Mallinckrodt Pharmaceuticals

Investor Briefing

December 7, 2015

Mallinckrodt Pharmaceuticals

Coleman Lannum
Senior Vice President, Investor Relations

Mallinckrodt Pharmaceuticals

Forward-Looking Statements

Statements in this document that are not strictly historical, including statements regarding future financial condition and operating results, economic, business, competitive and/or regulatory factors affecting Mallinckrodt's businesses and any other statements regarding events or developments that we believe or anticipate will or may occur in the future, may be "forward-looking" statements within the meaning of the Private Securities Litigation Reform Act of 1995, and involve a number of risks and uncertainties. There are a number of important factors that could cause actual events to differ materially from those suggested or indicated by such forward-looking statements and you should not place undue reliance on any such forward-looking statements.

These factors include risks and uncertainties related to, among other things:

- *General economic conditions and conditions affecting the industries in which Mallinckrodt operates;*
- *The commercial success of Mallinckrodt's products;*
- *Mallinckrodt's ability to realize anticipated growth, synergies and cost savings from its recently completed acquisitions;*
- *Conditions that could necessitate an evaluation of Mallinckrodt's goodwill and/or intangible assets for possible impairment;*
- *Changes in laws and regulations;*
- *Mallinckrodt's ability to identify, acquire or close future acquisitions;*
- *Mallinckrodt's ability to successfully integrate acquisitions of operations, technology, products and businesses generally and to realize anticipated growth, synergies and cost savings;*
- *Mallinckrodt's ability to successfully develop or commercialize new products;*
- *Mallinckrodt's ability to protect intellectual property rights;*
- *Mallinckrodt's ability to receive procurement and production quotas granted by the U.S. Drug Enforcement Administration;*

Forward-Looking Statements

- *Customer concentration;*
- *Mallinckrodt's reliance on certain individual products that are material to its financial performance;*
- *Cost containment efforts of customers, purchasing groups, third-party payers and governmental organizations;*
- *Product liability losses and other litigation liability;*
- *Ongoing governmental investigations;*
- *Material health, safety and environmental liabilities;*
- *Retention of key personnel;*
- *Conducting business internationally; and*
- *The effectiveness of information technology infrastructure.*

These and other factors are identified and described in more detail in the "Risk Factors" section of Mallinckrodt's Annual Report on Form 10-K for the fiscal year ended September 25, 2015. The forward-looking statements made herein speak only as of the date hereof and Mallinckrodt does not assume any obligation to update or revise any forward-looking statement, whether as a result of new information, future events and developments or otherwise, except as required by law.

Agenda for our session

When	Topic	Who
1:00 – 1:10pm	Welcome and Introduction	Cole Lannum, SVP, Investor Relations
1:10 – 1:25pm	MNK Strategic Overview	Mark Trudeau, President and CEO
1:25 – 2:15pm	Product & Portfolio Overview	Dr. Steve Romano, SVP and CSO Dr. Richard Furie, Chief of Rheumatology, NS-LIJ[1]
2:15 – 4:00pm	Poster Presentations	Various Medical and Commercial Experts
4:00 – 4:15pm	Break	All
4:15 – 5:00pm	Question and Answer Session	Lannum, Trudeau, Romano and Matt Harbaugh, SVP and CFO
5:00 – 5:45pm	Reception	All

1 North Shore-LIJ Health System

Mark Trudeau
President and Chief Executive Officer

Mallinckrodt Pharmaceuticals

Mallinckrodt – Managing complexity. Improving lives.

'*Acquire to invest*' model builds long-term value for patients and shareholders

Patient-centered:

- **Acquire durable, under-resourced** treatments for underserved patient populations
- **Invest in achieving products' full potential**
  - **Develop** compelling **clinical and health economic data**
  - **Engage** with payers to **maximize** patient **access**
  - **Expand indications,** markets; grow volume; **assure** product **continuity**

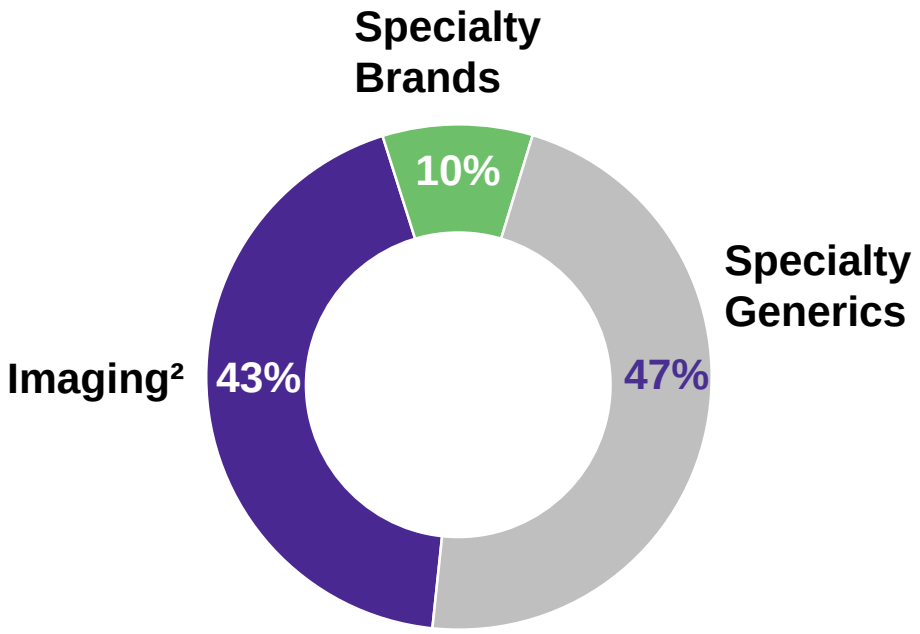
Shareholder focused:

- **Provide immediate value:** execute strategic transactions; maximize synergies; leverage durable Specialty Generics core
- **Expand the business, ensure sustainable long term growth:** invest in organic growth; continue strategic BD&L[1] to build out platforms

[1]BD&L: Business Development & Licensing

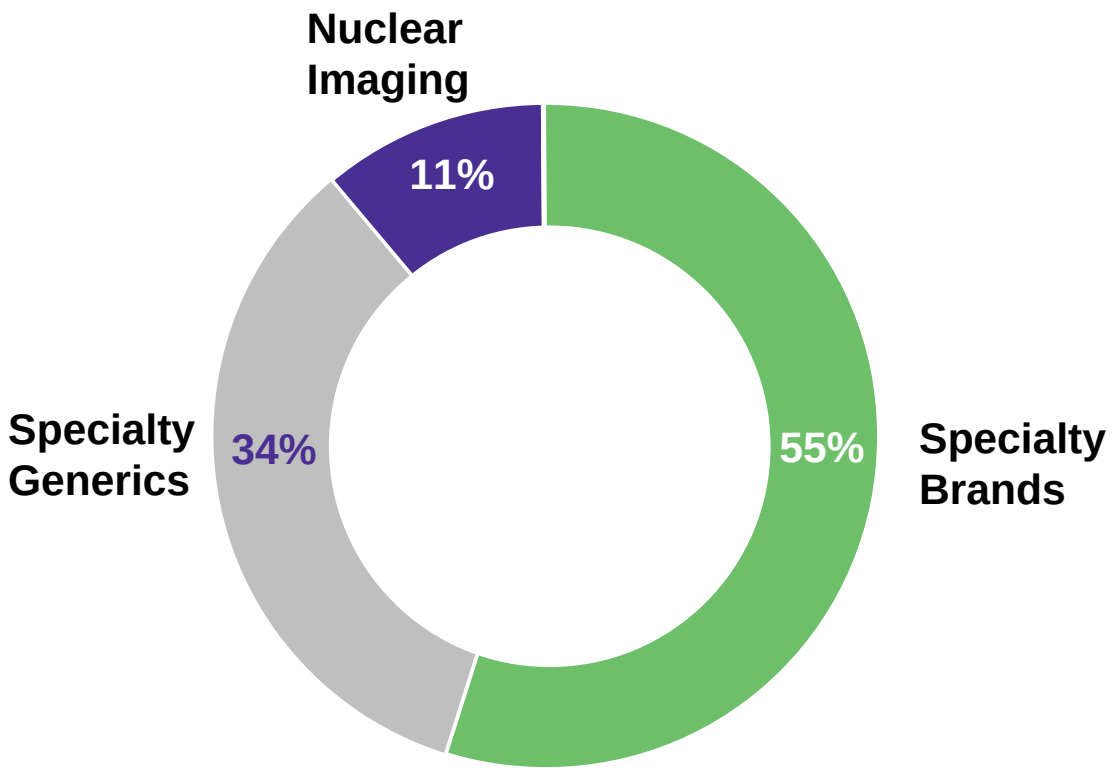
Evolving portfolio focused on specialty brands

FY2013[1] Net Sales $2.2B



Adjusted EPS: $3.13

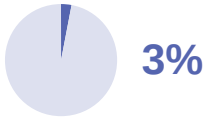
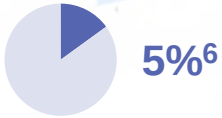
FY2015[1,3] Net Sales $3.7B



Adjusted EPS: $7.37 (CAGR[4]: 53%)

[1] Percentage calculation excludes sales to related parties
[3] Percentage calculation includes proforma sales for INOmax and Therakos
[2] Includes Contrast Media and Delivery Systems (CMDS) and Nuclear Imaging sales
[4] CAGR: Compounded annual growth rate over FY 2013 – FY 2015

Diverse, durable brand portfolio with low penetration

	Primary Indications	Targeted US Market Size and Penetration[1, 2]	Durability
H.P. Acthar GEL (repository corticotropin injection) 80 U/mL	▶ 19 FDA-approved autoimmune indications in 7 therapeutic areas: neurology, nephrology, rheumatology, pulmonology, ophthalmology, dermatology and allergic states	▶ ~300k patients  3%	Trade secret
INOmax (nitric oxide) FOR INHALATION	▶ FDA-approved for neonatal respiratory failure ▶ FDA-approved delivery system for nitric oxide ▶ Approved OUS[3] for pulmonary HTN[4] in cardiac surgery	▶ ~23k patients  50%	2031 LOE[7] Commercial model
OFIRMEV (acetaminophen) injection 1000 mg/100 mL (10 mg/mL)	▶ FDA-approved for pain and fever	▶ ~20M in-patient procedures  15%	2020 LOE Potential formulation extension
Therakos PHOTOPHERESIS	▶ FDA-approved for cutaneous T-cell lymphoma[5] ▶ OUS approval for photopheresis administration	▶ ~15k patients  5%[6]	2023+ LOE Commercial model
Terlipressin	▶ Phase 3 pivotal registration trial in type 1-hepatorenal syndrome (HRS-1)	▶ >10k patients	Orphan drug

1 Penetration rates of currently approved and marketed indications 2 Based on addressable patients across approved indications and management estimates 3 Outside United States 4 Hypertension
5 Approved for palliative treatment of skin manifestations of CTCL 6 Includes early-stage CTCL topical non-responders and late-stage CTCL patients 7 Loss of exclusivity

Organic growth delivered through data generation, commercial focus and payer engagement

	Key Value Drivers	Financial Objectives
H.P. Acthar GEL (repository corticotropin injection) 80 U/mL	▶ Increased patient penetration ▶ Clinical, HEOR[1] data generation ▶ Payer engagement at policy level	▶ Mid-single to low-double digit revenue growth
INOmax (nitric oxide) FOR INHALATION	▶ Increased patient penetration ▶ Contracting, 24/7 customer intimacy ▶ Label expansion	▶ Mid-single digit revenue growth
OFIRMEV (acetaminophen) injection 1000 mg/100 mL (10 mg/mL)	▶ Increased procedure penetration ▶ Clinical, HEOR data generation ▶ Expanded formulary access	▶ >$500M peak annual revenue
Therakos PHOTOPHERESIS	▶ Expanded system placement, kit/drug volume ▶ Label expansion ▶ Clinical, HEOR data generation	▶ High-single digit revenue growth
Terlipressin	▶ Achieve HRS-1 approval in the US ▶ Potential label expansion	▶ TBD[2]

1 Health Economic Outcomes Research
2 To be determined

Mallinckrodt Goal: Become a top-performing Specialty Biopharmaceutical business

Create sustainable long-term value balanced between organic and inorganic growth

Organic growth

- Achieve sustainable normalized revenue growth in mid-single digits
- Drive EPS at higher rates

Inorganic growth

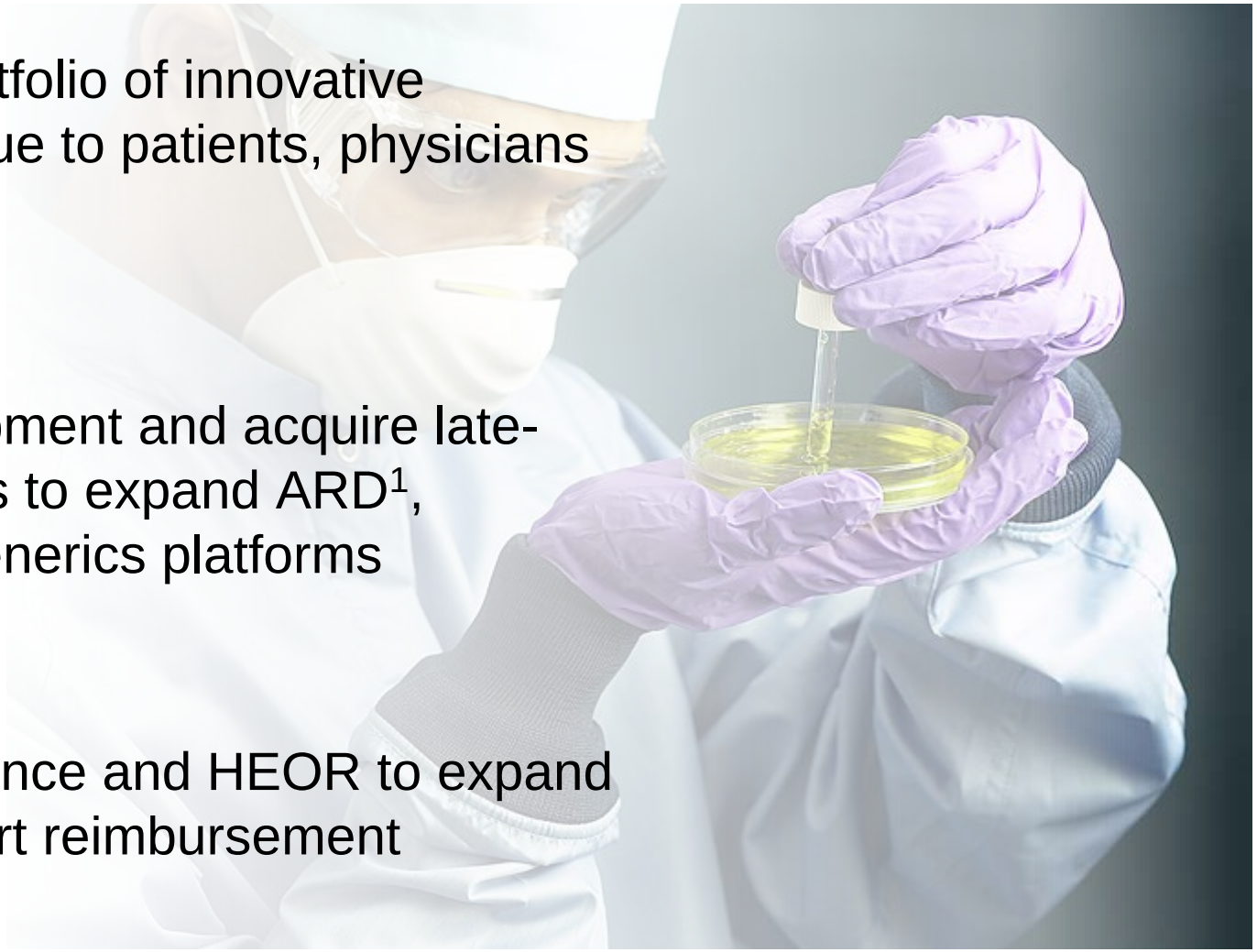
- Acquire commercial late-stage development assets across Specialty Brands and Specialty Generics
- Leverage significant cash generation capacity

Steve Romano, MD
Senior Vice President and Chief Scientific Officer

Mallinckrodt Pharmaceuticals

Mallinckrodt Science and Technology priorities to drive growth

- Build diverse, durable portfolio of innovative therapies that provide value to patients, physicians and payers
- Leverage organic development and acquire late-stage development assets to expand ARD[1], Hospital and Specialty Generics platforms
- Generate real world evidence and HEOR to expand patient access and support reimbursement



1 Autoimmune and Rare Diseases

Portfolio founded on durable specialty brands and generics

Specialty Brands

H.P. Acthar® GEL (repository corticotropin injection) 80 U/mL

- Complex, naturally derived organic mixture; approved in 19 debilitating diseases/conditions
- Marketed today in only 9 indications, serving <3% of addressable patient population

INOmax® (nitric oxide) FOR INHALATION

- Nitric oxide treatment for neonatal respiratory failure and pulmonary hypertension in cardiac surgery
- Replaces invasive external 'heart/lung' support; alternative to forced oxygen therapy for infants

OFIRMEV® (acetaminophen) injection

- IV acetaminophen for treatment of acute pain and fever
- Foundation of multimodal analgesia to optimize pain management, reduce opioid use

Therakos® PHOTOPHERESIS

- Immunotherapy treatment used in oncology, transplant & autoimmune diseases
- Integrated drug-device system used in hospitals, academic treatment centers

Specialty Generics

- Expertise in complex formulations
- Focus in controlled substances, including opioids and stimulants

Value-creating business development

IV: Intravenous

Clinical activities expand use of in-line brands; advance new indications and medicines

	THERAPY	INDICATION	PHASE 4
MARKETED / PHASE 4	H.P. ACTHAR® GEL (repository corticotropin injection)	*19 Indications*	*SLE, iMN, FSGS*
	OFIRMEV® (acetaminophen) injection	*Pain, Fever*	*Knee, UVB Burn*
	GABLOFLEN® (baclofen injection)	*Spasticity*	
	INOMAX® (nitric oxide) for inhalation	*HRF (neonates)*	
	UVADEX® (methoxsalen) sterile solution	*CTCL*	
PHASE 3 / REGISTRATION	TERLIPRESSIN	*HRS Type-1*	
	GABLOFLEN 3000 mg	*Spasticity*	
	IT MORPHINE	*Chronic pain*	
	IT HYDROMORPHONE	*Chronic pain*	
	UVADEX	*Acute GvHD (US), Chronic GvHD (JP)*	
PHASE 1 - 2	ACTHAR®	*ALS, DN*	
	SYNACTHEN (cosyntropin injection)	*(Pre-IND)*	

HRF: Hypoxic Respiratory Failure, CTCL: Cutaneous T-Cell Lymphoma, DN: Diabetic Nephropathy, FSGS: Focal Segmental Glomerulo-sclerosis, GvHD: Graft vs Host Disease, HRS: Hepatorenal Syndrome, iMN: idiopathic Membranous Nephropathy, IND: Investigational New Drug, JP: Japan, SLE: Systemic Lupus Erythematosus

Evaluating additional opportunities for investment

	H.P. Acthar GEL (repository corticotropin injection) 80 U/mL	INOmax (nitric oxide) FOR INHALATION	OFIRMEV (acetaminophen) injection	Therakos PHOTOPHERESIS	Terlipressin
Today	▶ 19 FDA-approved indications in 7 therapeutic areas	▶ HRF in newborns in US ▶ CV surgery in Japan, Australia	▶ Pain ▶ Fever	▶ FDA-approved for CTCL ▶ Broad immuno-therapeutic use globally	▶ Phase 3 pivotal registration trial in HRS-1
Future Potential	▶ Controlled data in key indications ▶ Strengthen MOA data ▶ Extensive HEOR	▶ Expand data in NIV ▶ Preemie registry ▶ Evaluate beyond pulmonary	▶ Phase 4 trials in knee replacement and UVB burn pain model ▶ Strengthen data in MMA	▶ Acute GvHD and chronic GvHD ▶ Evaluate use in transplant and other autoimmune diseases	▶ Planned FDA approval ▶ Evaluate new opportunities (EVH, SIRS, Sepsis)

CTCL: Cutaneous T-cell lymphoma, CV: Cardiovascular, EVH: Esophageal variceal hemorrhage, MMA: Multimodal analgesia, MOA: Mechanism of action, NIV: Non-invasive ventilation, SIRS: Systemic inflammatory response syndrome

Acthar is a complex, naturally derived organic mixture

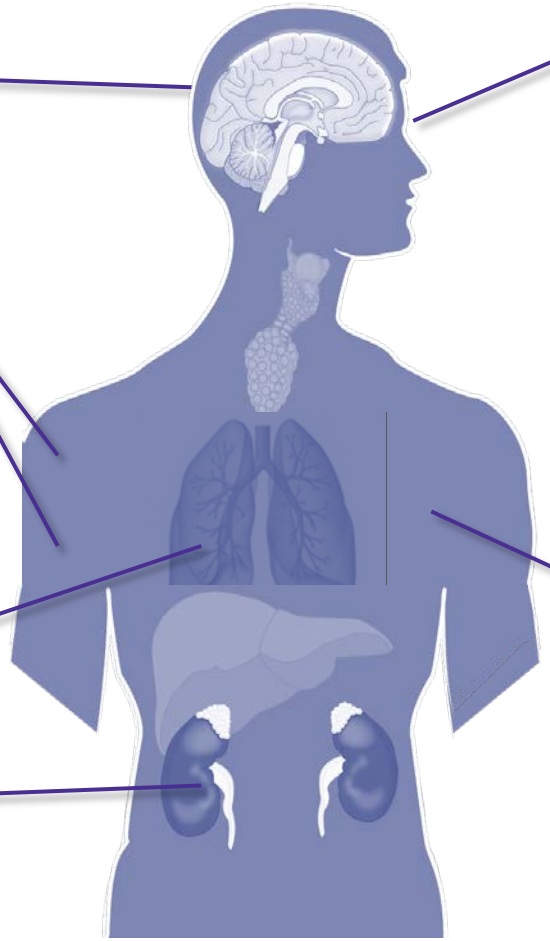
FDA approved in 19 debilitating diseases/conditions; currently marketed in only 9 indications*

Neurology
- Infantile spasms*
- Multiple sclerosis flares in adults*

Rheumatology
Multiple organs (including muscle and joint):
- Lupus*
- Dermatomyositis/polymyositis*
- Rheumatoid arthritis flares*
- Psoriatic arthritis flares*
- Ankylosing spondylitis flares*

Pulmonology
- Symptomatic sarcoidosis*

Nephrology
- Edematous state* (remission of proteinuria in nephrotic syndrome)



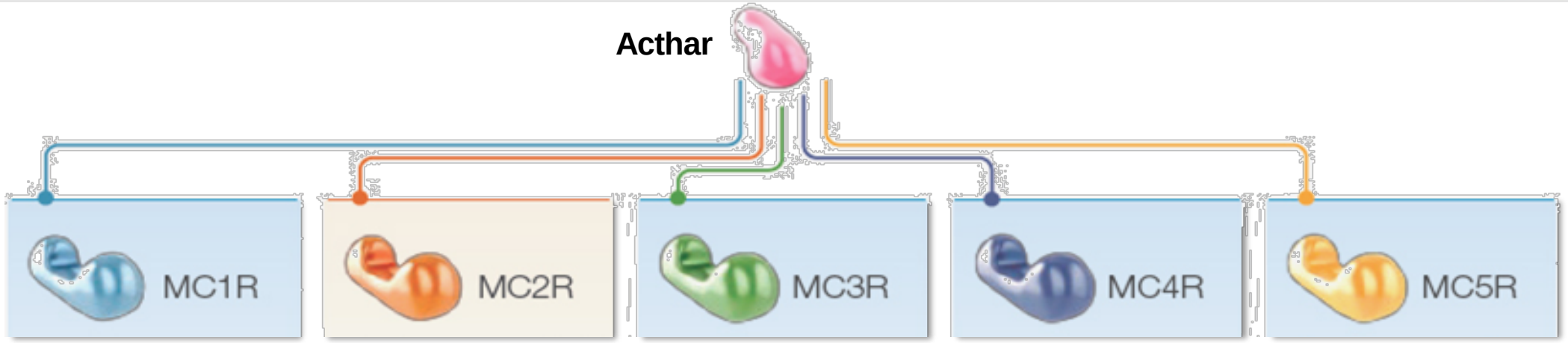
Ophthalmology
Eye inflammation such as:
- Keratitis
- Iritis
- Iridocyclitis
- Diffuse posterior uveitis
- Optic neuritis
- Chorioretinitis
- Anterior segment inflammation

Dermatology
Rare skin diseases such as:
- Stevens-Johnson syndrome
- Severe erythema multiforme

Allergic States
- Serum sickness

Full prescribing information can be found at http://www.acthar.com/pdf/Acthar-PI.pdf

Acthar binds to all 5 melanocortin receptors (MCRs) cells[1-5]

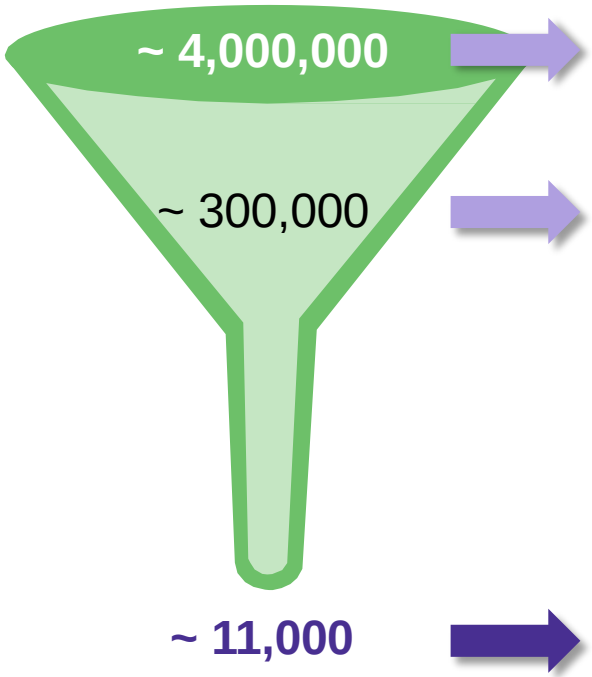


MC1R	MC2R	MC3R	MC4R	MC5R
▶ Immune cells ▶ Endothelial cells ▶ Epithelial cells ▶ Skeletal muscle cells ▶ Many other cells	▶ Adrenocortical cells	▶ CNS cells ▶ Immune cells ▶ Many other cells	▶ CNS microglia ▶ Immune cells ▶ Skeletal muscle cells ▶ Many other cells	▶ Immune cells ▶ Skeletal muscle cells ▶ CNS cells ▶ Many other cells
Steroid-independent properties	Steroid-dependent properties	Steroid-independent properties	Steroid-independent properties	Steroid-independent properties

1: Brzoska T, Luger TA, Maaser C, Abels C, Böhm M. α-melanocytestimulating hormone and related tripeptides: biochemistry, anti-inflammatory and protective effects *in vitro* and *in vivo*, and future perspectives for the treatment of immune-mediated inflammatory diseases. *Endocr Rev*. 2008;29(5):581-602. doi:10.1210/er.2007-0027.
2: Catania A, Gatti S, Colombo G, Lipton JM. Targeting melanocortin receptors as a novel strategy to control inflammation. *Pharmacol Rev*. 2004;56(1):1-29.
3: Gong R. The renaissance of corticotropin therapy. *Nat Rev Nephrol*. 2011;8:122-128.
4: Gong R. Leveraging melanocortin pathways to treat glomerular disease. *Adv Chronic Kid Dis.* 2014;21(2):134-151.
5: Data on file: RD-010-00. Mallinckrodt ARD, Inc.

Acthar has potential to reach more patients in need of therapeutic options

Only 3% of addressable patients are now treated



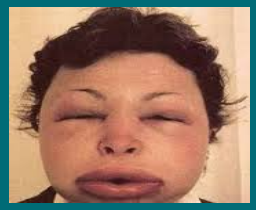
US patient population with Acthar-indicated conditions

Addressable but currently untreated

Patients currently treated with Acthar

Rheumatoid Arthritis

Infantile Spasms



Idiopathic Nephrotic Syndrome

Multiple Sclerosis

SLE (Lupus)

Source: Internal estimates FY2016 (11, 227 patients treated with Acthar)

Acthar has low patient penetration across majority of approved indications

Diagnosis	Share of addressable patients treated	
Infantile spasms		~2K
Multiple sclerosis		~25K
Proteinuria remission in idiopathic nephrotic syndrome		~10K
Rheumatoid arthritis (adjuvant therapy)		~85K
Dermatomyositis/polymyositis		~20K
Symptomatic sarcoidosis		~20K
SLE (lupus)		~75K
Psoriatic arthritis		~30K
Ankylosing spondylitis		~50K

Acthar R&D investment

Expand evidence base

Strengthen clinical profiles

Generate compelling value proposition

Defend integrity of drug product

Establish differentiation from steroids

Building evidence for Acthar with company-sponsored, controlled trials

Design / Primary Objectives	Patients	Status
SLE: Phase 4, double-blind, placebo-controlled study in patients with steroid-dependent, persistently active disease, with arthritic and/or cutaneous involvement		
▶ Part 1: 8 weeks (double-blind, placebo-controlled) Evaluate efficacy ▶ Part 2: 44 weeks (open label extension) Explore durability of response	36	▶ Complete
iMN: Phase 4, double-blind, placebo-controlled study in treatment-resistant subjects with persistent proteinuria and nephrotic syndrome due to iMN		
▶ Double-blind, placebo-controlled: 24-week treatment, 24-week taper & follow-up	60	▶ Ongoing
FSGS: Phase 4, randomized withdrawal study in Idiopathic FSGS subjects with treatment resistant or treatment intolerant Proteinuria		
▶ Part 1: 24 weeks (open label) Evaluate induction of remission ▶ Part 2: 24 weeks (placebo-controlled, double-blind, randomized withdrawal) Evaluate maintenance therapy	210	▶ Ongoing
ALS: Phase 2, randomized, controlled study; explore safety, tolerability in patients with ALS		
▶ Part 1: 8 weeks (randomized open label) Investigate safety, tolerability of 4 doses ▶ Optional 28 weeks (open-label extension) Explore effect on function, muscle strength, pulmonary function, quality of life, and survival	40	▶ Trial Complete, Analysis Ongoing
DN: Phase 2, double-blind, placebo-controlled study; explore safety, tolerability in patients with DN		
▶ Double blind, placebo-controlled: 36-week treatment, 16-week taper & follow-up	40	▶ Ongoing

Richard Furie, MD

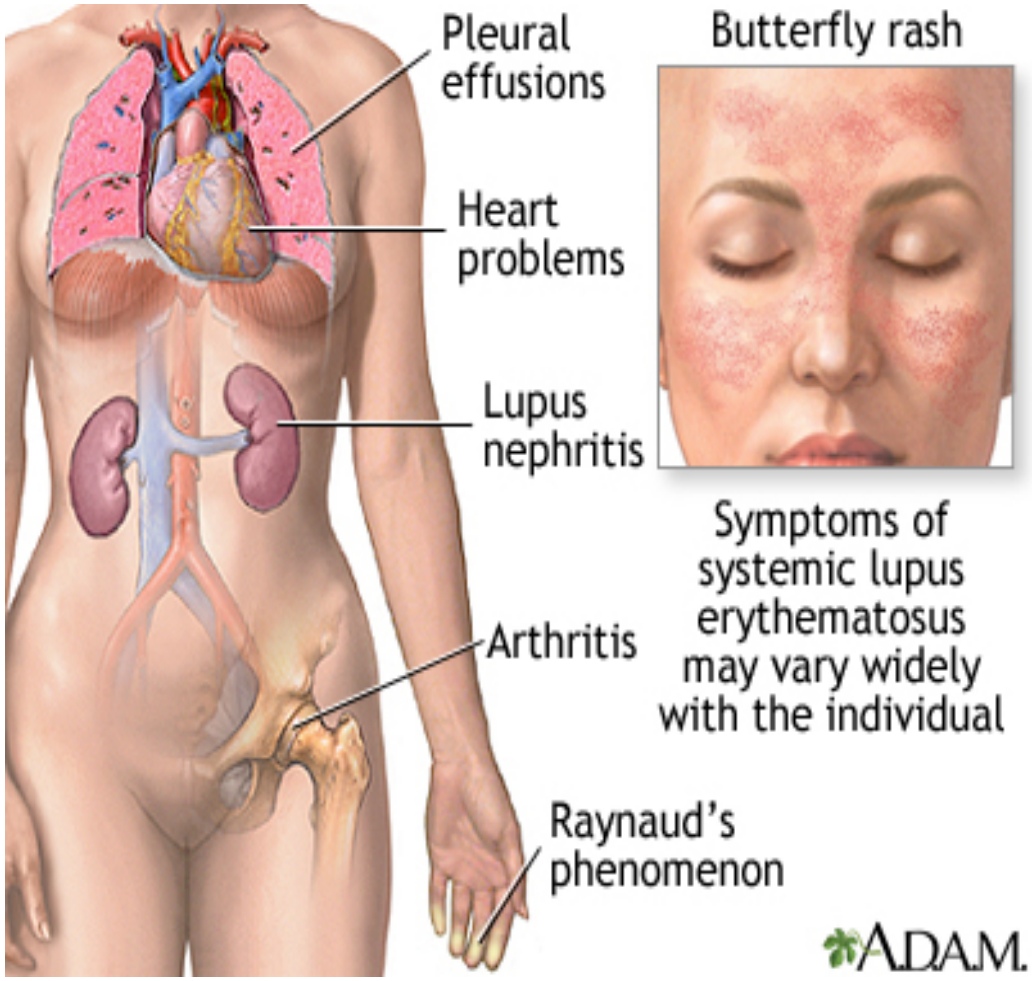
Chief, Division of Rheumatology,
North Shore-LIJ Health System

Professor of Medicine,
Hofstra North Shore-LIJ School of Medicine

Great Neck, NY

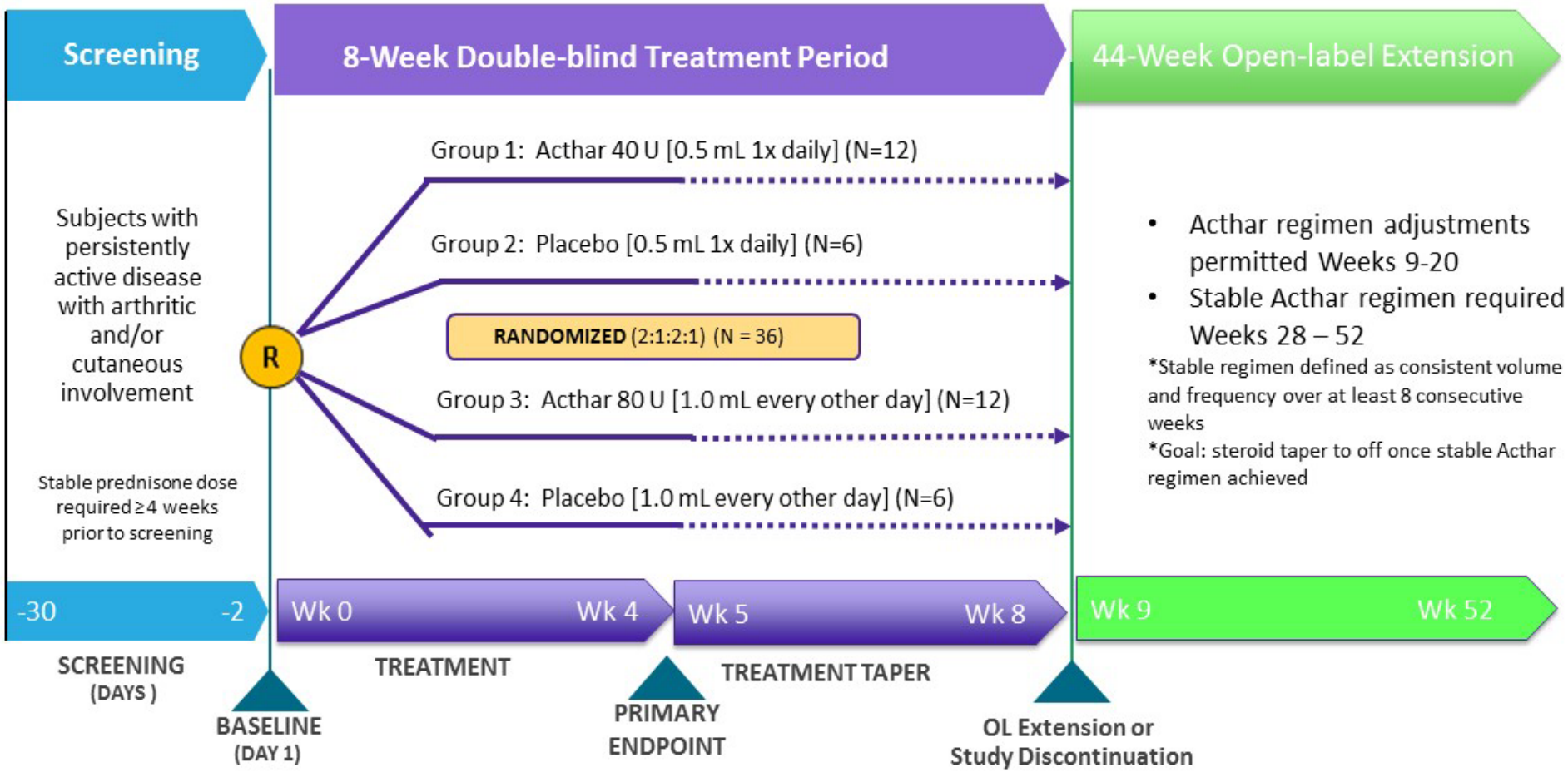
Acthar: SLE

- SLE is a heterogeneous disease which can affect any organ
- Loss of self-tolerance leads to organ dysfunction
- Lupus nephritis and infection remain most common causes of mortality
- Despite advances in therapy, up to 1/3 of patients may have disease manifestations that are refractory to conventional treatment
- Nonclinical and ex-vivo data support Acthar's clinical efficacy in SLE



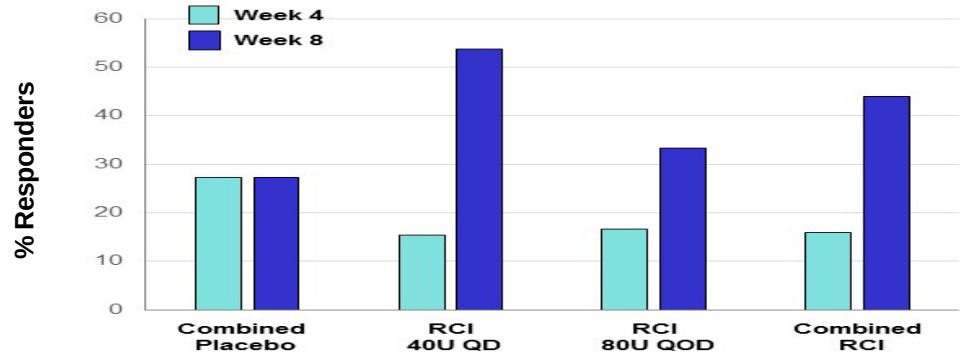
https://www.nlm.nih.gov/medlineplus/ency/article/000435.htm

Acthar: SLE Phase 4 study design - Double-blind, placebo-controlled

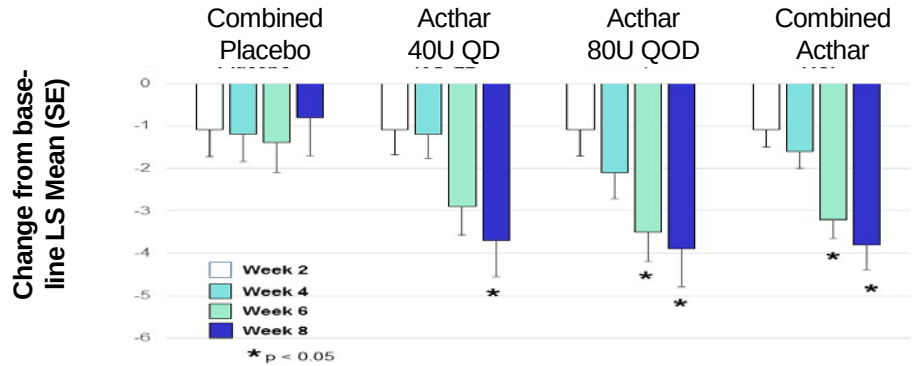


SLE Phase 4 pilot study: Evidence of efficacy for select patients with limited options

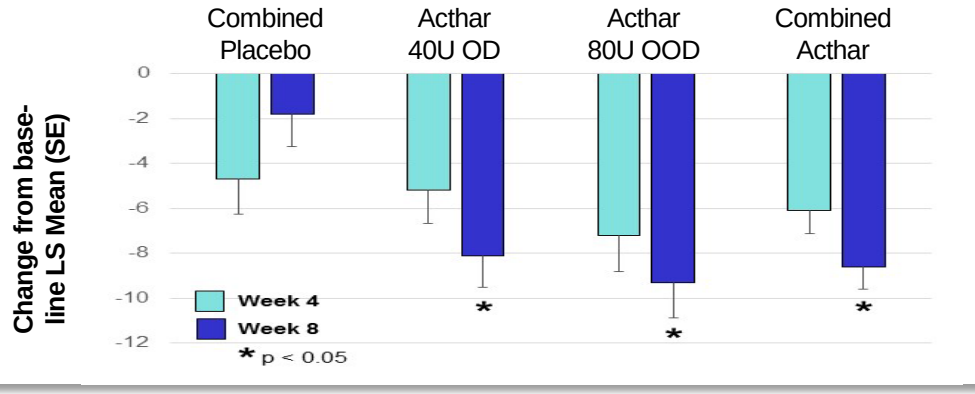
Responders, Primary Endpoint



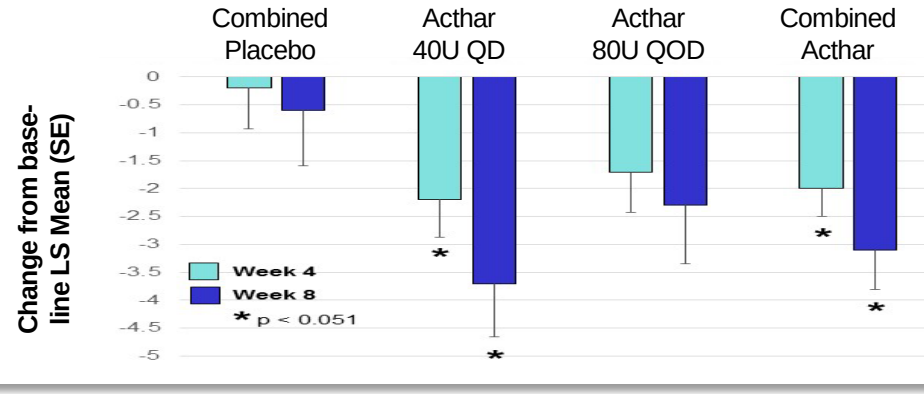
Hybrid SLEDAI*



BILAG (total score)*



CLASI (Activity score)*

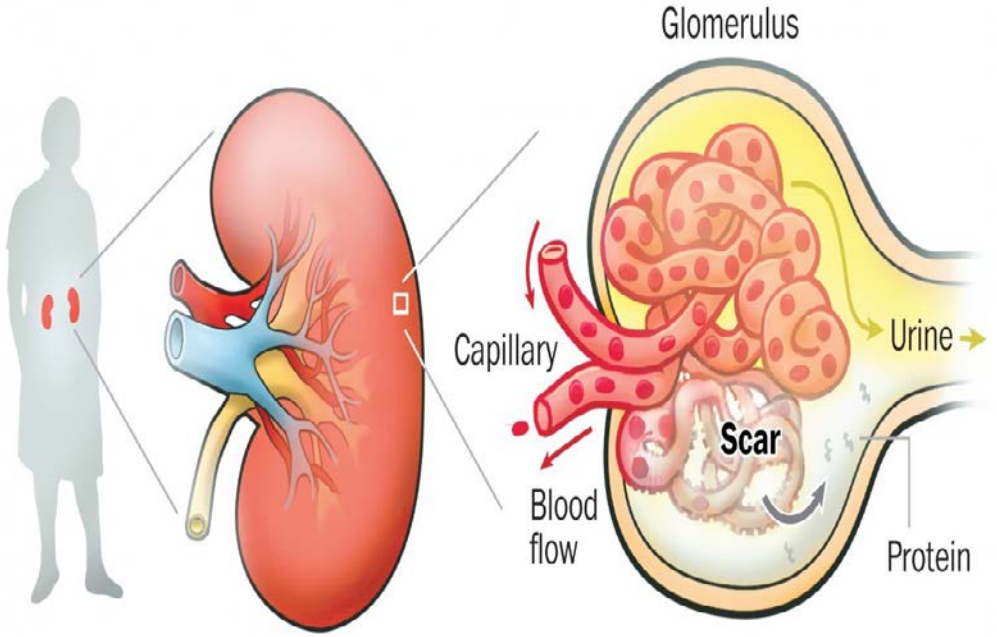


***hSLEDAI**: Hybrid Systemic Lupus Erythematosus Disease Activity Index, **BILAG**: British Isles Lupus Assessment Group, **CLASI**: Cutaneous Lupus Erythematosus Disease Area and Severity Index

Acthar: Treatment for patients with proteinuria due to nephrotic syndrome

- Acthar is approved to induce a diuresis or remission of proteinuria in idiopathic NS
- Major cause of idiopathic NS is FSGS
- FSGS is
  - Most common glomerular disorder causing end-stage renal disease (ESRD) in US
  - ~ 50% of affected patients develop ESRD over period of 5-8 years
  - Current treatments effective in < 50% patients
- Recently published data suggest 29% of Acthar-treated FSGS subjects achieved complete or partial remission of proteinuria

Idiopathic glomerular diseases can cause proteinuria and nephrotic syndrome



Source: NKF, National Kidney Foundation

Acthar: FSGS - Phase 4 study design

Confirm efficacy in induction of remission of proteinuria:
Subjects resistant to or intolerant of immunosuppressive therapies, including but not limited to corticosteroids or CNIs

- **Phase 4, randomized withdrawal**
- Multicenter, 80 sites globally
- 210 subjects

Two-Part Prospective Study

Part 1	*24-week open label: evaluate induction of remission (80 units (U) 3x/week)*
Part 2	*24-week PC, DB randomized withdrawal: evaluate maintenance therapy (80U 2x/week)*

CNIs: Calcineurin Inhibitors, DB: double-blind, PC: placebo-controlled

Established MS Relapse registry to strengthen clinical profiles

Study impact of Acthar in treatment of MS for acute relapse:
6-month monitoring following initial & any subsequent relapses

- **Prospective, observational, longitudinal study**
- Multicenter, 75 US sites
- 260 subjects

Objectives

- *Describe treatment history & characteristics*
- *Understand dosing regimens*
- *Document safety & tolerability profile*
- *Determine impact of therapy*

Endpoints

- *Kurtzke Expanded Disability Status score (EDSS)*
- *MS Impact scale (MSIS-29)*
- *Clinical Global Impression of Improvement Scale (CGI-I)*

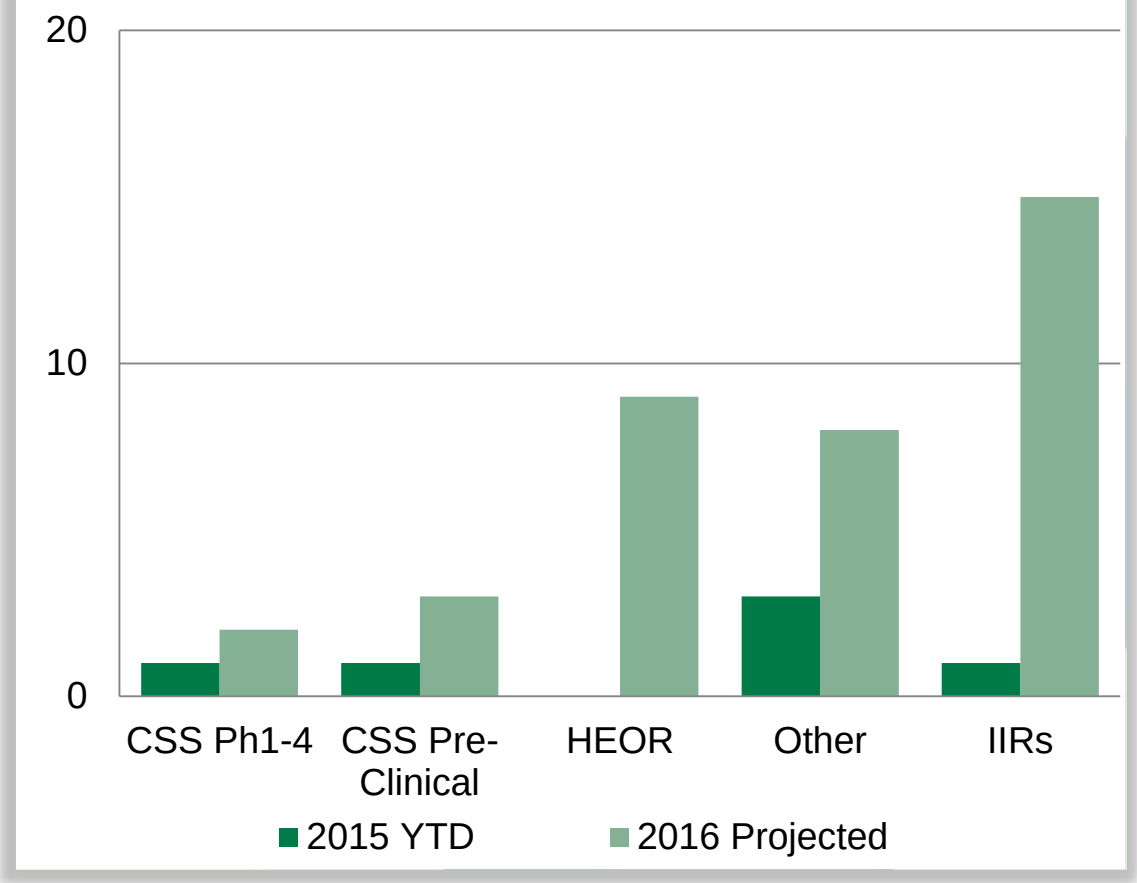
HEOR demonstrates Acthar value, differentiates from alternative therapies, addresses unmet needs

Leverage Large Datasets	Objectives	Completion
Physician Surveys Retrospective Chart Reviews	▸ Assess treatment patterns (e.g., dosing, therapy duration) & describe patient characteristics and treatment history across multiple indications	▸ 1H 2016
Cost-Offset Analyses: DM/PM & Sarcoidosis	▸ Understand healthcare resource & treatment costs & develop model comparing versus other therapies	▸ 1H 2016
Retrospective Studies: RA & SLE	▸ RA: understand factors in RA use & prescribing predictors ▸ SLE: assess patient characteristics & perform cost-offset analysis	▸ 1H 2016
Economic Model: MS Exacerbations	▸ Develop model & perform cost-benefit analysis comparing to other commonly used therapies in treating relapsing MS	▸ 1H 2016
AMCP Dossier Update	▸ Provide dossier & summary of clinical and economic value for use in formulary decision-making	▸ 1H 2016

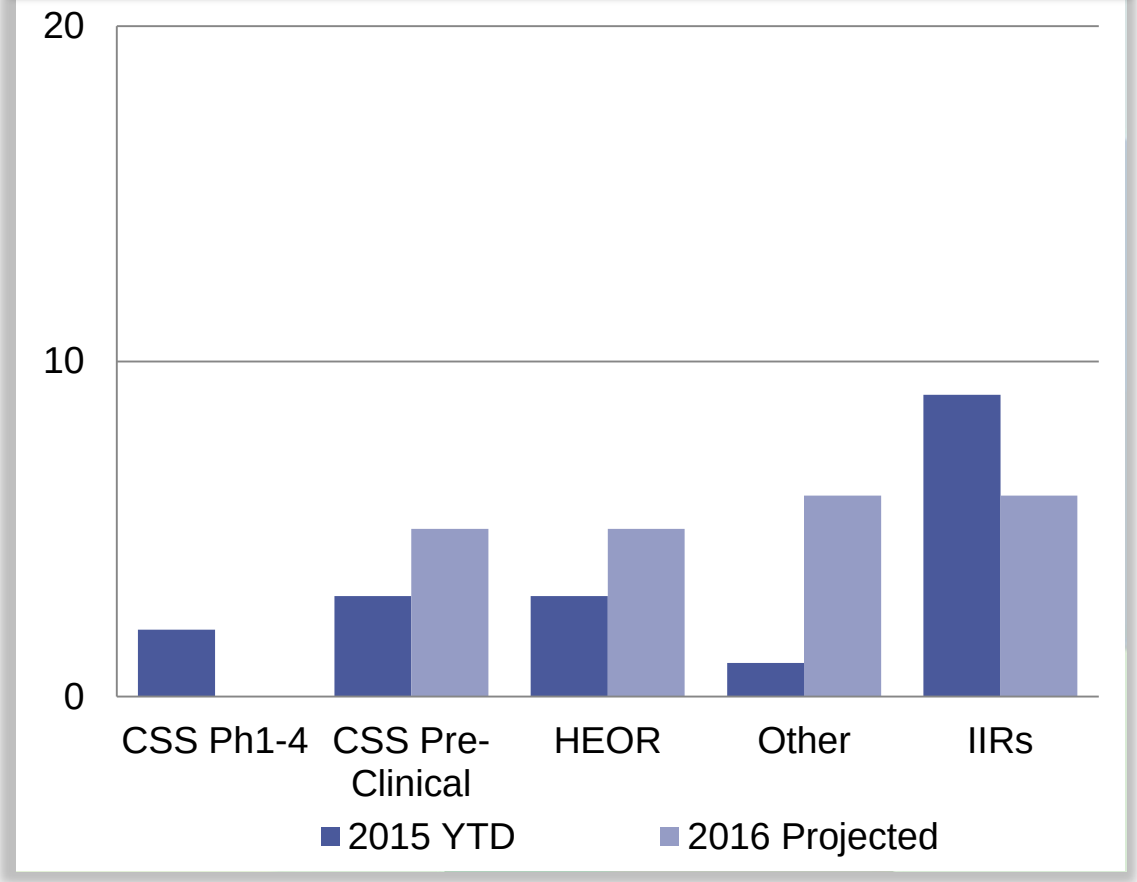
AMCP: Academy of Managed Care Pharmacy, DM/PM: Dermatomyositis/polymyositis

Accelerating communication of Acthar clinical and scientific data is critical for both providers and decision-makers

Manuscripts

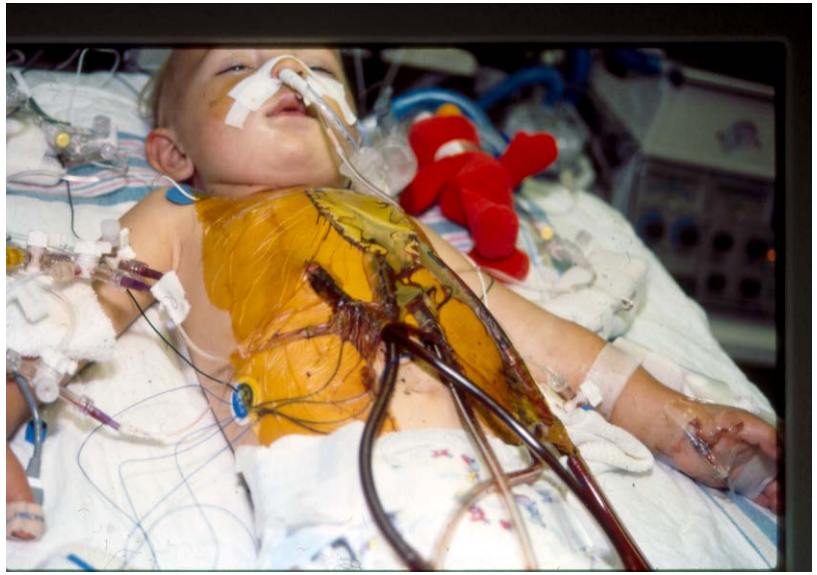


Presentations



CSS: Company-Sponsored Studies, IIRs: Investigator-Initiated Research, Ph: Phase

INOMAX: Only FDA-approved treatment for neonates with hypoxic respiratory failure[1]



INOmax (nitric oxide) FOR INHALATION

Standard of Care

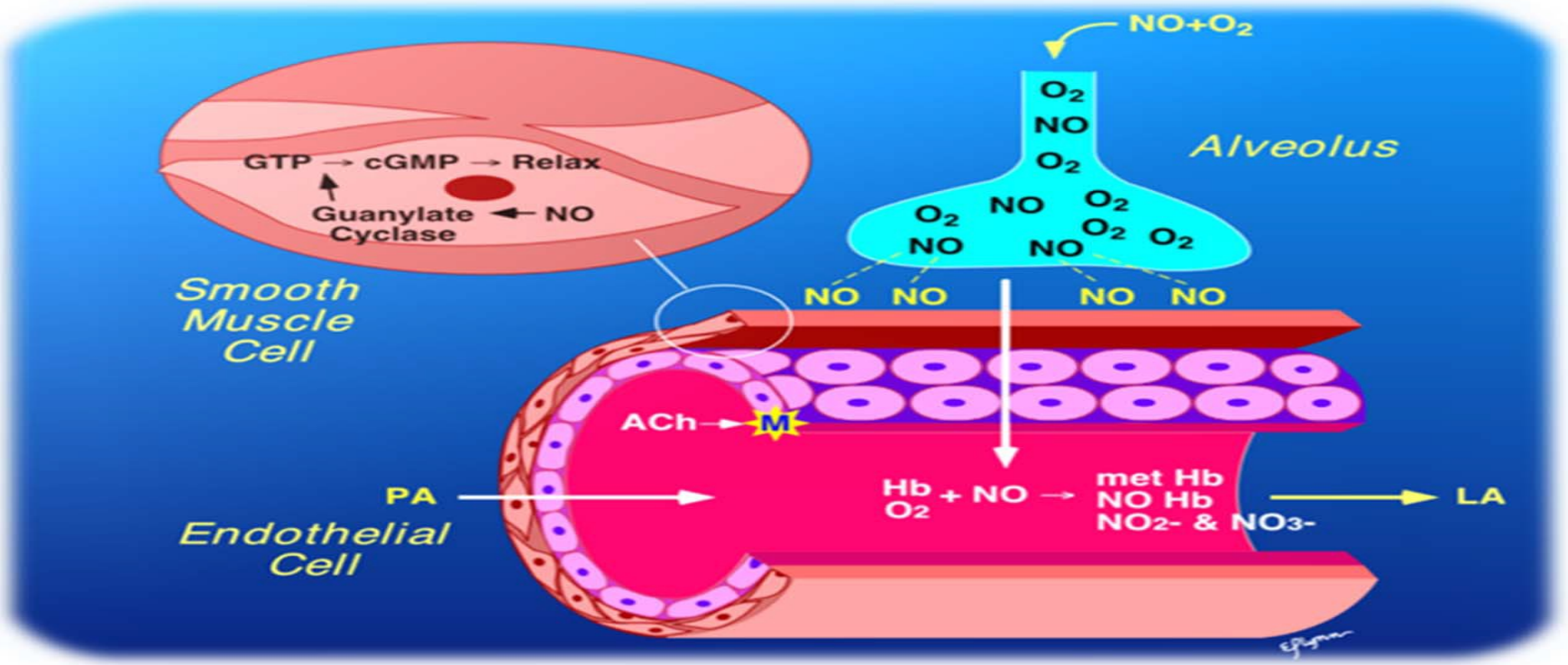
Replaces external ‘heart/lung’ support; alternative to forced oxygen therapy for infants

[1]Recent approval of device to be utilized along with MRI
Full prescribing information can be found at http://inomax.com/wp-content/uploads/2015/01/INOmax-PI-web-2013-03.pdf

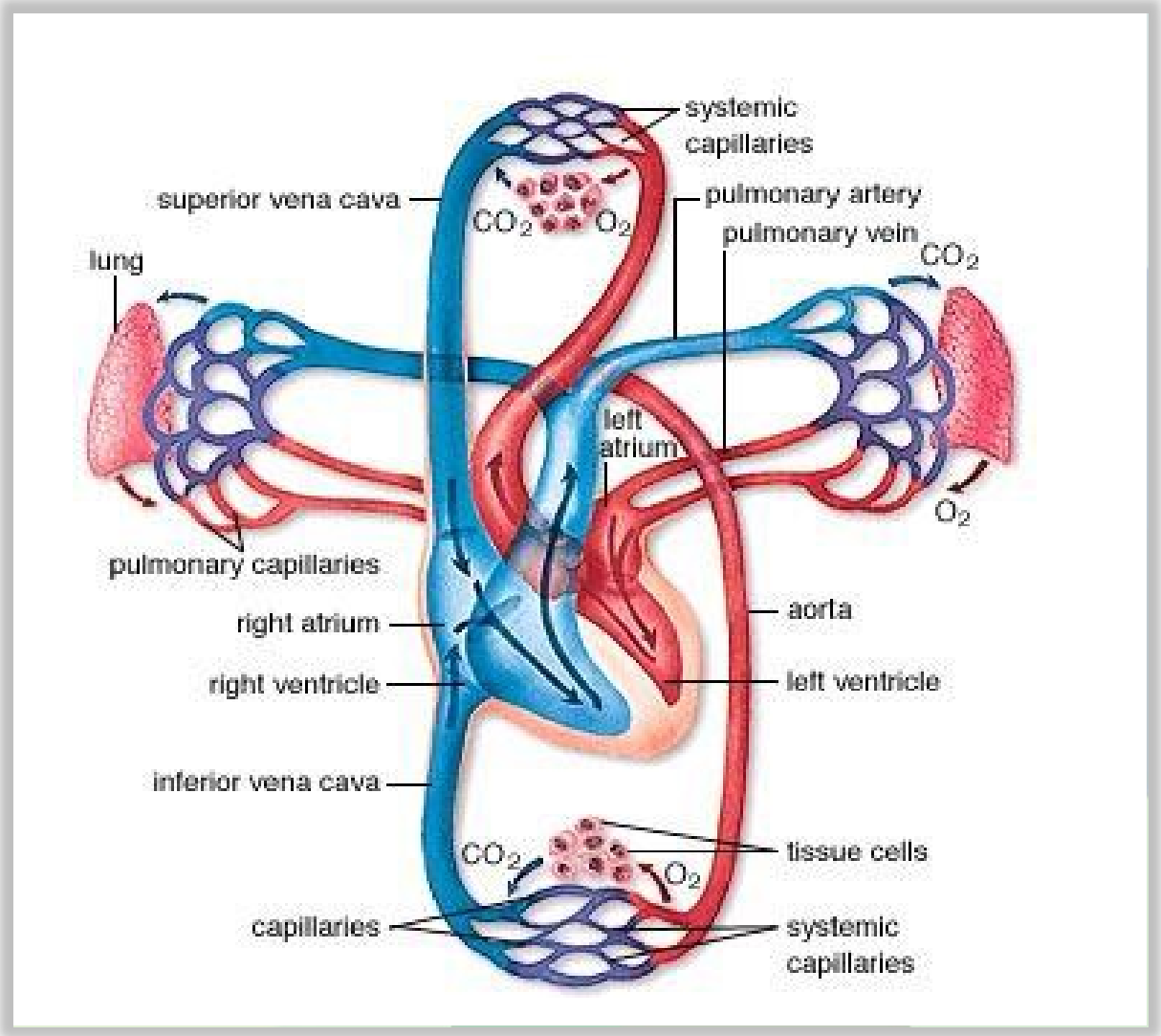
Inhaled nitric oxide (NO): a selective pulmonary vasodilator

Naturally occurring signaling molecule

- NO triggers complex biological cascade: relaxes vascular smooth muscle, dilates pulmonary vessels and improves oxygenation



INOMAX hemodynamic and peripheral effects support exploration of LCM[1] opportunities in CV[2], transplantation and neuroprotection



Peripheral

Hemodynamic

Vasodilation

Lungs

Heart & Lungs

Other Systems

Standard of Care Approved

Standard of Care in select OUS Markets

Proof of concept for iNO[3]

[1]LCM: lifecycle management [2]CV: pulmonary hypertension associated with cardiac surgery [3]iNO: inhaled nitric oxide

Recently published pediatric pulmonary hypertension guidelines suggest future opportunities for iNO[1]

AHA/ATS Guideline

Pediatric Pulmonary Hypertension

Guidelines From the American Heart Association and American Thoracic Society

Steven H. Abman, MD, Co-Chair; Georg Hansmann, MD, PhD, FAHA, Co-Chair; Stephen L. Archer, MD, FAHA, Co-Chair; D. Dunbar Ivy, MD, FAHA; Ian Adatia, MD; Wendy K. Chung, MD, PhD; Brian D. Hanna, MD; Erika B. Rosenzweig, MD; J. Usha Raj, MD; David Cornfield, MD; Kurt R. Stenmark, MD; Robin Steinhorn, MD, FAHA; Bernard Thébaud, MD, PhD; Jeffrey R. Fineman, MD; Titus Kuehne, MD; Jeffrey A. Feinstein, MD; Mark K. Friedberg, MD; Michael Earing, MD; Robyn J. Barst, MD†; Roberta L. Keller, MD; John P. Kinsella, MD; Mary Mullen, MD, PhD; Robin Deterding, MD; Thomas Kulik, MD; George Mallory, MD; Tilman Humpl, MD; David L. Wessel, MD; on behalf of the American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Surgery and Anesthesia; and the American Thoracic Society

Abstract—Pulmonary hypertension is associated with diverse cardiac, pulmonary, and systemic diseases in neonates, infants, and older children and contributes to significant morbidity and mortality. However, current approaches to caring for pediatric patients with pulmonary hypertension have been limited by the lack of consensus guidelines from experts in the field. In a joint effort from the American Heart Association and American Thoracic Society, a panel of experienced clinicians and clinician-scientists was assembled to review the current literature and to make recommendations on the diagnosis, evaluation, and treatment of pediatric pulmonary hypertension. This publication presents the results of extensive literature reviews, discussions, and formal scoring of recommendations for the care of children with pulmonary hypertension. (***Circulation***. **2015;132:00-00. DOI: 10.1161/CIR.0000000000000329.**)

Key Words: AHA Scientific Statements ▪ bronchopulmonary dysplasia ▪ congenital diaphragmatic hernia ▪ congenital heart disease ▪ genetics ▪ persistent pulmonary hypertension of the newborn ▪ sickle cell disease

Pediatric Recommendations

- Persistent pulmonary hypertension of the Newborn
- Congenital diaphragmatic hernia
- Bronchopulmonary dysplasia
- Pediatric heart disease

[1]*Circulation November 24, 2015, http://circ.ahajournals.org, DOI: 10.1161/CIR.0000000000000329*

Establishing preemie registry to evaluate INOMAX benefit

Assess effectiveness of iNO in premature neonates with pulmonary hypertension (PH)

- Prospective, 2 cohort, registry
- Multicenter, 60 US sites
- 150 subjects

Objectives

- *Highlight frequency of PH*
- *Collect data to support iNO use*
- *Obtain real-world experience*
- *Characterize need for iNO in high-risk neonates*

Effectiveness Evaluation

Measures being evaluated:

- *Meet ECMO criteria*
- *All cause mortality*
- *Respiratory response*
- *Days on ventilation & in ICU*
- *Acute response*

ECMO: extracorporeal membrane oxygenation, ICU: intensive care unit

OFIRMEV: Acute pain management

OFIRMEV™
(acetaminophen) injection
1000 mg/100 mL (10 mg/mL)

Clinical trials done in multiple surgical conditions:

- Orthopedic surgery
- Acute renal colic
- Abdominal laparoscopy
- Abdominal hysterectomy

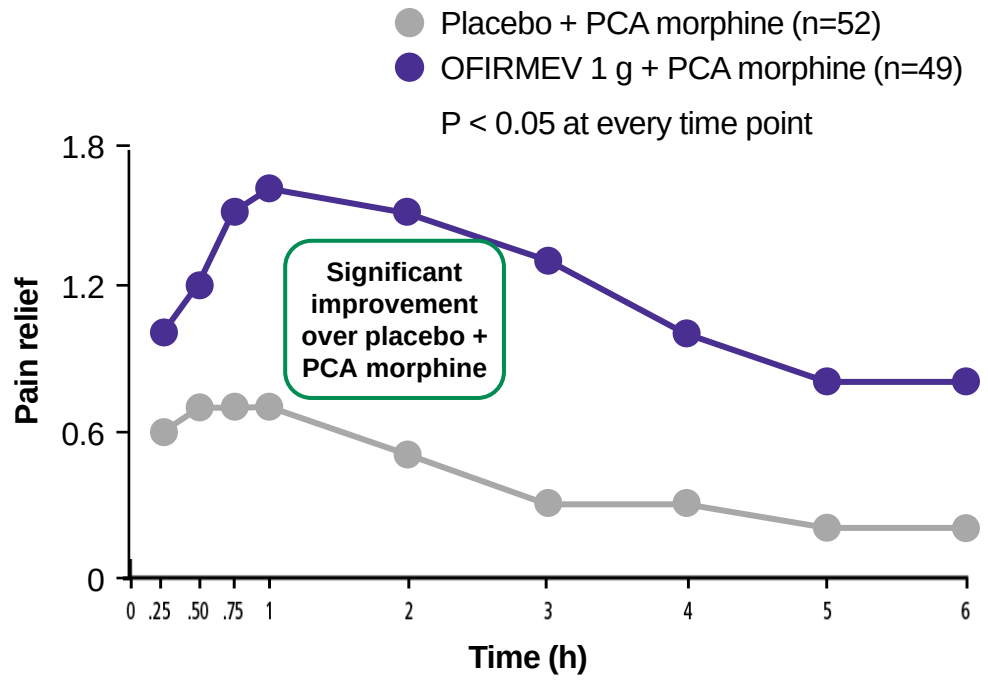
Additional Phase 4 trials currently being conducted:

- UVB burn pain model
- Knee replacement
- Opioid interaction

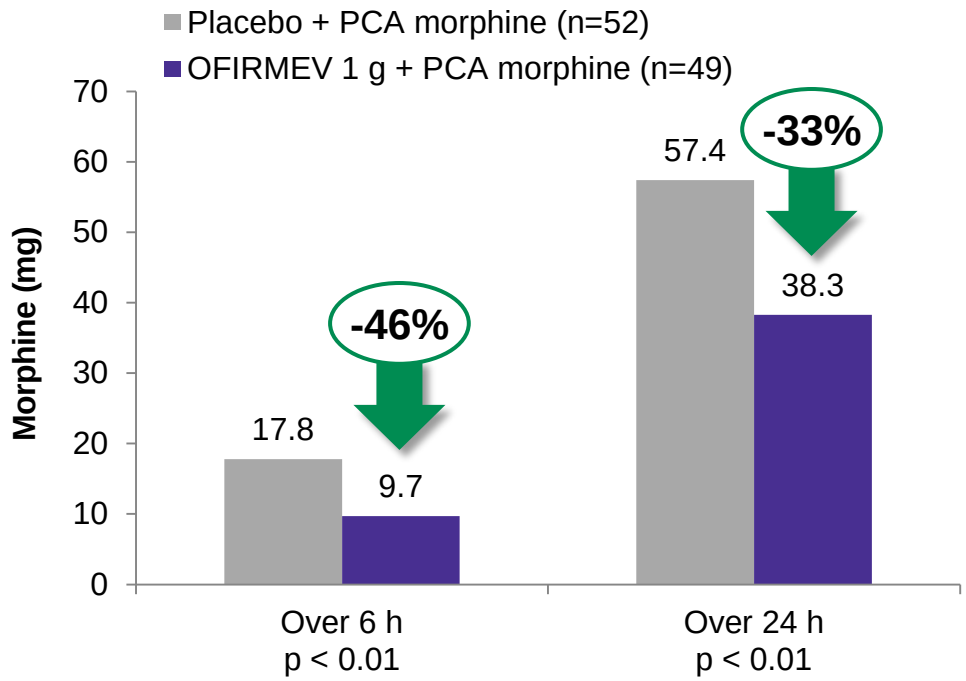
UVB: Ultraviolet B
Full prescribing information can be found at http://www.ofirmev.com/Prescribing-Information.aspx

IV acetaminophen improves pain management and reduces opioid requirements in surgical patients

Mean pain relief scores, single dose[1] (Total hip or knee replacement surgery)



Reduction in morphine consumption (Total hip or knee replacement surgery)



Sinatra et al. (Pain Study 1) Randomized, double-blind, placebo-controlled, single- and repeated-dose 24-h study (n=101). Patients received OFIRMEV 1 g + PCA morphine or placebo + PCA morphine the morning following total hip or knee replacement surgery. Primary endpoint: pain relief measured on a 5-point verbal scale over 6 h. Morphine rescue was administered as needed.
[1]OFIRMEV + PCA morphine significantly reduced morphine consumption vs placebo + PCA morphine

HEOR demonstrates OFIRMEV value, differentiates from alternative therapies, addresses unmet need

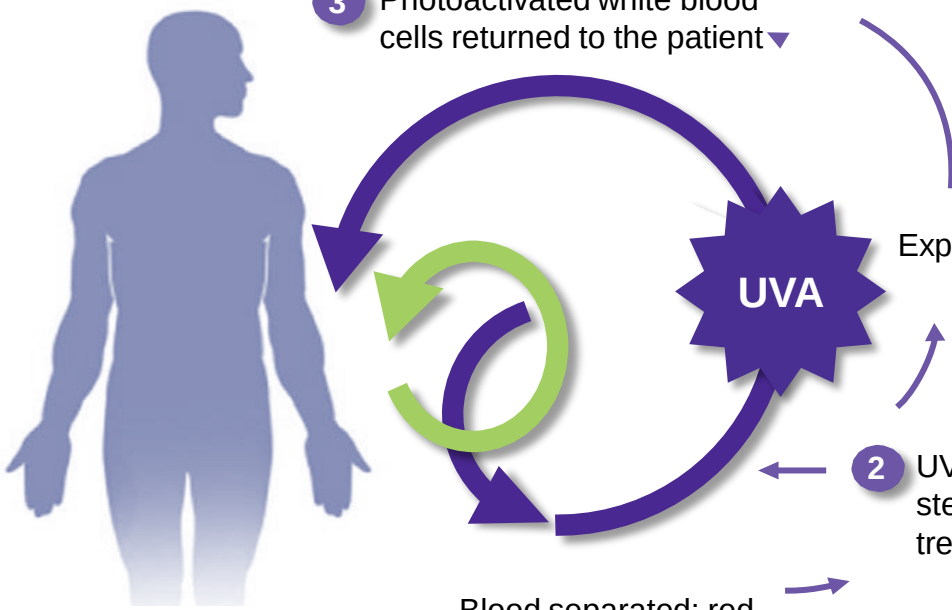
Leverage Large Datasets	Objectives	Completion
Retrospective Study: Marketscan	▸ Compare resource use & cost of IV acetaminophen ± other analgesics vs. IV opioid monotherapy in post-op pain	▸ 1H 2016
Retrospective Study: Premier	▸ Compare resource use & cost of IV acetaminophen ± other analgesics vs. IV opioid monotherapy in post-operative pain	▸ 1H 2016
Retrospective Study: Crimson	▸ Estimate cost savings related to decreased opioid use and increased OFIRMEV use	▸ 1H 2016
Systemic Review: MMA	▸ Conduct MMA literature review of IV acetaminophen vs. IV opioid monotherapy	▸ 2H 2016
Pooled Analysis of RCTs	▸ Examine benefits of reduced opioid consumption (pain relief, satisfaction, adverse events, outcomes)	▸ 1H 2016
AMCP Dossier Update	▸ Provide dossier & summary of clinical and economic value for use in formulary decision-making	▸ 2H 2016

RCT: randomized controlled trial

Therakos immunotherapy used globally in oncology, transplant and autoimmune diseases

Therakos™ PHOTOPHERESIS

- Average 25-40 treatments/year per patient
- One vial of UVADEX and one sterile kit per treatment
- Over 120,000 treatments globally in 2014



UVA: Ultraviolet-A
Full prescribing information can be found at http://www.therakos.com/#!full-prescribing-information/c1vn5

ECP effects systemic immunomodulation across a variety of cell populations and processes

Targeted cell / process	Immunoscience category
Eradication of malignant T-cell populations • Eradication or downregulation of clonal populations	Immuno-oncology
Shift in APC populations • Modulation of myeloid and plasmacytoid dendritic cell populations	Immuno-oncology Transplant immunology
Shift in cytokine secretion • From Th1 cytokine profile (pro-inflammatory) to Th2 cytokine profile (anti-inflammatory)	Transplant immunology Inflammation & immunology
Induction of Tregs • Establish and maintain self tolerance • Selectively modulate the activation of self-reactive T-cells	Transplant immunology Inflammation & immunology
Alteration of B-cell signaling/populations • ECP response is associated with decreased BAff signaling and lower proportion of immature B cells	Transplant immunology Inflammation & immunology
Increase in myeloid-derived suppressor cells • Establish and maintain self tolerance • Selectively modulate the activation of self-reactive T-cells	Transplant immunology Inflammation & immunology

Source: Whittle RM, et al. Mechanism of action of ECP – clinical evidence. In: Greinix HT, Knobler R, eds. Extracorporeal Photopheresis: Cellular Photoimmunotherapy. Berlin/Boston: Walter de Gruyter GmbH & Co.; 2012:65-81. APC: antigen-presenting cell, BAff, B-cell associated factor, ECP: extracorporeal photopheresis, Th1/2: T helper cell type 1/2

UVADEX: aGvHD - Phase 3 study design

Evaluate Efficacy of UVADEX in conjunction with CELLEX® Photopheresis System in pediatric patients with steroid-refractory aGvHD

- **Phase 3, single-arm, open-label, multicenter**
- 48 subjects with steroid-refractory aGvHD grade B-C
- 12 weeks of ECP study treatment:
  - Weeks 1-4: 3 treatments per week
  - Weeks 5-12: 2 treatments per week

Primary Efficacy Endpoint

ECP Efficacy

Proportion of patients who achieve overall response after 4 weeks (day 28) of ECP treatment

Patients will be assessed for presence or absence of aGvHD manifestations of skin, liver, and gut

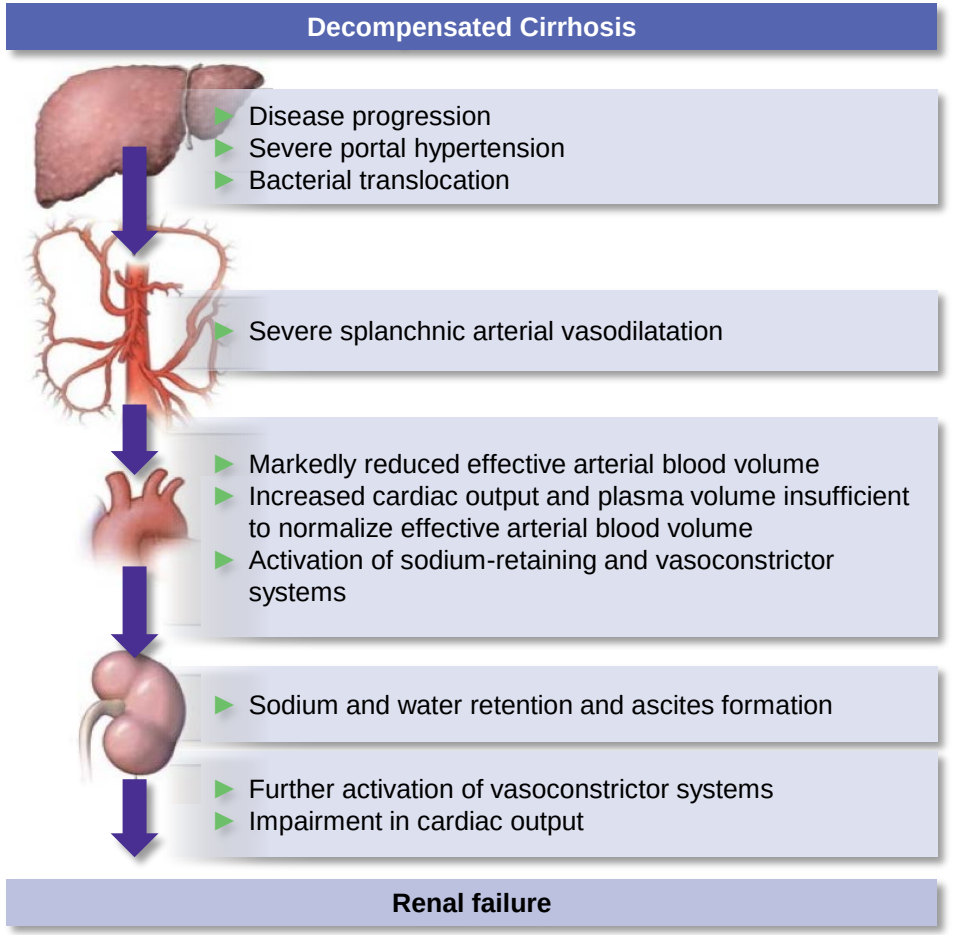
Terlipressin is global standard of care for type 1-hepatorenal syndrome (HRS-1)

Ongoing Phase 3 US development program

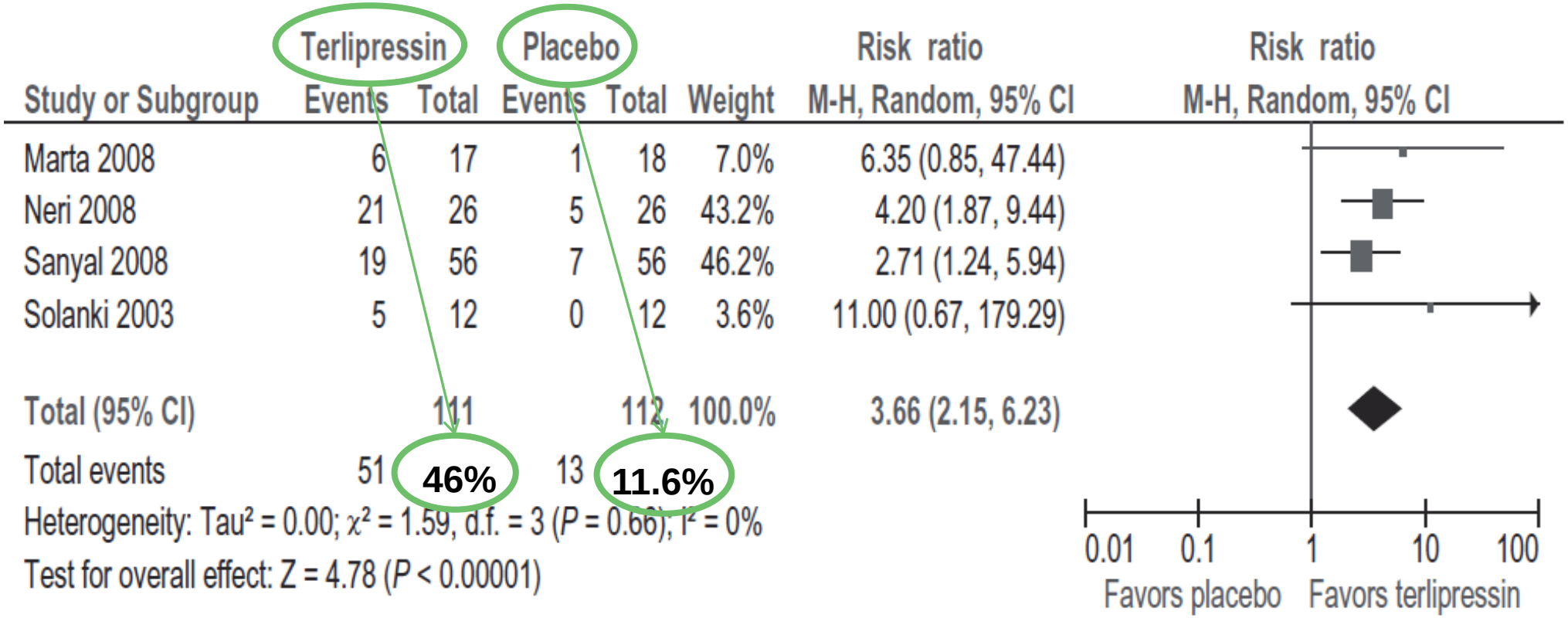
- HRS-1 is rare, life-threatening complication of cirrhosis of the liver
- Affects >10,000 patients in US[1-4]; high mortality rates
- Condition leads to multi-organ failure[5,6] including acute kidney failure [5,6]
- Kidneys appear structurally normal on diagnostic imaging[5,6]
- Survival improves with early diagnosis and treatment[5,6]

1. Boyer TD et al. *Open Access Journal of Clinical Trials*. 2012;4:39-49.
2. Marrero J *et al. Am J Respir Crit Care Med.* 2003;168:1421-1426.
3. Muir AJ et al. *Liver Transpl.* 2002;8:957-961.
4. Gines A et al. *Gastroenterology.* 1993;105:229-236.
5. Barbano B et al. *Curr Vasc Pharmacol*. 2014;12:125-135.
6. Low G et al. *Gastroenterol Res Pract.* 2015;2015:207012. doi: 10.1155/2015/207012. Epub 2015 Jan 12.

Pathophysiology of HRS

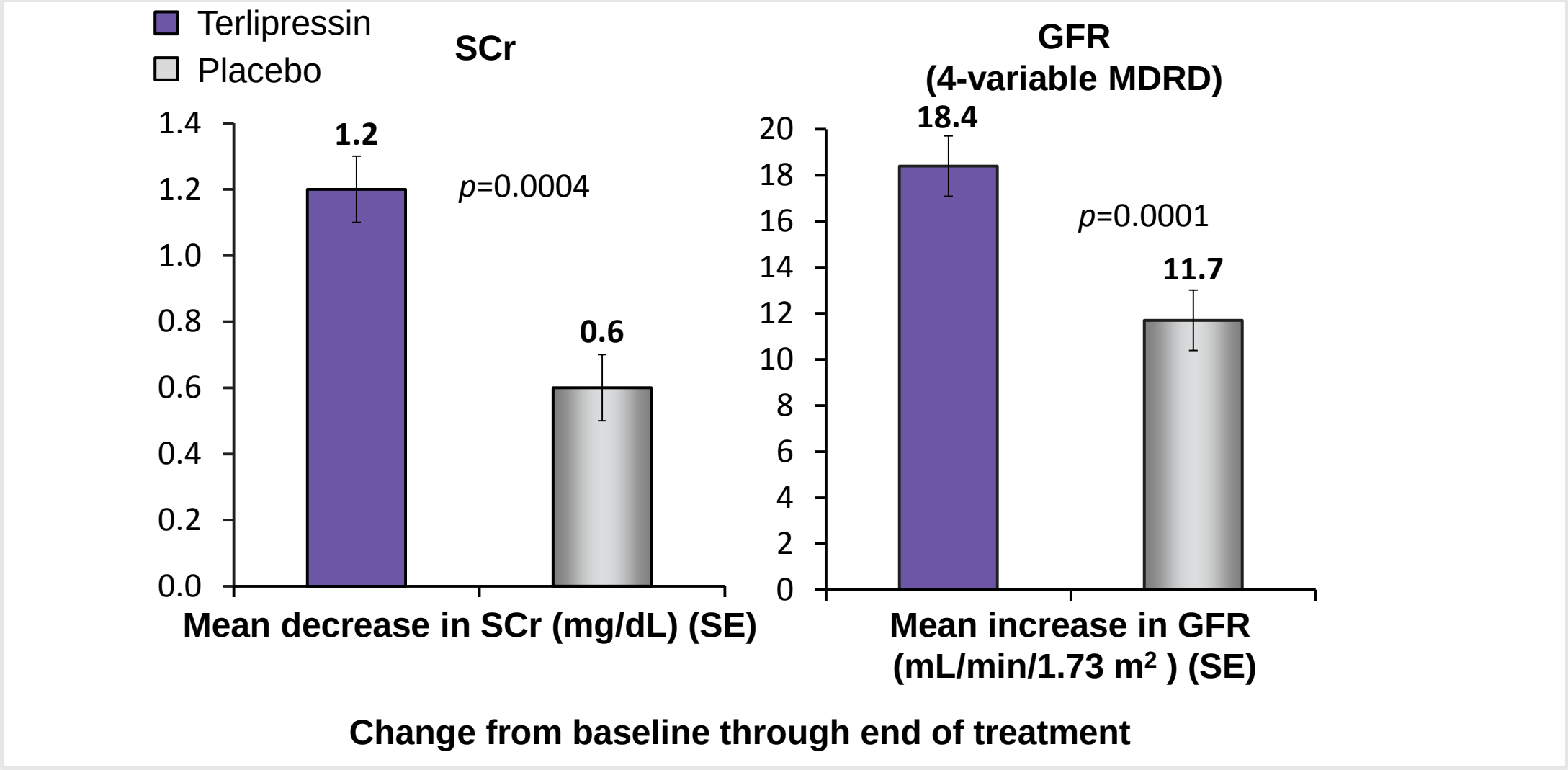


Terlipressin treatment reverses HRS-1 across all studies



Modified from: Sagi SV, et al. *J Gastroenterol Hepatol.* 2010;25:880-885.

REVERSE: Significant improvement in renal function



Boyer TD, Sanyal AJ, Wong F, et al. Initial report of a large, randomized, double-blind, placebo-controlled, phase 3 trial of terlipressin plus albumin for the treatment of Type 1 hepatorenal syndrome (HRS-1): The REVERSE study. *Hepatology.* 2014;60:255A.

GFR: glomerular filtration rate, MDRD: Modification of Diet in Renal Disease, SCr: serum creatinine

Terlipressin: HRS Type-1 Phase 3 CONFIRM study design

Evaluate efficacy of terlipressin in subjects with cirrhosis, ascites, and a diagnosis of HRS type I

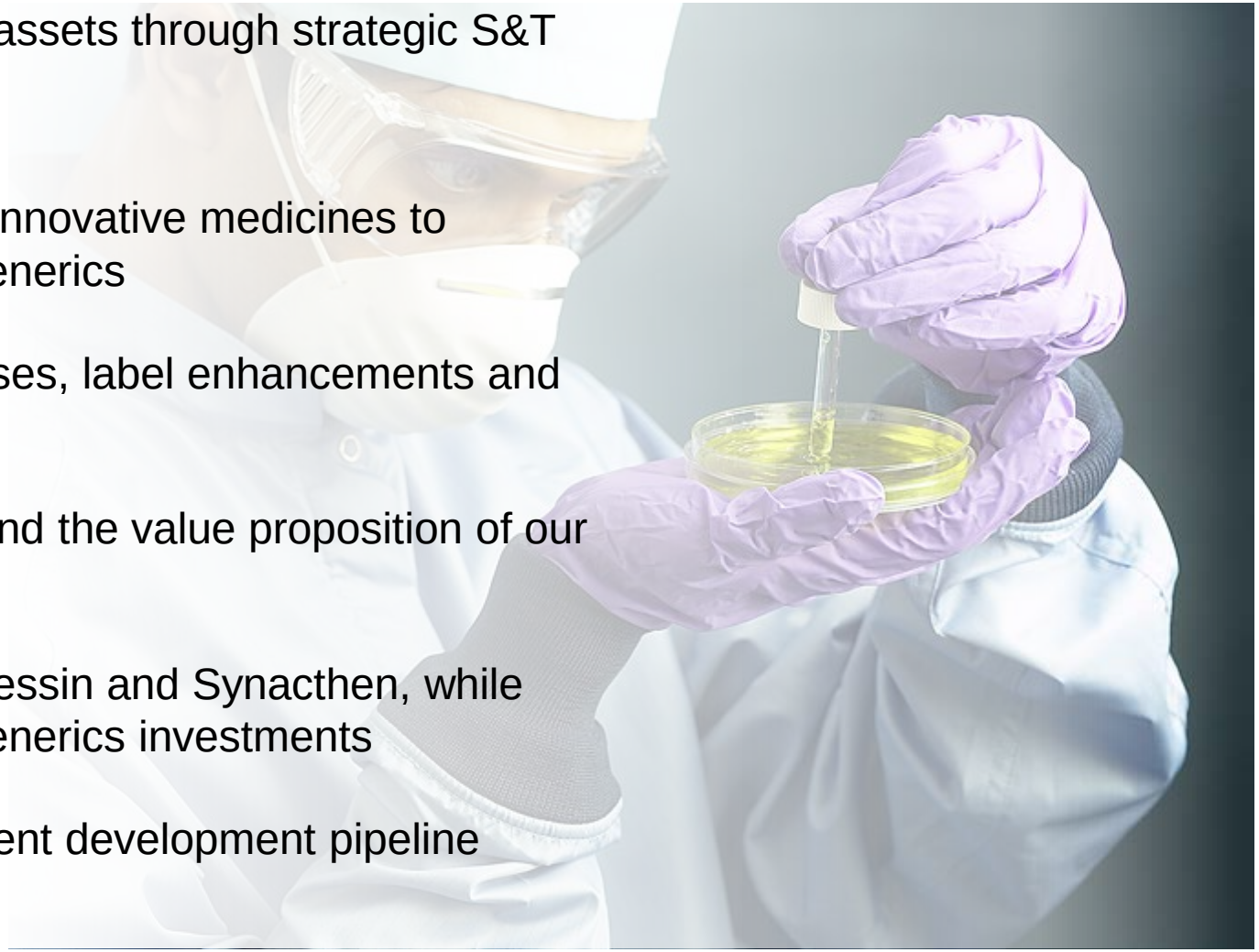
- **Phase 3, randomized, double-blind, placebo-controlled**
  - Evaluating terlipressin (1 mg IV q6h) vs placebo
  - ~200 subjects
  - Multicenter, 25-45 sites

Primary Efficacy Endpoint

Confirm HRS reversal
% of subjects with SCr ≤ 1.5 mg/dL on treatment by / before Day 14 or discharge

Mallinckrodt Science and Technology: Building for the future

- Enhance the value of acquired assets through strategic S&T priorities
- Establish a portfolio of durable innovative medicines to complement legacy specialty generics
- Extend evidence in approved uses, label enhancements and new indications
- Invest in HEOR studies to expand the value proposition of our brands
- Advance development of terlipressin and Synacthen, while supporting targeted specialty generics investments
- Evaluate opportunities to augment development pipeline through BD&L



Medical Experts Hosting Poster Stations

Acthar

Richard Furie, MD
Chief, Division of Rheumatology, North Shore-LIJ Health System
Professor of Medicine, Hofstra North Shore-LIJ School of Medicine
Great Neck, NY

James Tumlin, MD
Professor of Medicine, University of Tennessee College of Medicine
Director, Southeast Renal Research Institute, Nephrology Associates
Chattanooga, TN

Terlipressin

Samuel Sigal, MD, FACG
Chief of Clinical and Translational Liver Research
Montefiore Medical Center and the Albert Einstein College of Medicine
Transplant Hepatologist
New York, NY

Acthar

Patrice Becker, MD
Vice President, Medicines Team Lead
Autoimmune & Rare Diseases
Mallinckrodt Pharmaceuticals

George J Wan, PhD, MPH
Vice President, Head of Health Economics Outcomes Research
Mallinckrodt Pharmaceuticals

Terlipressin

Khurram Jamil, MD
Senior Medical Director, Clinical Sciences
Mallinckrodt Pharmaceuticals

INOMAX

Ravi Tayi, MD, MPH
Vice President, Medical Affairs
Mallinckrodt Pharmaceuticals

UVADEX

Dennis Briggs, MBA
Vice President, R&D at Therakos, Inc.
Mallinckrodt Pharmaceuticals

Christian Peters, MD, PhD
Chief Medical Officer, R & D at Therakos, Inc.
Mallinckrodt Pharmaceuticals

OFIRMEV

Lawrence A Hill, PharmD, MBA, RPh, BCPS
Senior Director, Clinical Sciences
Mallinckrodt Pharmaceuticals

Poster Session Stations

Acthar

- Scientific Posters
  - ACR 2015: SLE
  - HEOR AMCP Nexus Posters
    - Benefits of Early vs. Late Treatment in Infantile Spasms
    - Resource Use and Costs in Multiple Sclerosis Relapse
    - Healthcare Resource Use and Work Productivity Loss Burden of Dermatomyositis/Polymyositis
- Brand/disease overview
- Therapeutic areas overview
- Pre/non-clinical overview
- FSGS study design

INOMAX

- INOMAX product overview
- Brand/disease overview
- INOMAX product for demonstration

Terlipressin

- Scientific Poster: (AASLD 2014) Reversal of Hepatorenal Syndrome Type 1 (HRS-1) with Terlipressin plus Albumin versus Placebo plus Albumin - Not All Responses Are Created Equal: An Analysis of the REVERSE and OT-0401 Trials
- CONFIRM study design
- Brand/disease overview

UVADEX/THERAKOS

- Scientific Poster (ASH): Efficacy of Extracorporeal Photopheresis (ECP) Monotherapy in the Treatment of Cutaneous T-Cell Lymphoma
- Brand/disease overview
- aGVHD study design
- THERAKOS product for demonstration

OFIRMEV

- Clinical data poster
- Brand/disease overview