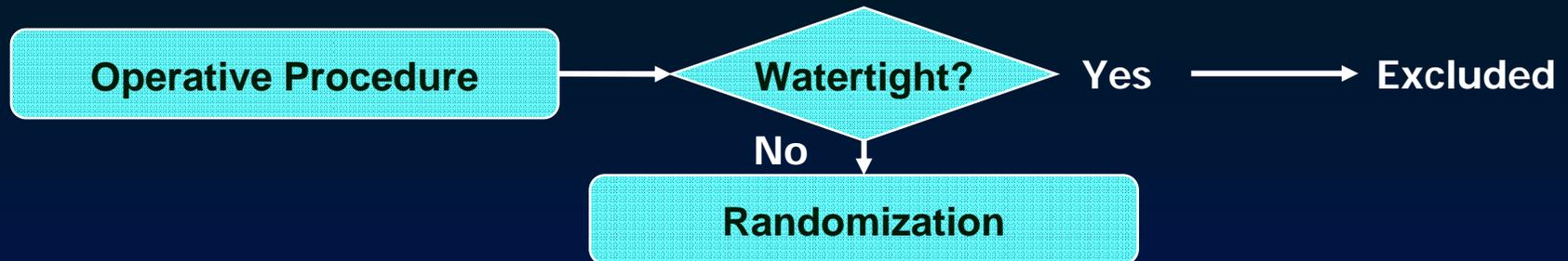
■ Exclusion

- Patients who require use of non-autologous duraplasty material
- Dural gap of greater than 2mm after closure

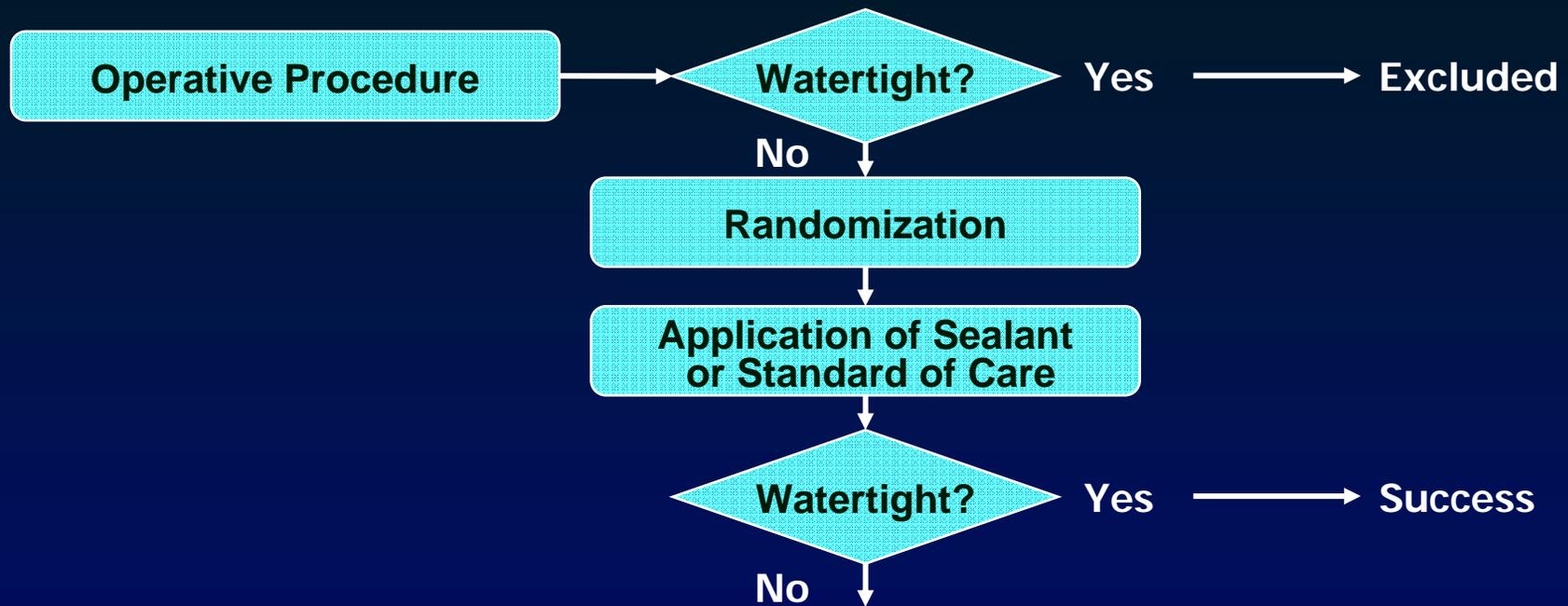
Patient Disposition – Screen Failures vs. Enrolled Patients



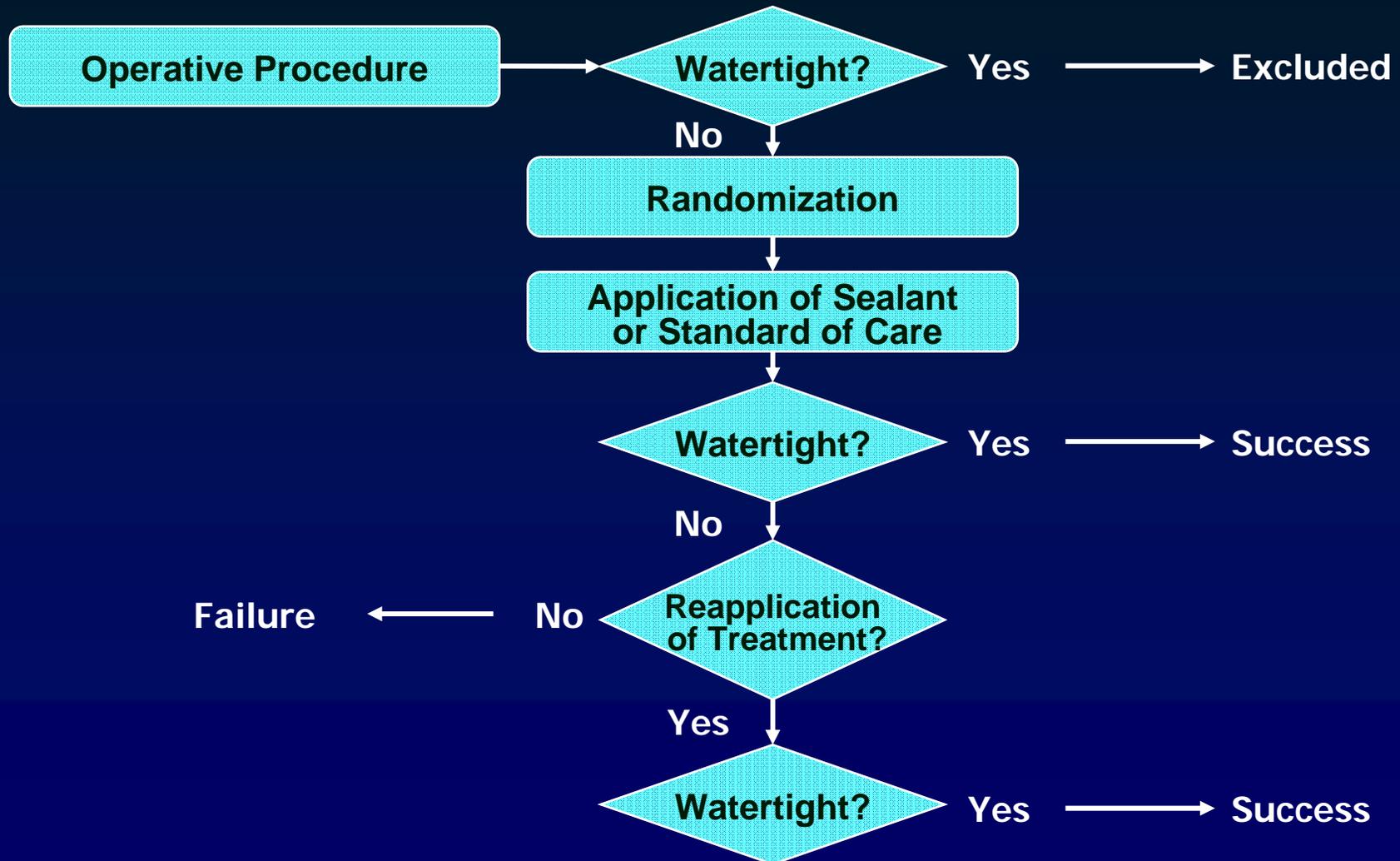
Pivotal Trial Design



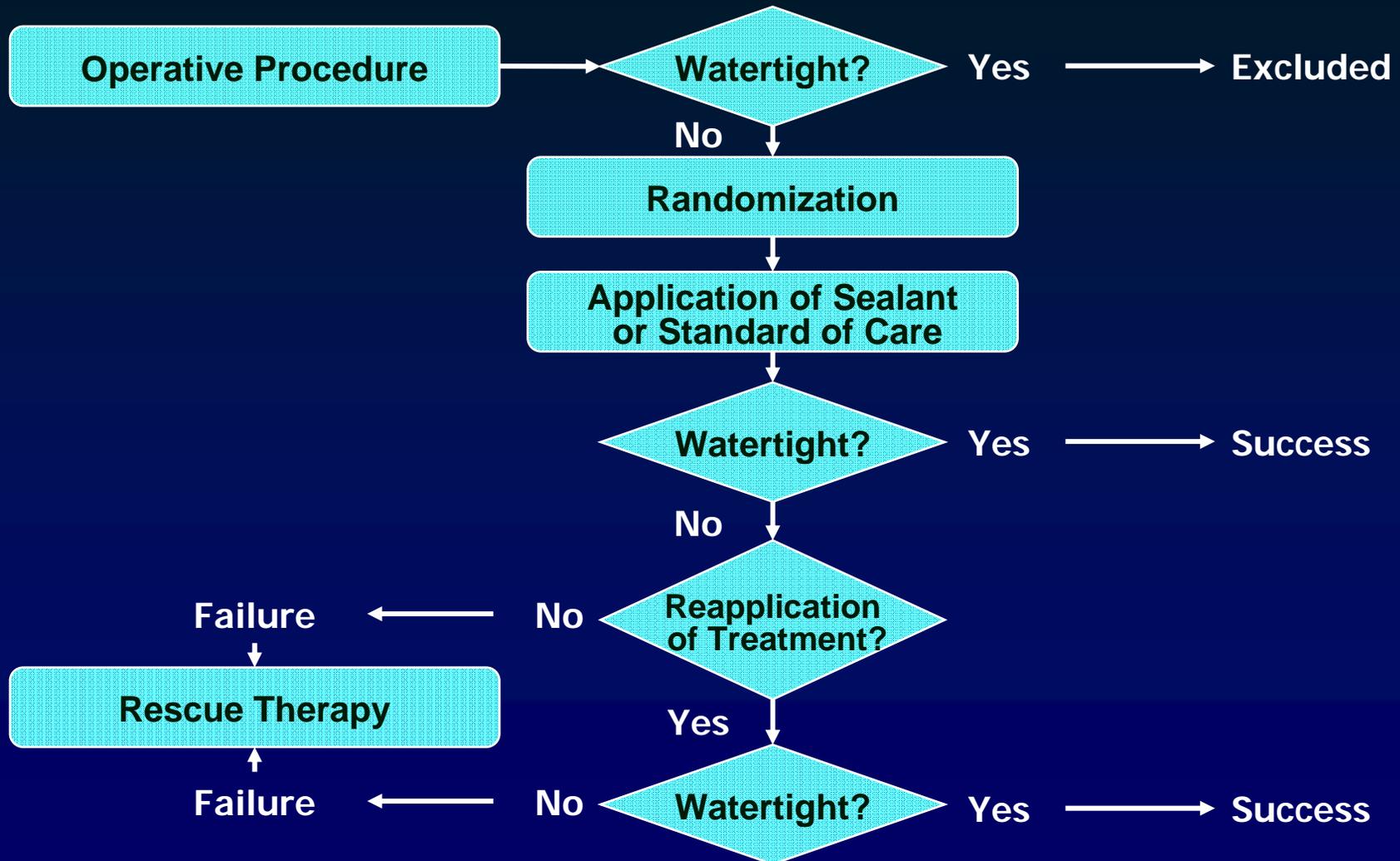
Pivotal Trial Design



Pivotal Trial Design



Pivotal Trial Design



Protocol Required Assessments

| | Baseline Visit | Procedure | Discharge or within 7 Days Postop | One Month Postop | Three Month Postop |
|------------------------------------|----------------|-----------|-----------------------------------|------------------|--------------------|
| Physical exam / history | √ | | √ | √ | √ |
| Neurological exam | √ | | √ | √ | √ |
| Laboratory tests | √ | | √ | √ | √ |
| CSF leak evaluation | | √ | √ | √ | √ |
| Surgical site infection evaluation | | | √ | √ | √ |
| Wound healing assessment | | | √ | √ | √ |
| Adverse events | | √ | √ | √ | √ |

Clinical Perspective and Study Demographics and Effectiveness Results

Kee D. Kim, MD

Associate Professor

Department of Neurological Surgery

University of California Davis School of Medicine

“Watertight” Dural Closure Has Been Elusive

- Watertight dural closure is a basic objective of neurosurgical practice
- Controlling intra-operative leakage is important to prevent subsequent CSF leakage
- CSF leakage can lead to complications

Case Study – Woman in her 30s, Tethered Spinal Cord

- Uneventful surgery, sutured closure and fibrin glue
- Presented 10 days postop, headache, unremarkable surgical wound
- Presented 1 month later, fluctuant mass, pseudomeningocele requiring another surgery



Case Study – 22 year old Woman with Cerebral Palsy and Baclofen Pump for Spasticity

- **October 8th**
 - Pump removed due to pump nonfunctional and spasticity well-controlled with po meds
 - Visible leak sutured after catheter removed
 - CSF fistula
- **October 9th**
 - Re-sutured and placed dural graft matrix
- **October 19th**
 - Readmitted for recurrent CSF leak with meningitis
 - Fascia leak closed
- **October 22nd**
 - Returned to OR for persistent leak
 - Area of leak re-sutured and lumbar drain placed
 - Discharged 10/28/04 with IV antibiotics

FDA Unapproved Biologic Treatments are Currently Being Used to Obtain Watertight Closure

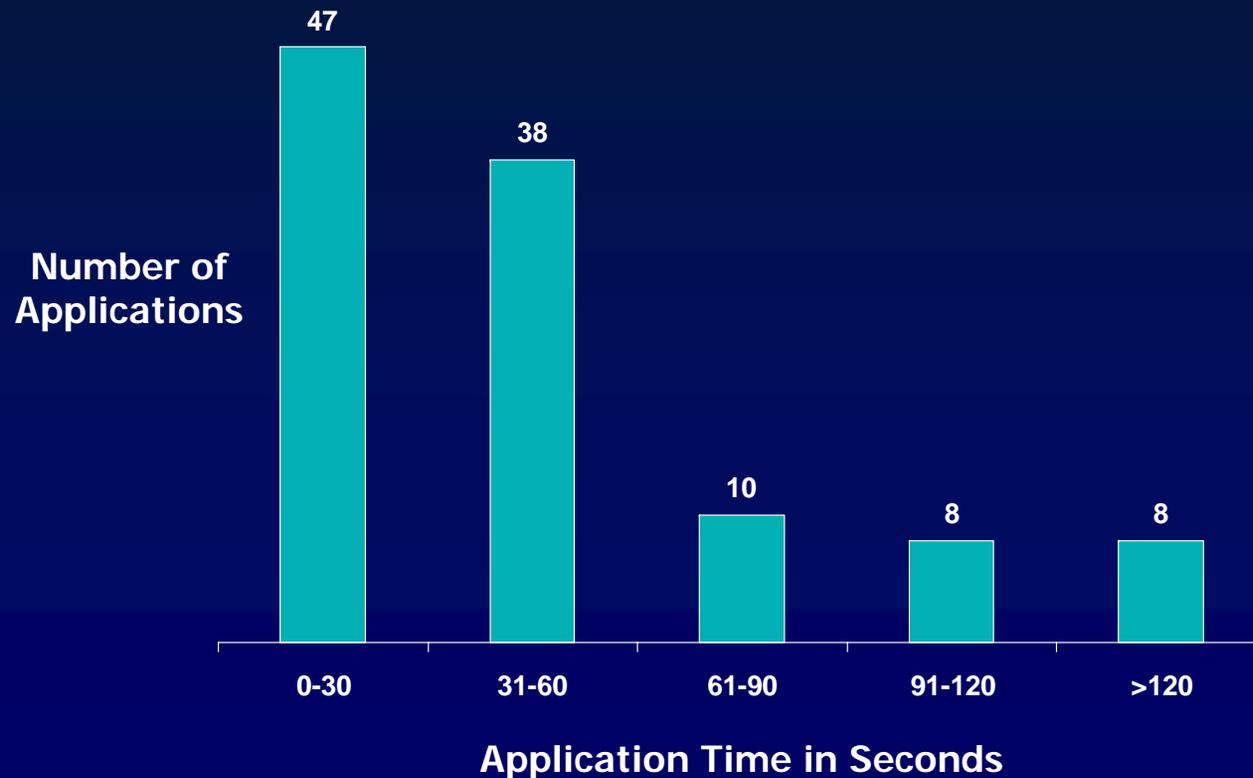
- Unapproved
- Wide variety of treatments
- Animal-derived or Human-derived Products
 - Risk of disease transmission
 - Screening for pathogens is limited

CDC Statement on Safety of Blood-derived Products

“Since blood is a biologic product, it is unlikely that the risk for transfusion-transmitted infection will ever be reduced to zero. The approach to emerging infections associated with transfusion of blood and blood products includes... surveillance for known, as well as emerging and poorly characterized, transfusion-transmitted agents. Vigilance is needed to help ensure proper balance between safety and the availability of blood.”

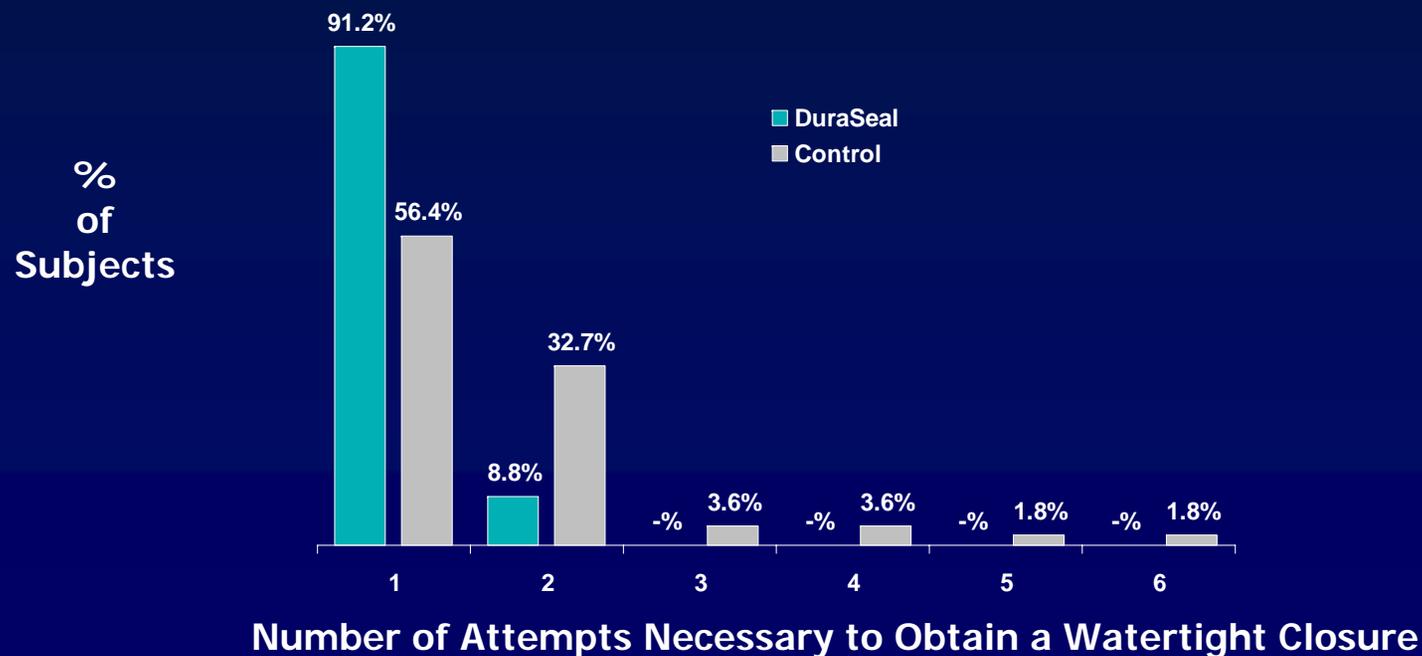
DuraSeal Attributes

- Easy to apply
- Quick to create a watertight seal



DuraSeal Attributes

- Easy to apply
- Quick to create a watertight seal
- Capable of reliably producing a watertight seal



DuraSeal Attributes

- Easy to apply
- Quick to create a watertight seal
- Capable of reliably producing a watertight seal
- Conforms to incision site
- Visual Aid (Blue)
- Quick and simple to prepare
- Easy to store
- No disease transmission

Clinical Study Demographics and Effectiveness Results

Study Population was Representative and Randomization Balanced

| Characteristics | Spinal Sealant (N=102) | Control (N=56) |
|------------------------------------|-----------------------------------|---------------------------|
| Mean age (SD) | 47.7 (13.7) | 42.3 (14.6) |
| Gender, female % | 52.9% | 53.6% |
| Mean height (ft) (SD) | 5.57 (0.4) | 5.57 (0.4) |
| Mean weight (lbs) (SD) | 178 (45) | 185 (54) |
| Mean BMI (Kg/m ²) (SD) | 27.8 (6.1) | 29.0 (7.7) |
| Current smoking status % | 18.6% | 16.1% |
| ASA score, n (%) | | |
| I | 12.7% | 7.1% |
| II | 64.7% | 71.4% |
| III | 22.6% | 21.4% |

Study Population was Representative and Randomization Balanced

| | Spine Sealant (N=102) | Control (N=56) |
|--|----------------------------------|---------------------------|
| Tumor removal | 62.7% | 62.5% |
| Chiari malformations | 21.6% | 32.1% |
| Cyst | 7.8% | 0.0% |
| Syringomyelia | 3.9% | 1.8% |
| Tethered cord | 2.9% | 1.8% |
| Syringomyelia with arachnoid cyst | 1.0% | 0.0% |
| A-V malformation | 0.0% | 1.8% |

Neurological Procedural Characteristics Balanced Between Arms

Spinal Sealant

46%



38%



25%



9%



Control

57%



27%



27%



2%



Primary Effectiveness Endpoint

| | Pre-specified Intent-to-treat | |
|----------------|-------------------------------|-----------|
| | n | Success % |
| Spinal Sealant | 102 / 102 | 100% |
| Control | 36 / 56 | 64% |
| p-value | <0.001 | |

p-values based on two-sided Fisher's Exact test testing for a difference between treatments.

Sensitivity Analysis: Four patients who received rescue therapy with an allowed controlled method, but one different than the initial therapy

| | Pre-specified Intent-to-treat | |
|-----------------------|--------------------------------------|------------------|
| | n | Success % |
| Spinal Sealant | 102 / 102 | 100% |
| Control | 40 / 56 | 71% |
| p-value | <0.001 | |

p-values based on two-sided Fisher's Exact test testing for a difference between treatments.

Statistically Significant Difference in Achieving Watertight Dural Seal at First Attempt

| | Pre-specified Intent-to-treat | |
|----------------|-------------------------------|-----------|
| | n | Success % |
| Spinal Sealant | 93 / 102 | 91% |
| Control | 35 / 56 | 63% |
| p-value | <0.001 | |

p-values based on two-sided Fisher's Exact test testing for a difference between treatments.

Safety Evaluation

Neill M. Wright, MD

Associate Professor

Neurological and Orthopedic Surgery

Washington University School of Medicine

St Louis, Missouri

Inclusive Approach to AE Reporting

- All adverse events captured
 - Healthcare professionals were not blinded to treatment
 - Potential for over-reporting in the DuraSeal group
- Included independent adjudication committee
 - Three independent neurosurgeons
 - Reviewed all adverse events
 - Reports were not blinded

Independent Clinical Events Committee Conclusions

- Events consistent in type and severity considering disease state and procedures
- No events determined to be device-related

One Case Reported by Investigator as Device Related

- Surgery for Chiari Malformation
- Pseudomeningocele 42 days postop
- Return to OR, 1 cm dural rent observed and repaired
- CEC determined event as procedure related
 - incomplete dural closure
 - increased pressure due to constipation

Investigator-reported Adverse Events Overview

| Category | Spine Sealant (N=102) | Control (N=56) | p-value |
|--------------------------------------|------------------------------|-----------------------|----------------|
| Patients with at least one AE | 93.1% | 91.1% | 0.639 |

p-values based on two-sided Fisher's Exact test testing for a difference between treatments.

Investigator-reported Adverse Events Overview

| Category | Spine Sealant (N=102) | Control (N=56) | p-value |
|---------------------------------------|------------------------------|-----------------------|----------------|
| Patients with at least one AE | 93.1% | 91.1% | 0.639 |
| Patients with at least one SAE | 29.4% | 17.9% | 0.110 |

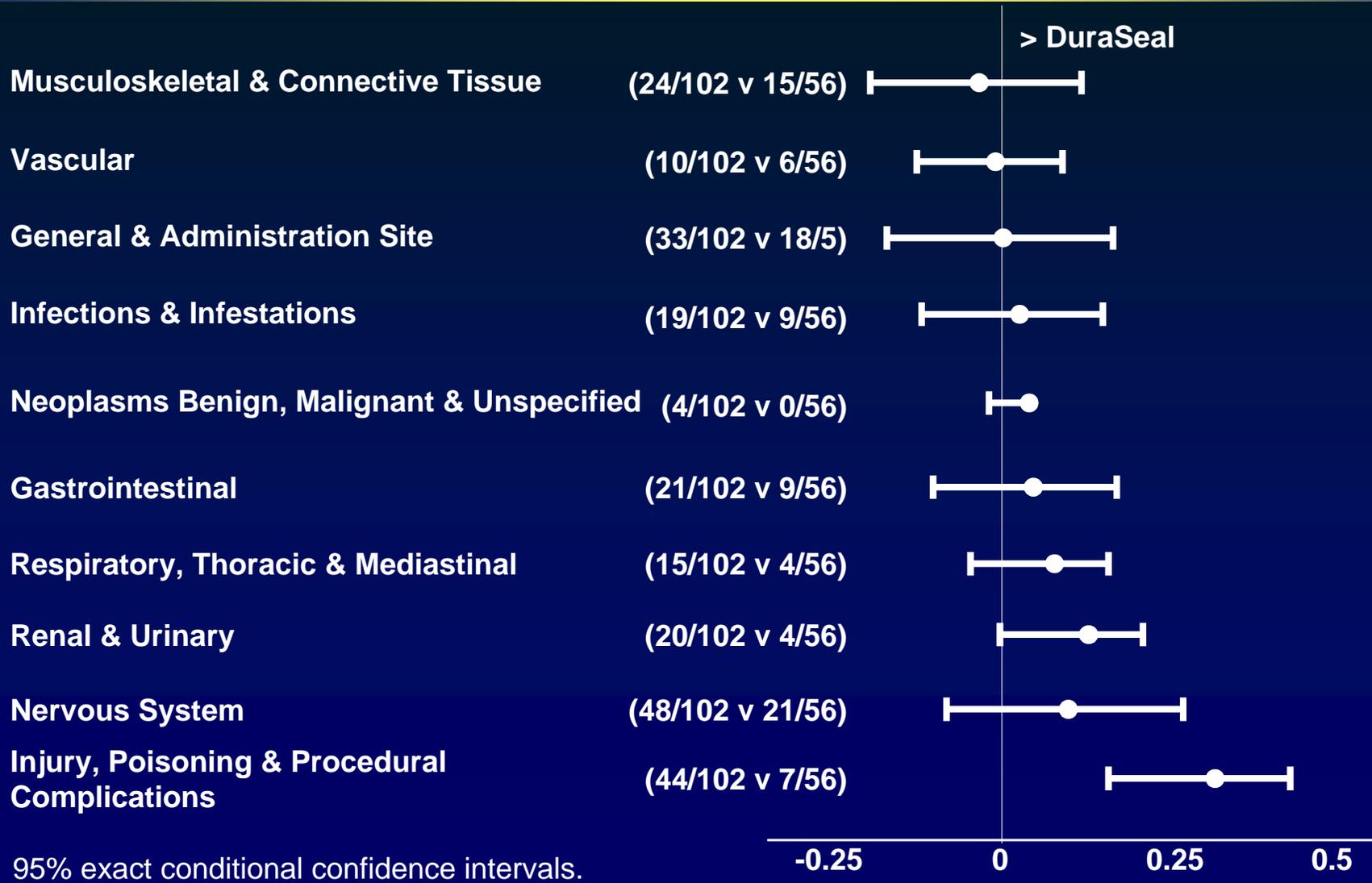
p-values based on two-sided Fisher's Exact test testing for a difference between treatments.

Investigator-reported Adverse Events Overview

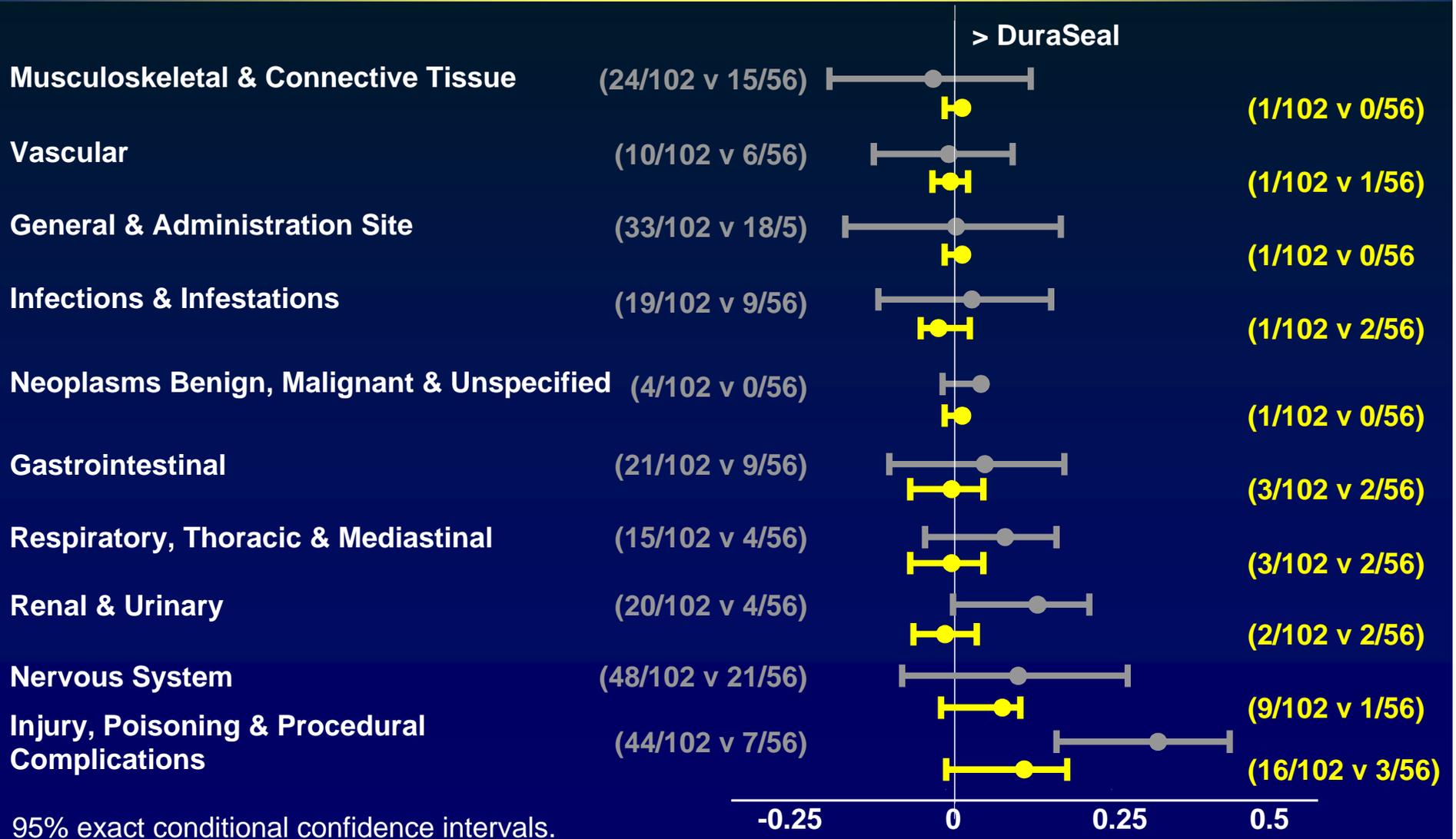
| Category | Spine Sealant (N=102) | Control (N=56) | p-value |
|---|------------------------------|-----------------------|----------------|
| Patients with at least one AE | 93.1% | 91.1% | 0.639 |
| Patients with at least one SAE | 29.4% | 17.9% | 0.110 |
| Unanticipated adverse device effects | 0% | 0% | - |

p-values based on two-sided Fisher's Exact test testing for a difference between treatments.

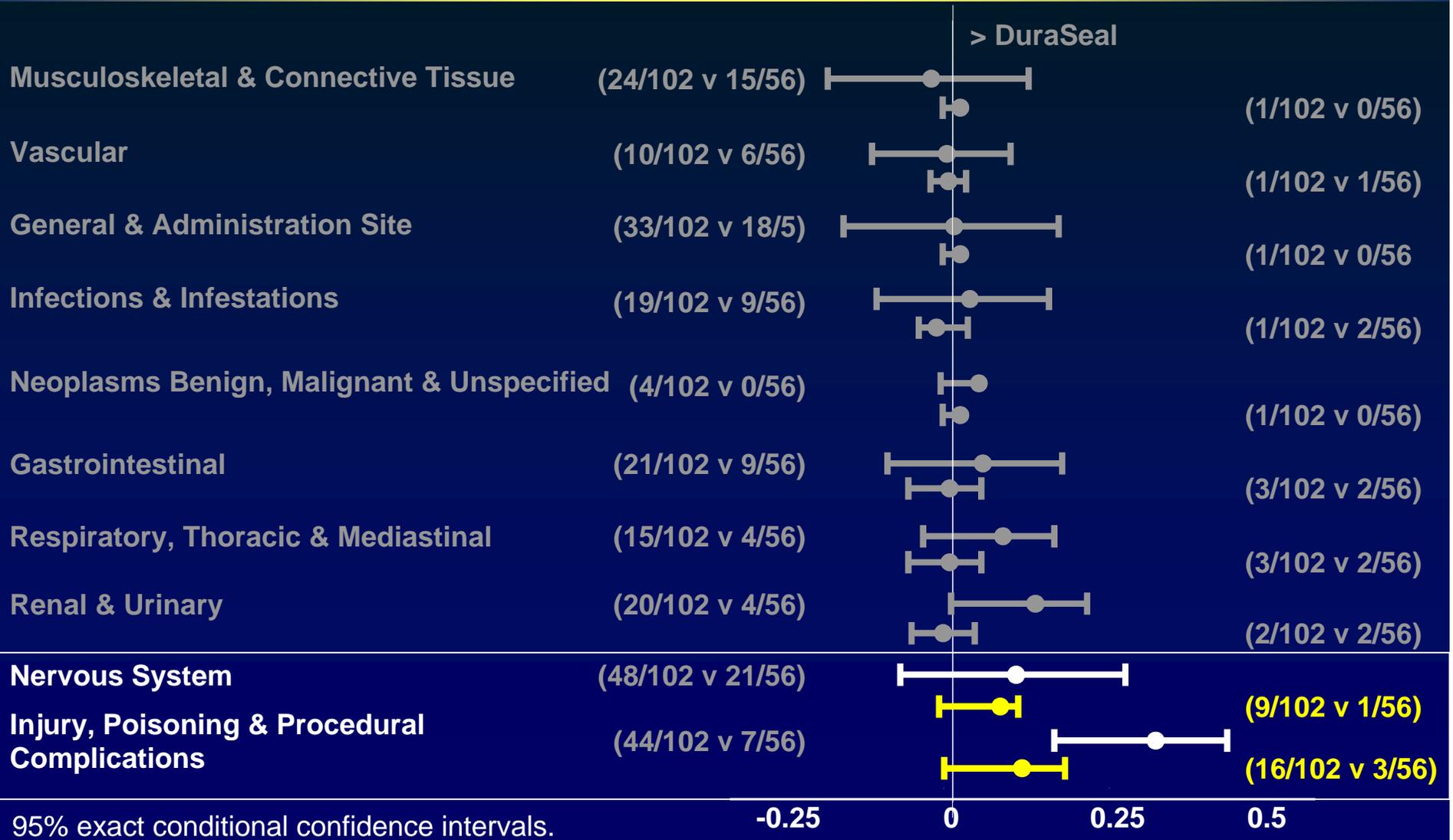
Selected Adverse Events



No Statistically Significant Differences in Serious Adverse Events



No Statistically Significant Differences in Serious Adverse Events



Injury, Poisoning and Procedural Complications

| Sub-category | Spine Sealant (N=102) | | Control (N=56) | |
|----------------------------|--------------------------|------|-------------------|------|
| | n | % | n | % |
| Total | 44 | 43.1 | 7 | 12.5 |
| Incision site complication | 17 | 16.7 | 2 | 3.6 |

Injury, Poisoning and Procedural Complications (continued)

| Sub-category | Spine Sealant (N=102) | | Control (N=56) | |
|----------------------------|--------------------------|------|-------------------|------|
| | n | % | n | % |
| Total | 44 | 43.1 | 7 | 12.5 |
| Incision site complication | 17 | 16.7 | 2 | 3.6 |
| Pseudomeningocele | 8 | 7.8 | 3 | 5.4 |

Injury, Poisoning and Procedural Complications (continued)

| Sub-category | Spine Sealant (N=102) | | Control (N=56) | |
|-----------------------------------|--------------------------|-------------|-------------------|-------------|
| | n | % | n | % |
| Total | 44 | 43.1 | 7 | 12.5 |
| Incision site complication | 17 | 16.7 | 2 | 3.6 |
| Pseudomeningocele | 8 | 7.8 | 3 | 5.4 |
| Procedural pain | 4 | 3.9 | 1 | 1.8 |
| Post lumbar puncture syndrome | 4 | 3.9 | 0 | - |
| Fall | 2 | 2.0 | 0 | - |
| Postoperative ileus | 2 | 2.0 | 0 | - |
| Wound dehiscence | 2 | 2.0 | 0 | - |
| Nerve injury | 2 | 2.0 | 0 | - |
| Graft complication | 1 | 1.0 | 0 | - |
| Airway complication of anesthesia | 1 | 1.0 | 0 | - |
| Subdural hematoma | 1 | 1.0 | 0 | - |

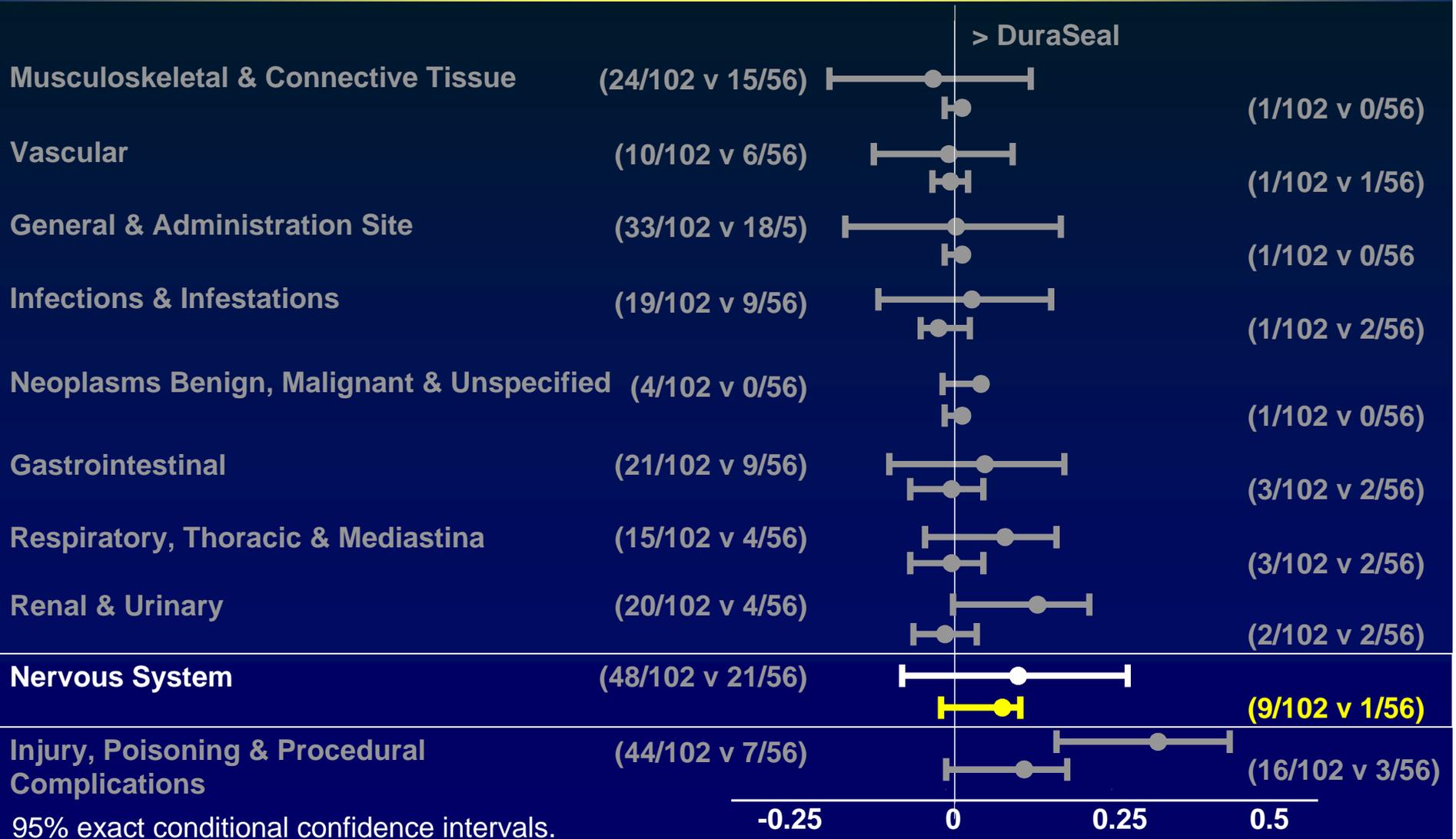
Injury, Poisoning and Procedural Complications (continued)

| Sub-category | Spine Sealant (N=102) | | Control (N=56) | |
|---------------------------------|--------------------------|-----|-------------------|-----|
| | n | % | n | % |
| Corneal abrasion | 1 | 1.0 | 0 | - |
| Postoperative agitation | 1 | 1.0 | 0 | - |
| Radiation associated pain | 1 | 1.0 | 0 | - |
| Skin laceration | 1 | 1.0 | 0 | - |
| Seroma | 1 | 1.0 | 0 | - |
| VII th nerve injury | 1 | 1.0 | 0 | - |
| XII th nerve injury | 1 | 1.0 | 0 | - |
| Superficial injury of the eye | 1 | 1.0 | 0 | - |
| Skin injury | 1 | 1.0 | 0 | - |
| Incision site erythema | 0 | - | 1 | 1.8 |
| Meningitis chemical | 0 | - | 1 | 1.8 |
| Urinary retention postoperative | 0 | - | 1 | 1.8 |

Injury, Poisoning and Procedural Complications – Serious Adverse Events

| Category | Spine Sealant (N=102) | | Control (N=56) | | p-value |
|---|----------------------------------|--------------|---------------------------|-------------|----------------|
| | n | % | n | % | |
| Injury, Poisoning and Procedural Complications | 16 | 15.7% | 3 | 5.4% | 0.073 |

No Statistically Significant Differences in Serious Adverse Events



Summary of Nervous System Disorders in Spinal Sealant

| Case | Event | Procedure | Days Post Op | Observations | CEC adjudication |
|--------|------------------------|-----------------------------|--------------|---|--------------------|
| 22-004 | Loss of Proprioception | T12-L1 Tumor removal (IM) | 4 days | Ataxia and LE weakness / numbness; ambulating independently at end of study | Not device related |
| 10-015 | Paraplegia | C4-C7 Tumor removal (IM) | 1 day | Sensory ataxia, incomplete paraplegia; ambulating with cane and brace at end of study | Not device related |
| 10-002 | Radiculopathy | T1-T2-T3 Tumor removal (IM) | 0 days | Worsening of RLE weakness and BLE numbness; ambulating with walker at end of study | Not device related |
| 06-010 | Sensory Loss | T9-T12 Tumor removal (IM) | 0 days | Worsened right leg numbness / weakness | Not device related |
| 09-003 | Paralysis | T3-T4 Meningioma | 1 day | LE weakness, MRI showed intramedullary hematoma; hematoma evacuated; no improvement at end of study | Not device related |

Summary of Nervous System Disorders in Spinal Sealant (continued)

| Case | Event | Procedure | Days Post Op | Observations | CEC adjudication |
|--------|---------|--|--------------|---|--------------------|
| 15-005 | Fistula | Chiari malformation with syringomyelia | 22 days | Developed CSF leak after biking. Failed attempt at over sewing required re-operation. | Not device related |
| 21-002 | Fistula | C-5 Syringomyelia | 8 days | Readmitted to hospital. Lumbar drain Protocol violation: 16 prior syringomyelia procedures, no dura at C-5, Alloderm® used | Not device related |

Summary of Nervous System Disorders in Spinal Sealant (continued)

| Case | Event | Procedure | Days Post Op | Observations | CEC adjudication |
|--------|----------|---------------------|--------------|---|---------------------|
| 13-001 | Syncope | T7-T8 Tumor removal | 4 days | Subjective disequilibrium, hot-flash, lightheadedness; resolved with observation | Unable to determine |
| 15-008 | Headache | Chiari malformation | 14 days | With history of migraines, developed severe headache and was re-hospitalized for evaluation. Workup CT/LP negative. Resolved with steroids. | Not device related |

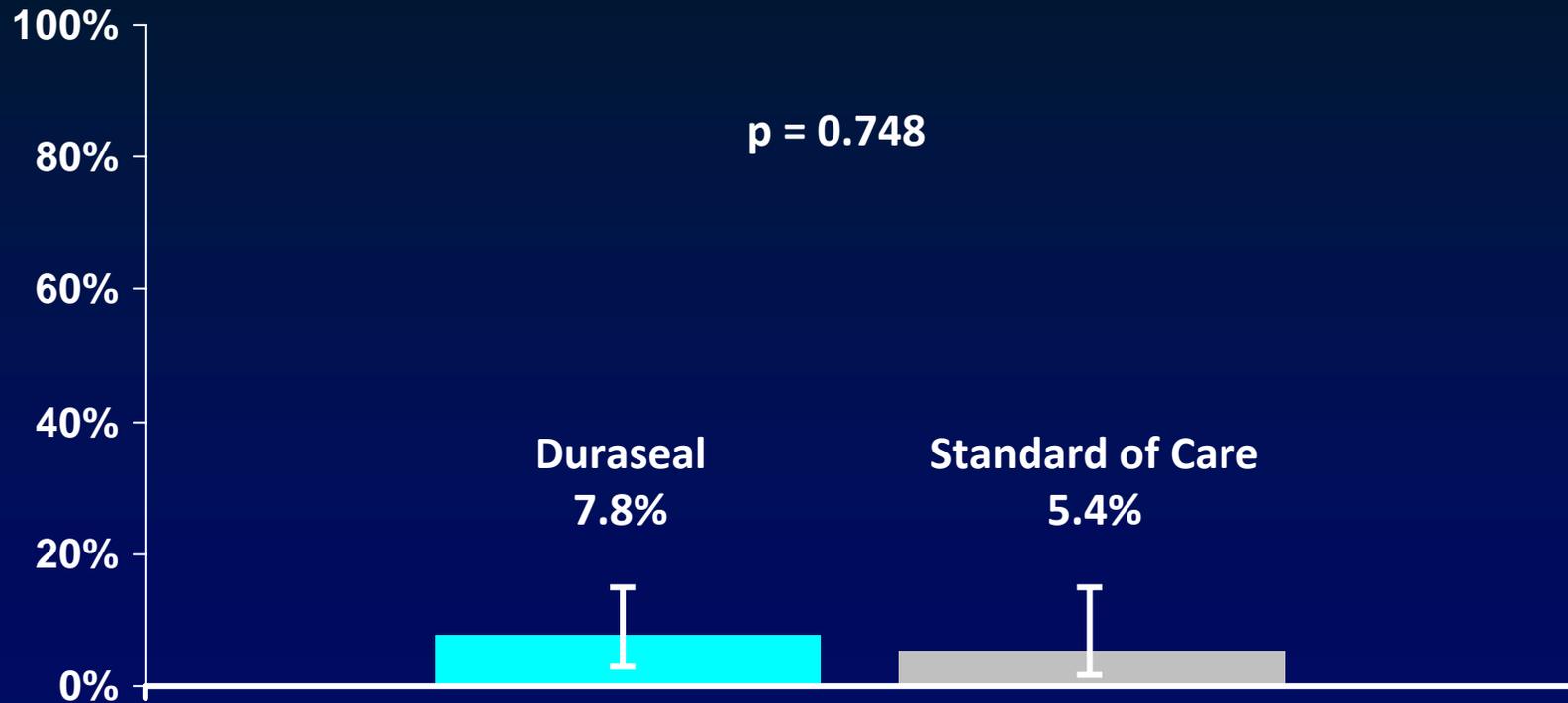
Review of Protocol Specified Adverse Events

- Post-operative CSF leaks within 90 days post-procedure
- Surgical site infection within 90 days post-procedure
- Additional safety assessments
 - Neurological status
 - Laboratory testing
 - Wound healing

Protocol Definition of Post Operative CSF Leak

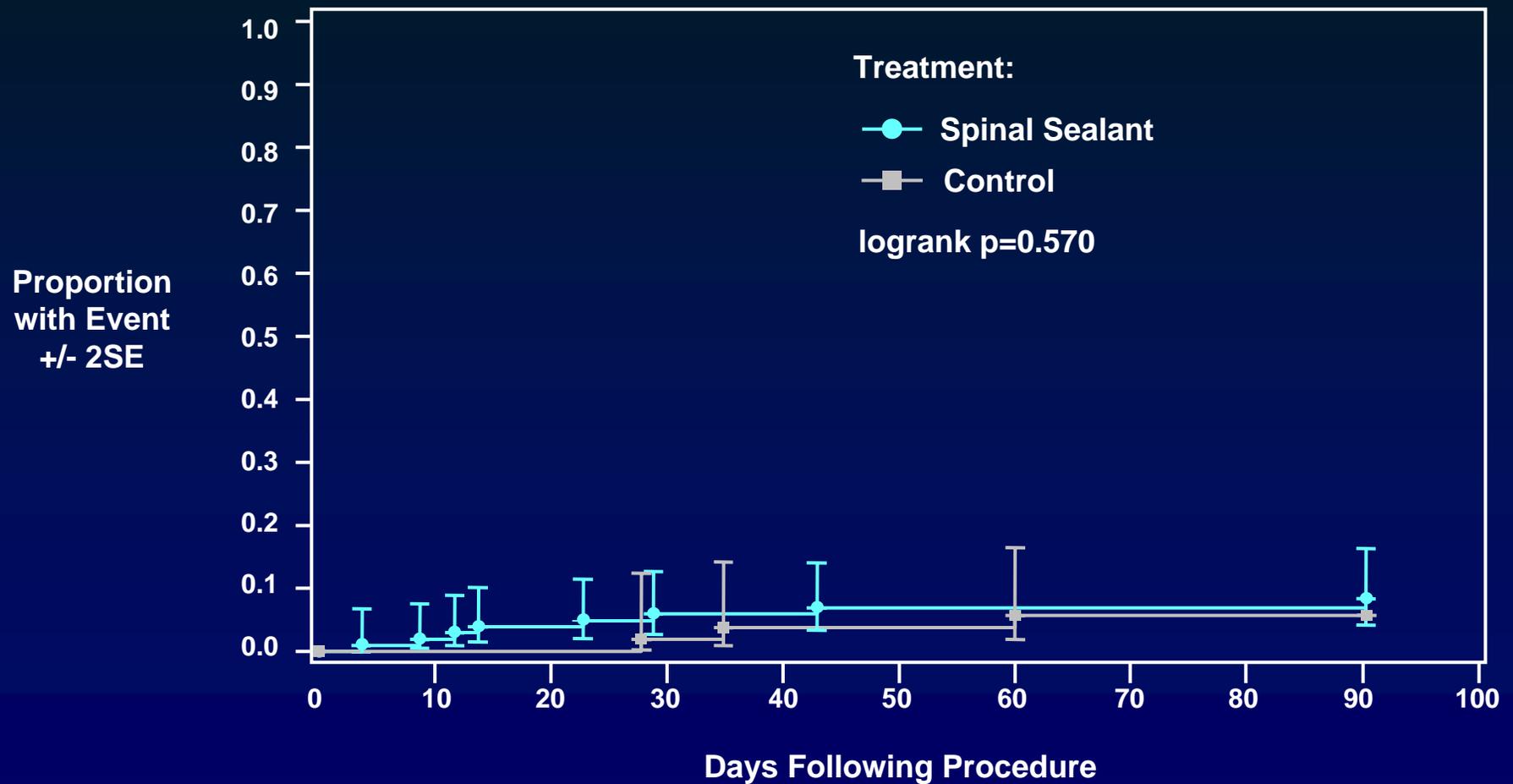
- Incisional leaks and pseudomeningoceles requiring surgical intervention (e.g., aspiration)

No Significant Difference in Postop CSF Leaks Within 90 Days

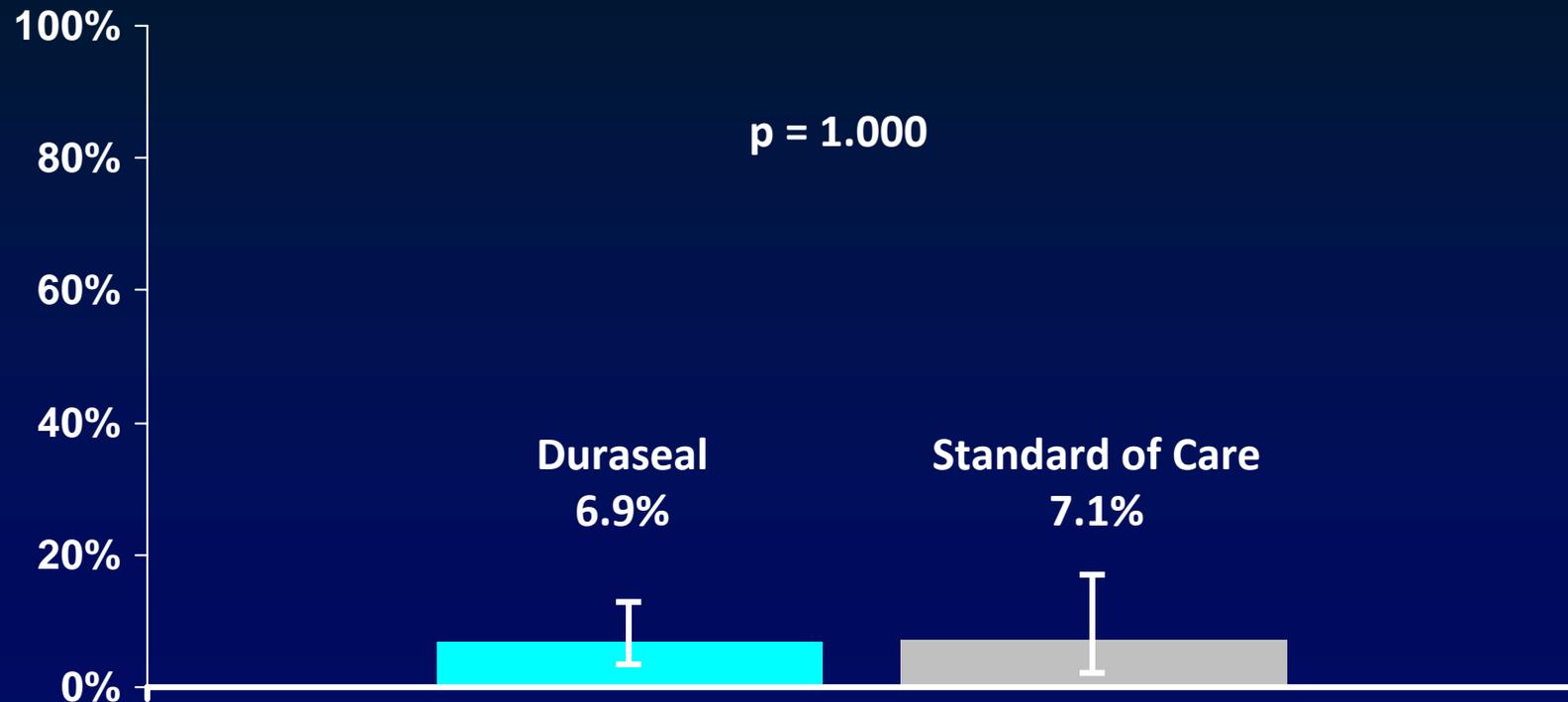


p-value based on two-sided Fisher's Exact test testing for a difference between treatments.

Time to CSF Leakage

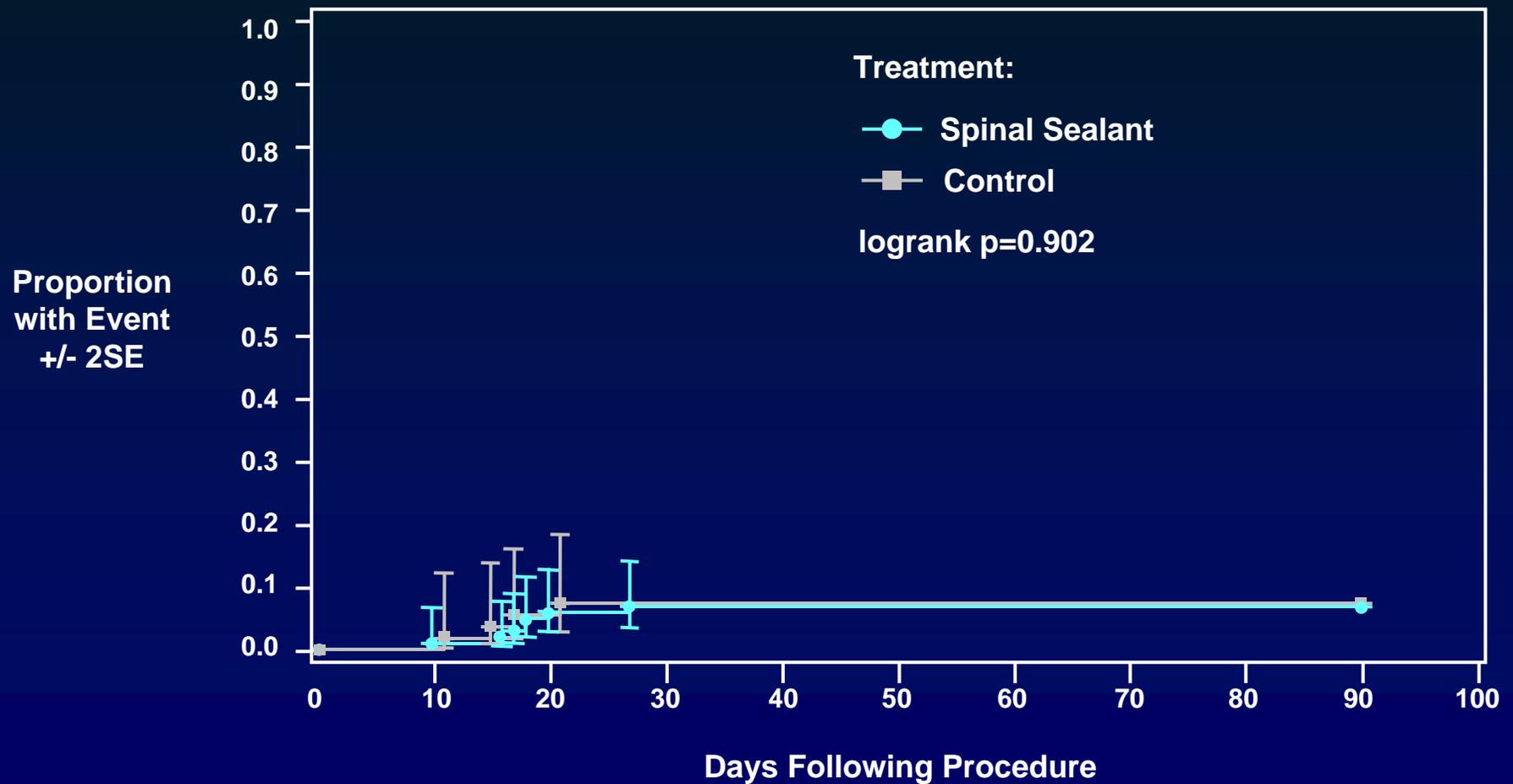


No Significant Difference in Postoperative Surgical Site Infections



p-value based on two-sided Fisher's Exact test testing for a difference between treatments.

Time to Surgical Site Infection



Laboratory Evaluations – No Clinically Relevant Differences

- Renal function
 - BUN
 - Creatinine

- Liver Function
 - Alkaline phosphatase
 - Total bilirubin
 - ALT
 - AST

Neurological Assessments – No Clinically Relevant Differences

- Vital sign instability, level of consciousness, personality changes, speech disorder, visual changes
- Cranial Nerve
- Motor Exam
- Sensory Exam
- Deep Tendon Reflex
- Radicular Pain
- Ankle Clonus
- Gait

Additional Safety Assessments – Protocol Defined Assessment – Wound Healing

| Assessment | % Well Healed |
|------------|---|
| Discharge | <ul style="list-style-type: none">■ Spine Sealant: 69.6%■ Control: 71.4% |
| 30 day | <ul style="list-style-type: none">■ Spine Sealant: 96.0%■ Control: 94.5% |
| 90 day | <ul style="list-style-type: none">■ All wounds were well healed, except one patient in the Spine Sealant group was partially healed |

Post-marketing experience
Post-marketing commitment
Risk / Benefit

Xavier Lefebvre, PhD

Global Vice President, Clinical Affairs
Covidien Surgical Devices

Market Data Further Support Safety and Efficacy

- Spine / cranial post market data from outside United States
- Cranial post market data from the United States
- DuraSeal US cranial post approval study

Significant Real-World Use

- 177,000 units sold in the United States
 - 0.03%; N=52 MDR reports, 53 events
 - CSF leak n=20
 - Infection n=25
 - Other n=8

- 43,000 units sold outside the United States
 - 0.07% N=31 MDR reports, 31 events
 - CSF leak n=9
 - Infection n=21
 - Other n=1

DuraSeal Cranial Post Approval Study

DuraSeal Cranial and DuraSeal Spine
Products are Identical Formulations

DuraSeal Cranial Post Approval Study

- Design:
 - Prospective, single blind, multi-center
 - 1-to-1 randomization; DuraSeal or standard of care
- 100% monitoring of all patients, all events
- 30 Day follow-up period
- Primary endpoint: incidence of neurosurgical complications
- Study Population: clean, elective cranial surgery that entails a dural incision

DuraSeal Cranial Post Approval Study: Current Status

- Enrollment completed April 30, 2009
- Currently in follow-up phase
- N=237
 - n=118 DuraSeal
 - n=119 Control
- 16 US sites

DuraSeal Cranial Post Approval Study: Overall 30-Day Infection and Postop Leaks

| Category | Post Approval Study (30D) | | | |
|------------------|----------------------------|-----|----------------------------|-----|
| | Cranial Sealant (N=109) | | Cranial Control (N=110) | |
| | n | % | n | % |
| Superficial SSIs | 2 | 1.8 | 4 | 3.6 |
| Deep SSIs | 0 | - | 0 | - |
| Organ/space SSIs | 1 | 0.9 | 0 | - |
| Post-op CSF leak | 1 | 0.9 | 3 | 2.7 |

As of March 2009 Annual Progress Report. Database has not been locked and patient follow-up is ongoing.

Consistent SSIs and Post-Operative CSF Leak Rates Across Studies

| Category | Post Approval Study (30D) | | | | Cranial Pivotal Study (90D) | |
|------------------|---------------------------|-----|-------------------------|-----|-------------------------------------|-----|
| | Cranial Sealant (N=109) | | Cranial Control (N=110) | | Cranial Pivotal Study (90D) (N=111) | |
| | n | % | n | % | n | % |
| Superficial SSIs | 2 | 1.8 | 4 | 3.6 | 1 | 0.9 |
| Deep SSIs | 0 | - | 0 | - | 8 | 7.2 |
| Organ/space SSIs | 1 | 0.9 | 0 | - | 0 | - |
| Post-op CSF leak | 1 | 0.9 | 3 | 2.7 | 5 | 4.5 |

As of March 2009 Annual Progress Report. Database has not been locked and patient follow-up is ongoing.

Proposed DuraSeal Spine Post Approval Study

Proposed DuraSeal Spine Post Approval Study Outline

- Objective
 - Obtain real world clinical outcome data for DuraSeal
- Design
 - Prospective, multi-center, single arm, consecutive enrollment, n=300 to 500 patients
- Follow-Up / Endpoint
 - 30 days, CSF leak, pseudomeningocele, SSI
- Monitoring
 - 100% safety outcome

Training to Promote Safe Use

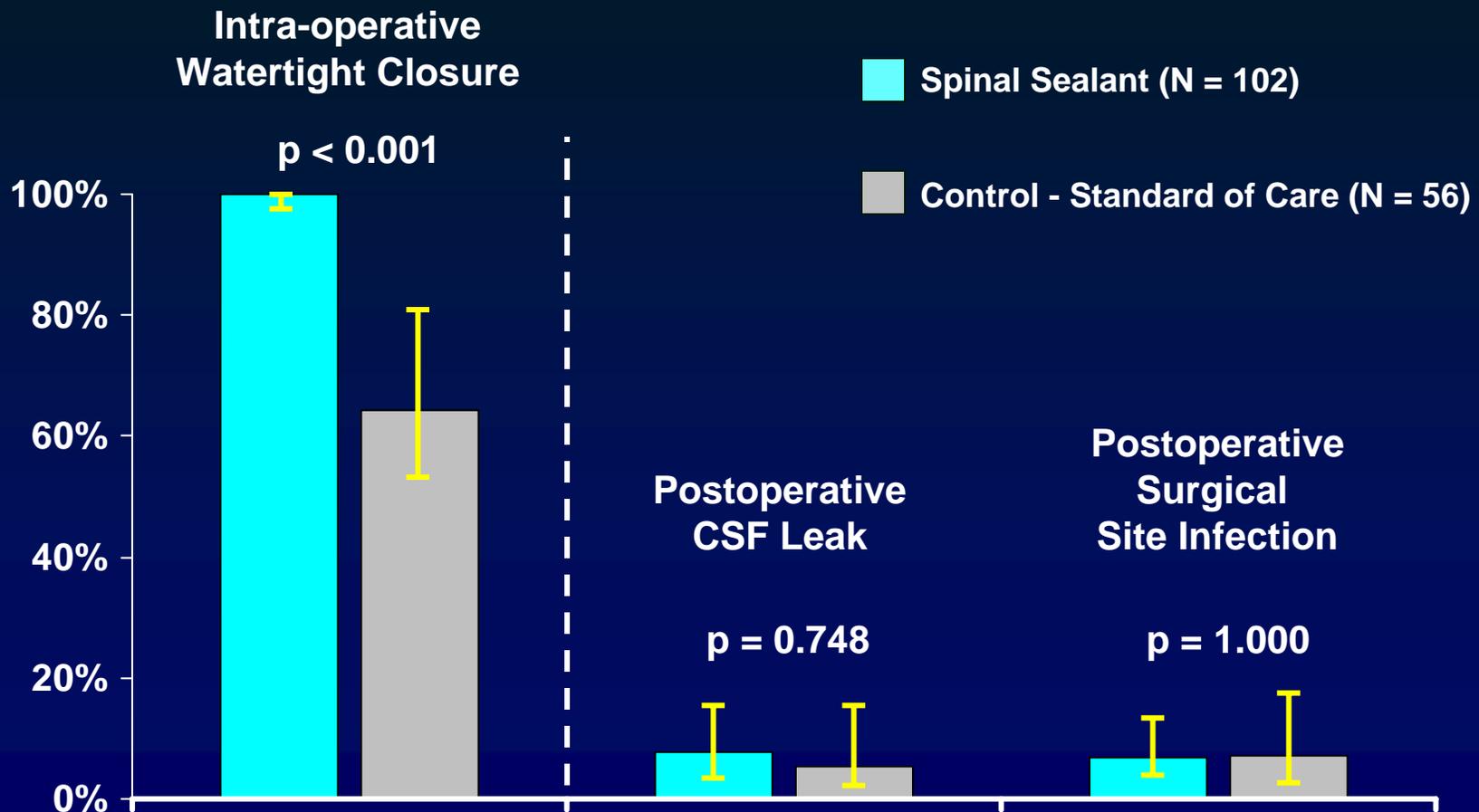
- Product Specialist will provide training
 - Prior to first use
 - Training material provided to surgeon
- Product Specialist will contact site every 6 months
- Customer may contact Product Specialist for refresher training at any time

Labeling to Promote Safe Use

- Clear language in the package insert
- Contraindication
 - Do not use as void filler
- Warnings – DuraSeal not studied in patients
 - With renal impairment
 - Requiring chronic steroid treatment
 - Undergoing chemotherapy

Risk / Benefit

Spine Sealant: Superior Efficacy and Equivalent Safety to Other Options



p-value based on two-sided Fisher's Exact test testing for a difference between treatments.

Spine Sealant: Effective and Easier to Use

- Ease of use
 - Fast to set up and apply
 - Less time than alternatives
 - Very important for incidental durotomies
 - Reliable
- Synthetic Material
 - Eliminates risk of disease transmission
- No FDA-approved devices

DuraSeal Spine Sealant System (P080013) Adjunct to Sutured Dural Repair to Obtain Watertight Closure During Spine Surgery

Neurological Device Panel of the
Food and Drug Administration
May 14, 2009