Mallinckrodt Pharmaceuticals:

Investor Briefing 2017 Presentation
Research and Development

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Executive Vice President and
Chief Scientific Officer

October 4, 2017

Mallinckrodt Pharmaceuticals

Mallinckrodt's pipeline spans all phases of development

- Building diverse, durable portfolio of innovative therapies that provide value to patients, physicians and payers
- Extending the value of our in-line portfolio through Phase 4 studies and product enhancements
- Advancing substantial set of development programs to key milestones

We've transformed and strengthened S&T[1] leadership and capabilities

Evolved organization to enhance capabilities and functional leadership

- ✓ Created **Clinical Development** organization distinct from **Research** technical platforms
- ✓ Deepened scientific and **Therapeutic Area** knowledge across functions
- ✓ Established dedicated **Specialty Generics R&D[2]** to support productivity targets
- ✓ Established a **CMO[3]** organization to provide branded medical support
  - ✓ Enhanced customer-centric **Medical Affairs** capabilities (Medical Directors and MSLs[4])
  - ✓ Built value-based evidence generation expertise in **HEOR[5]**
  - ✓ Transitioned **PV[6]/Safety** focus from reporting to analytics
- ✓ Established **Device Engineering** center of excellence in Dublin
- ✓ Expanded **Regenerative Medicine** expertise through acquisition of StrataGraft/ExpressGraft
- ✓ Created **Strategy & Innovation** function to steward BD&L[7] activities
- ✓ Reorganized **Regulatory Affairs** to augment strategic regulatory capabilities

1 Science & Technology
2 Research & Development
3 Chief Medical Office
4 Medical Science Liaisons
5 Health Economics Outcomes Research
6 Pharmacovigilance
7 Business Development & Licensing

Established premier Specialty Brands R&D expertise to support a growing innovative portfolio

Research Support

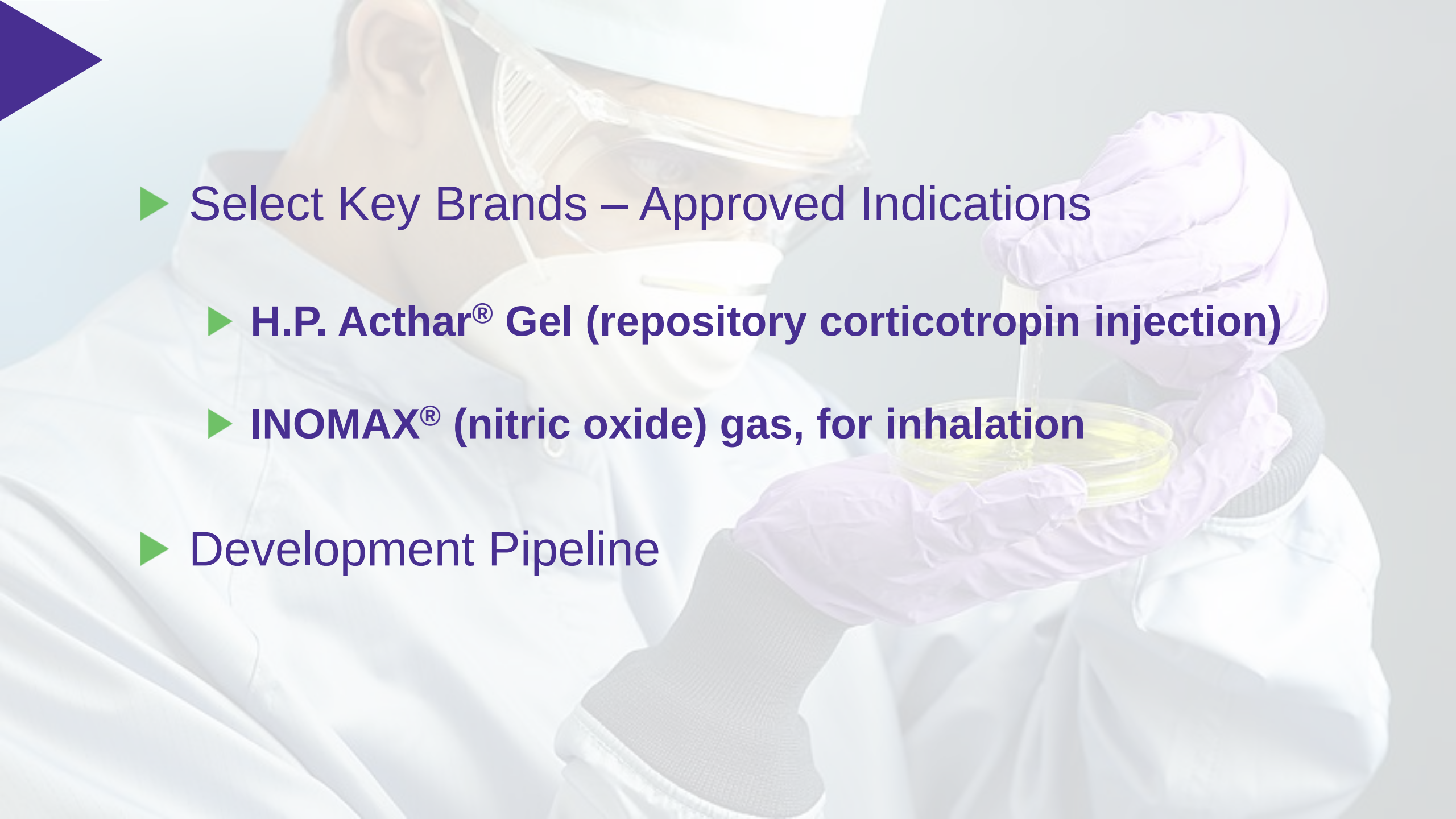
- *Analytical Chemistry*
- *Synthetic Chemistry*
- *Formulation Sciences*
- *Biological Sciences*
- *Pharmacology & Toxicology*

Asset Management

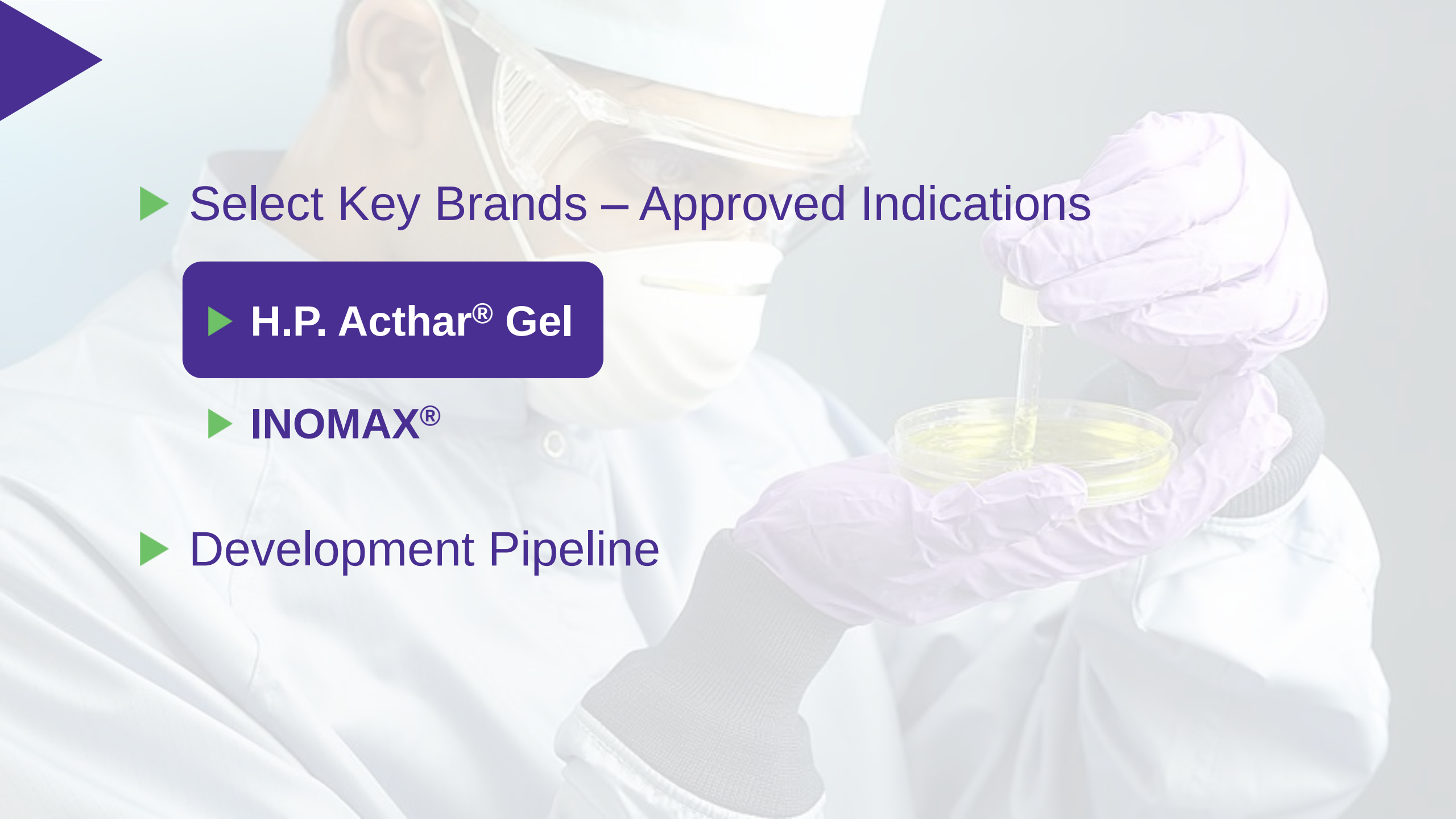
- *Development Planning*
- *Lifecycle Management / Product Enhancements*
- *Clinical Trial Methodology*
- *Clinical Trial Execution*
- *Scientific Communications*
- *Therapeutic Area / Disease Area Insight Generation*
- *Health Economics & Outcomes Research / Real World Analytics*

Regulatory Affairs Support

- *Global Regulatory Strategy*
- *Strategic Labeling*
- *Regulatory Intelligence*



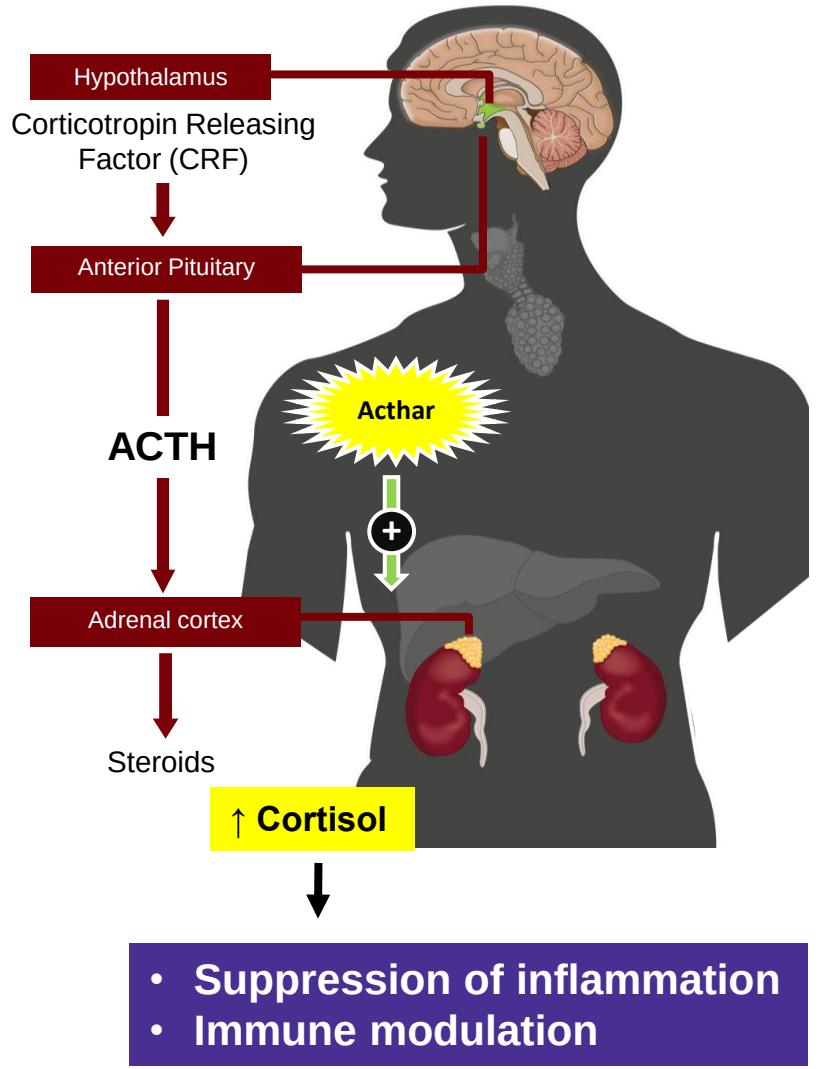
- Select Key Brands – Approved Indications
  - **H.P. Acthar® Gel (repository corticotropin injection)**
  - **INOMAX® (nitric oxide) gas, for inhalation**
- Development Pipeline



- Select Key Brands – Approved Indications
  - **H.P. Acthar® Gel**
  - **INOMAX®**
- Development Pipeline

How H.P. Acthar Gel is believed to work

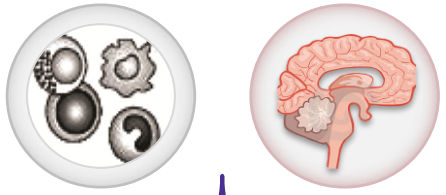
- H.P Acthar Gel delivers ACTH[1] in a prolonged-release formulation
- ACTH is believed to suppress inflammation in part via induction of steroidogenesis
  - One endogenous steroid produced is cortisol
  - Cortisol has anti-inflammatory properties
- Identification of the receptor mediating cortisol production led to the discovery that ACTH can bind to related receptors (called melanocortin receptors) expressed in cells and tissues throughout the body
- **While the exact mechanism of action of Acthar is unknown, further investigation is being conducted.**



1 adrenocorticotropic hormone

This information is based on nonclinical data and the relationship to clinical benefit is unknown.

H.P. Acthar Gel binds to the five melanocortin receptors (MCRs)[1-5]



MC1R

Immune cells

- Macrophages
- Monocytes
- Lymphocytes
- Neutrophils
- Dendritic cells
- Mast cells

Many other cells

MC3R

CNS cells

Immune cells

- Macrophages
- Lymphocytes
- Monocytes

Many other cells

MC4R

CNS microglia

Immune cells

- Macrophages
- Lymphocytes

Many other cells

MC5R

Immune cells

- Macrophages
- Lymphocytes
- Mast cells

- Many other cells

MC2R

Adrenal cortical cells

↓

Endogenous corticosteroids

↓

Steroid-dependent effects

Steroid-independent effects

Decreased Immune-Mediated Inflammation[1-4]

Possible Neuroprotection[4-5]

Steroidogenesis[1]

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.

Multiple indications supported by extensive clinical experience, published literature and clinical trials

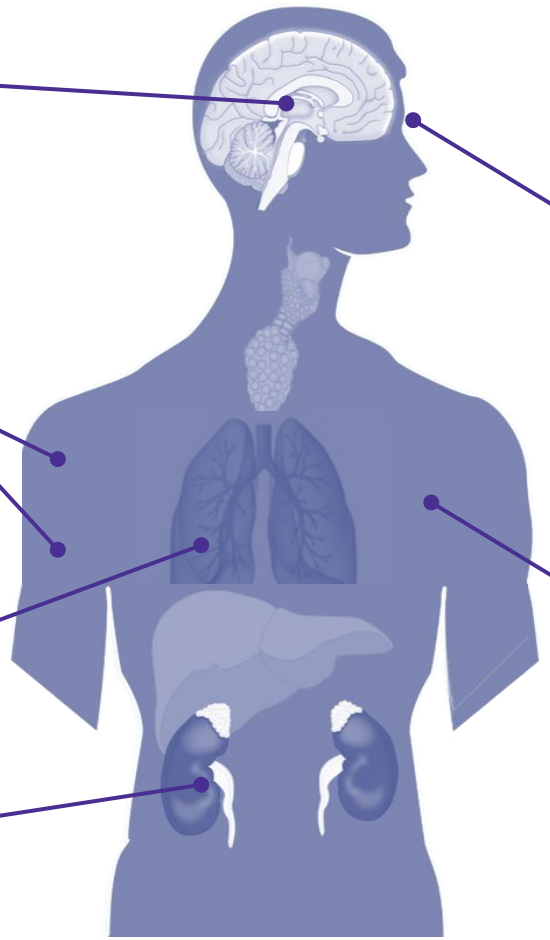
FDA-approved in 19 debilitating diseases/conditions; currently marketed in only 10 indications*

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

Since acquisition, H.P. Acthar Gel investments exceed $250 million, including R&D

Five Areas of Focus

- Expand evidence base
- Strengthen clinical profiles
- Generate compelling value proposition
- Deepen drug product knowledge base
- Establish differentiation from steroids

Five Areas of Focus

Expand evidence base

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Since acquiring H.P. Acthar Gel, Mallinckrodt has initiated critical controlled trials

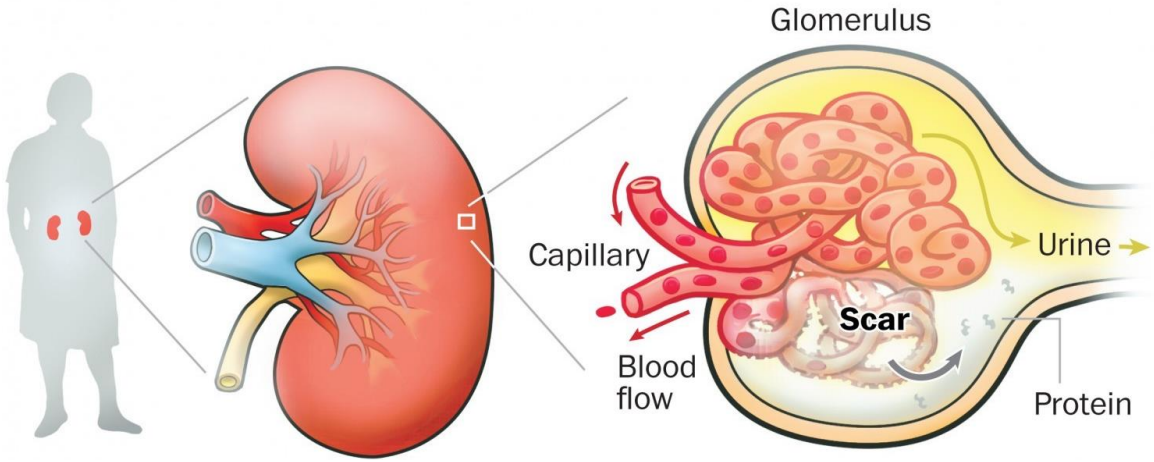
Design / Primary Objectives	Patients	Status	LPLV[6]	Data
FSGS[1]: Phase 4, randomized withdrawal study in Idiopathic FSGS subjects with treatment-resistant or treatment-intolerant proteinuria				
• Part 1: 24 weeks (open label), to evaluate induction of remission • Part 2: 24 weeks (placebo-controlled, double-blind, randomized withdrawal), to evaluate maintenance therapy	210	▶ Ongoing	1H2021	1H2022
SLE[2]: Phase 4, double-blind, placebo-controlled study in subjects with persistently active disease, despite moderate dose corticosteroids				
• Double-blind, placebo-controlled parallel group, 24-week treatment	~120	▶ Ongoing	1H2019	2H2019
MS[3]: Phase 4, pilot, randomized, placebo-controlled study in MS relapse subjects not responsive to corticosteroids				
• Double-blind, placebo-controlled parallel group: 14-day treatment, followed by ~45 day follow-up period	~65	▶ Ongoing	2H2018	1H2019
RA[4]: Phase 4, 2-part study in treatment-resistant subjects with persistently active rheumatoid disease				
• Part 1: 12 weeks (open label) • Part 2: 12 weeks (double-blind, placebo-controlled, randomized maintenance)	~230	▶ Ongoing	2H2020	1H2021
ALS[5]: Phase 2, double-blind, placebo-controlled study in subjects with ALS				
• Double-blind, placebo-controlled parallel group, 36-week treatment	~180	▶ Ongoing	2H2019	1H2020

1 Focal Segmental Glomerulosclerosis
2 Systemic Lupus Erythematosus
3 Multiple Sclerosis
4 Rheumatoid Arthritis
5 Amyotrophic Lateral Sclerosis
6 Last Patient Last Visit

FSGS: Focal Segmental Glomerulosclerosis

- H.P. Acthar Gel is approved to induce a diuresis or remission of proteinuria in idiopathic nephrotic syndrome (NS)
- Major cause of idiopathic NS is FSGS
- FSGS is:
  - Most common glomerular disorder causing end-stage renal disease (ESRD) in U.S.
  - ~50% of affected patients develop ESRD over period of 5 to 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[1]

Idiopathic glomerular diseases can cause proteinuria and nephrotic syndrome



Source: NKF, National Kidney Foundation

1 Clin J Am Soc Nephrol. 2013 Dec 6; 8(12): 2072–2081. Published online 2013 Sep 5. doi: 10.2215/CJN.02840313

FSGS Phase 4 study design: Randomized withdrawal

Confirm efficacy in induction and maintenance of remission of proteinuria:
Subjects resistant to or intolerant of immunosuppressive therapies, including but not limited to corticosteroids or CNIs[1]

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

Two-Part Prospective Study

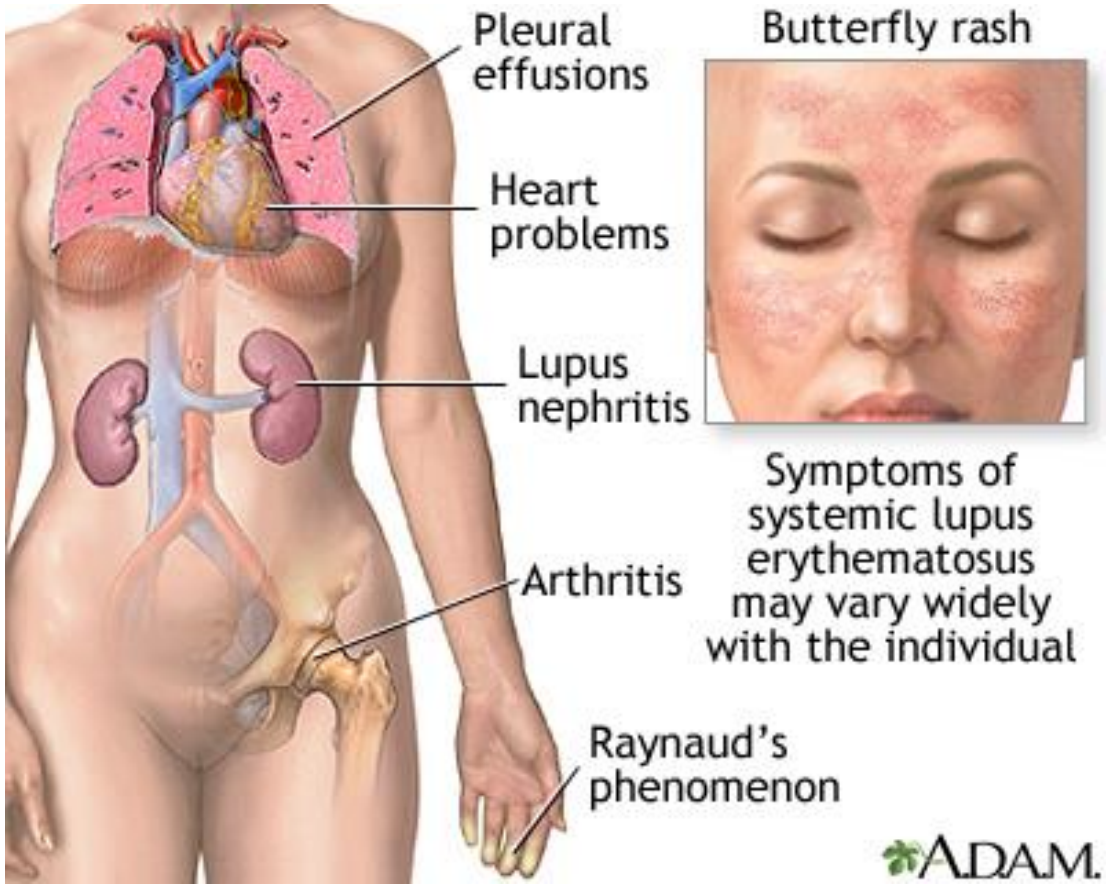
Part 1
24-week open label: evaluate induction of remission (80 units (U) 3x/week)

Part 2
24-week PC[2], DB[3] randomized withdrawal: evaluate maintenance therapy (80U 2x/week)

1 calcineurin inhibitors
2 placebo-controlled
3 double-blind

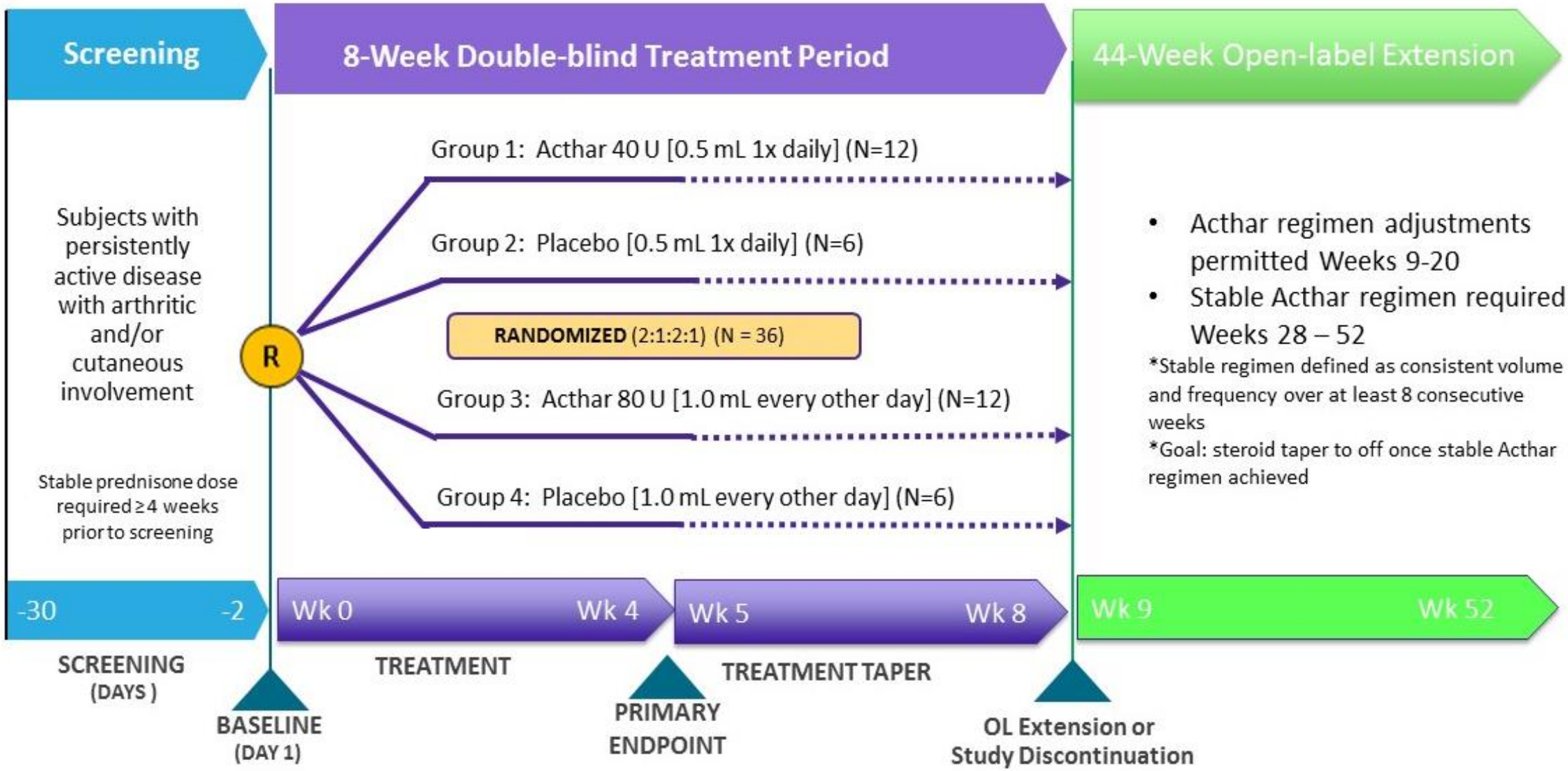
SLE: Systemic Lupus Erythematosus

- SLE is a heterogeneous autoimmune disease that 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 refractory to conventional treatment
- Nonclinical and ex-vivo data support H.P. Acthar Gel's clinical efficacy in SLE

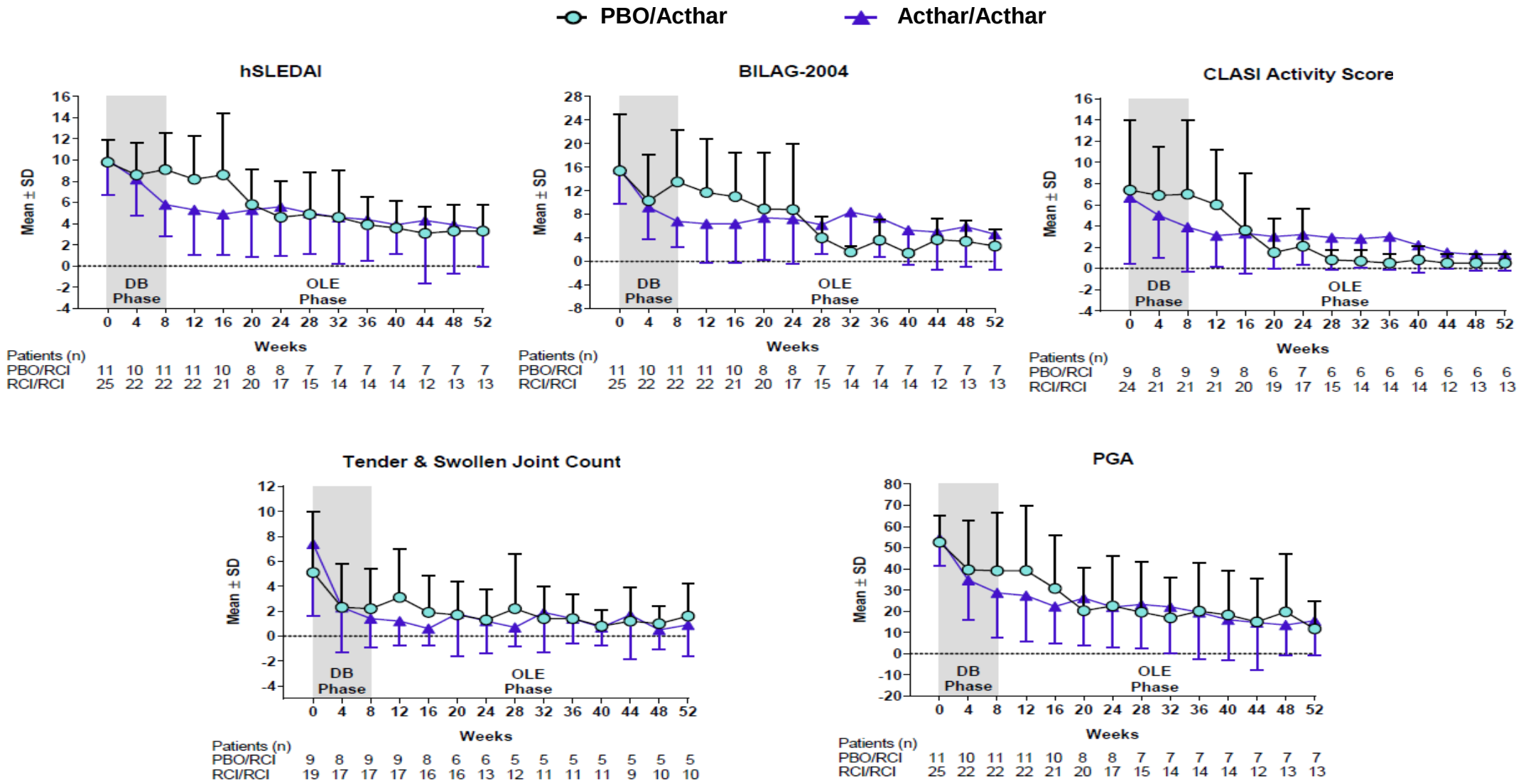


https://www.nlm.nih.gov/medlineplus/ency/article/000435.htm

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

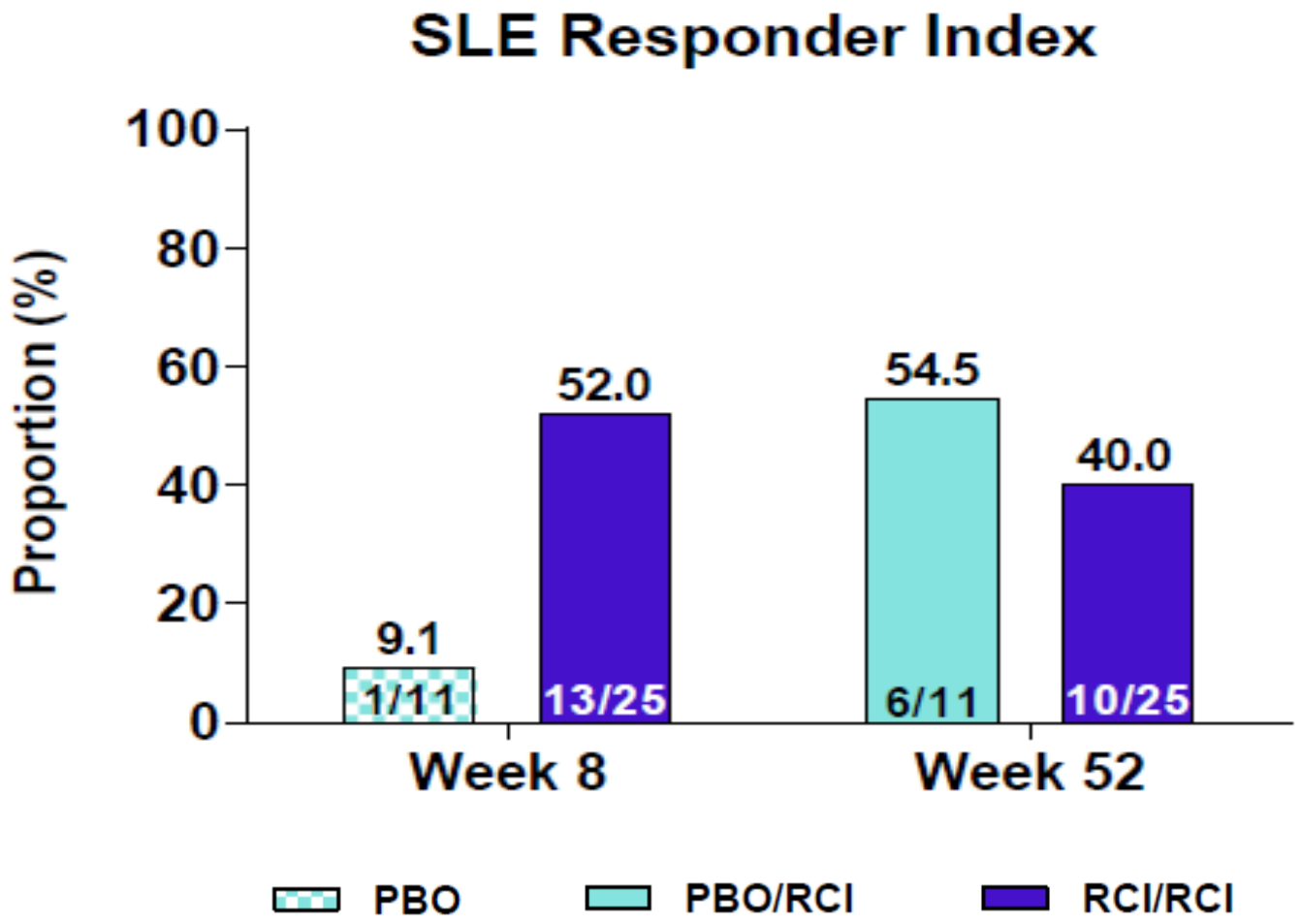


SLE Phase 4 pilot study results: Disease activity measures over time favored H.P. Acthar Gel



PBO: placebo, RCI: repository corticotropininjection

SLE Phase 4 pilot study results: Proportion of responders



PBO: placebo, RCI: repository corticotropininjection

Five Areas of Focus

Expand evidence base

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Prospective MS[1] relapse registry established to strengthen clinical profile: over 100 patients enrolled to date

Study impact of H.P. Acthar Gel in treatment of acute MS relapse:
six-month monitoring following initial and any subsequent relapses

- **Prospective, observational, longitudinal study**
- Multicenter, 75 U.S. sites
- 260 subjects

Objectives

Describe treatment history and characteristics

Understand dosing regimens

Document safety and tolerability profile

Determine impact of therapy

Endpoints

Kurtzke Expanded Disability Status score (EDSS)

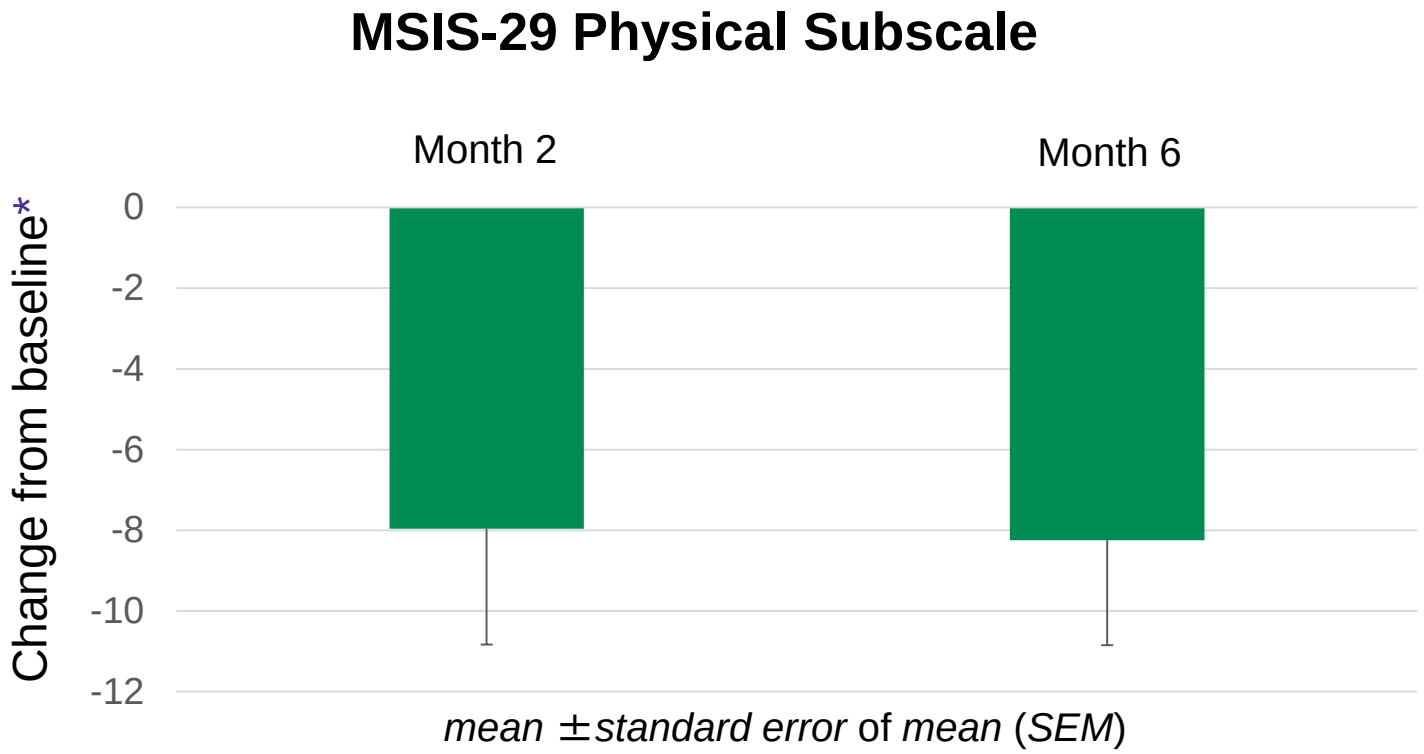
MS Impact scale (MSIS-29)

Clinical Global Impression of Improvement Scale (CGI-I)

1 Multiple Sclerosis

MS Relapse Registry: Preliminary results show clinically meaningful improvements are sustained over time

- Change from baseline in MS Impact Score-29 Physical subscale for first 67 patients enrolled in the registry



* ≥ 8 point reduction from baseline in MSIS-29 physical subscale is considered a clinically meaningful improvement[1]

1 Costelloe et al. 2007

Five Areas of Focus

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Generating health economics and outcomes research data to reinforce value of H.P. Acthar Gel in appropriate patients

Research Priorities

- Demonstrate value in real world settings

Key Value Messages

- Reduced resource use
- Medical cost offsets
- Reduced medication use (corticosteroids)

Highlights of Recent Data Presentations

Advances in Therapy 2017: Epub ahead of print.

- Summary review of **16 clinical** and **six economic studies** on Acthar

Journal of Medical Economics 2017: Epub ahead of print.

- **SLE**[1]: Acthar showed **medical cost offset of 32-37%** due to reduced hospitalization costs
- **RA**[2]: **Medical cost offset of 14-30%** due to reduced costs for all medical services

ClinicoEconomics and Outcomes Research 2017; 9:271-279.

- **DM/PM**[3]: Acthar's **medical costs lower (23%-75%)** than IVIG[4], rituximab, or IVIG + rituximab

Advances in Therapy 2016; 33(8): 1279-1292.

- **MS**[5]: Acthar vs. Plasmapheresis/IVIG showed medical cost offsets due to decreases in inpatient and outpatient costs (**93% cost offset at 12 months; full cost offset at 24 months**)

Journal of Pharmacy Technology 2017; 33(4): 151-155.

- **RA, SLE, DM/PM**: After Acthar initiation, **use of corticosteroids significantly reduced**

There are currently 30 new and ongoing HEOR[6] studies

1 Systemic Lupus Erythematosus
2 Rheumatoid Arthritis
3 Dermatomyositis/Polymyositis
4 Intravenous Immunoglobulin
5 Multiple Sclerosis
6 Health Economics and Outcomes Research

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- **Deepen drug product knowledge base**
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- **Establish differentiation from steroids**

Ongoing basic research further clarifies H.P. Acthar Gel's mechanism of action

Research Priorities

1 Develop support for disease-specific MOA[1]

- Evaluating efficacy in animal and cell culture models relevant to:
  - MS[2]
  - Glomerular diseases
  - SLE[3], autoimmune arthritis
  - Uveitis

2 Differentiate from steroids

- Evaluating unique immunomodulatory effects

Clinical Evidence and Data Generation

Uveitis

- Acthar reduced progression of autoimmune uveitis and suppresses acute uveitis in respective animal models

MS

- Acthar attenuated inflammation and nerve injury in autoimmune animal model
- **Current Studies:** Effects of Acthar on inflammation and demyelination using cell culture models

RA[4]

- Acthar diminished inflammation, bone and bone remodeling in rat models of immune-mediated arthritis
- **Current Studies:** Effects of Acthar vs. steroid on bone cells

SLE

- Acthar reduced B cell maturation, autoantibodies and disease manifestations in mouse models
- **Current Studies:** Differential effects of Acthar and steroid on human B cells

Glomerular disease

- Acthar attenuated proteinuria in iMN[5] animal model
- **Current studies:** Differential effects of Acthar and steroid in FSGS[6] animal model

1 Mechanism of Action
2 Multiple Sclerosis
3 Systemic Lupus Erythematosus
4 Rheumatoid Arthritis
5 idiopathic Membranous Nephritis
6 Focal Segmental Glomerulosclerosis

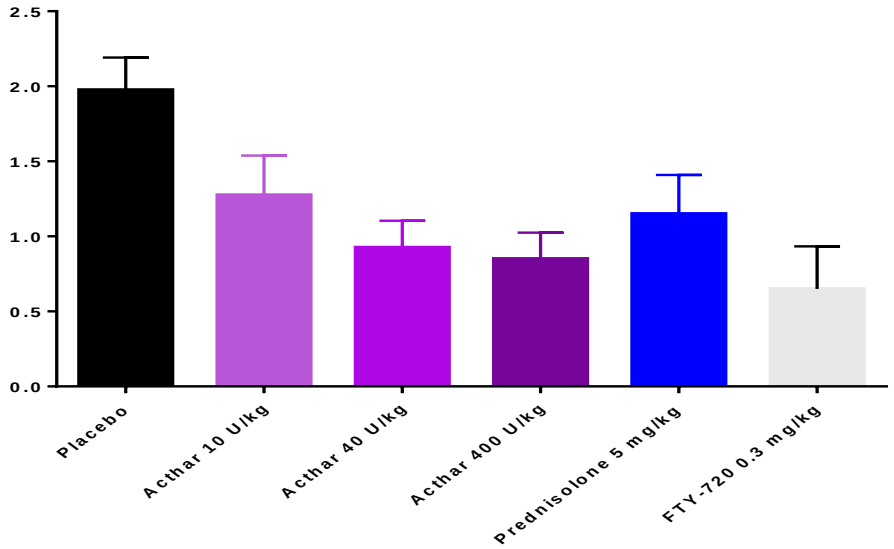
H.P. Acthar Gel in Ophthalmology: Results of treatment in models of uveitis in rats

Objective: Evaluate Acthar efficacy in autoimmune uveitis and endotoxin-induced uveitis animal models

Presented at ARVO[1] 2017
Treatment with repository corticotropin injection reduced the progression of experimental autoimmune uveitis in rats

Presented at AAI[2] 2017
Treatment with repository corticotropin injection resulted in suppression of acute uveitis

Clinical Score in Autoimmune Uveitis



Model of Endotoxin-Induced Uveitis

Treatment Group	Ocular Clinical Score (mean ± sem)	IL-1a[3] (pg/ml) (mean ± sem)	MIP2a[4] (pg/ml) (mean ± sem)
Placebo	15.5 ± 1.2	207.1 ± 68.9	240 ± 47
Acthar 160 IU/kg	9.4 ± 1.0	130.3 ± 34.6	158 ± 43
Acthar 400IU/kg	2.0 ± 0.3*	95.7 ± 20.3	114 ± 18*
Acthar 800 IU/kg	0.9 ± 0.2*	50.9 ± 8.3*	126 ± 32*
Dex[5]	2.6 ± 0.5*	54.4 ± 10.5*	92 ± 10*

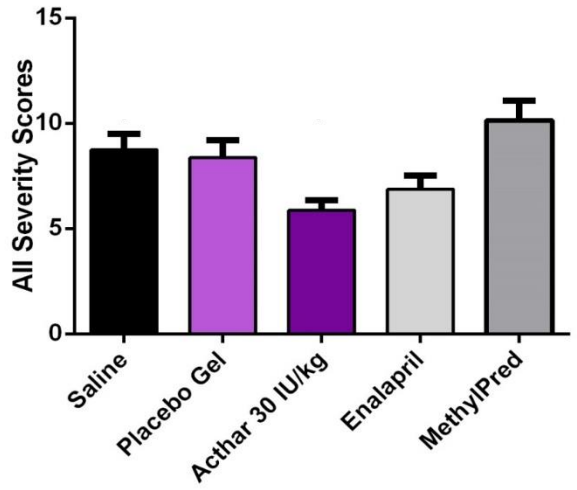
1 Association for Research in Vision and Ophthalmology
2 American Association of Immunologists
3 Interleukin 1 alpha
4 Macrophage inflammatory protein 2-alpha
5 Dexamethasone

This information is based on nonclinical data and the clinical benefit is unknown.

H.P. Acthar Gel in Nephrology: New evidence demonstrates MOA[1] and potential differentiation from steroids

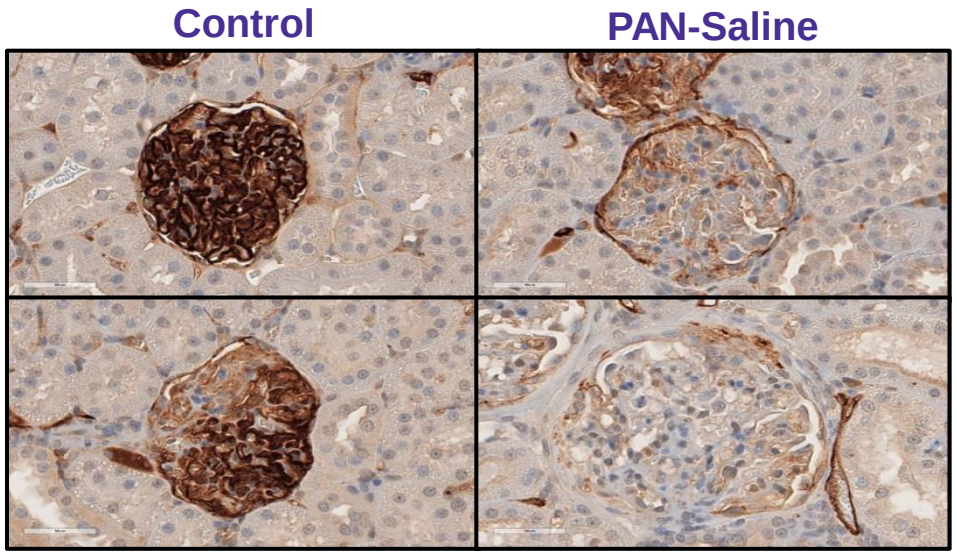
Objective: Demonstrate Acthar efficacy in FSGS[2] animal model and differentiate from steroids

Pathology Kidney Injury Score



Acthar decreased kidney injury score in PAN[3] Induced rat kidney injury model

Podoplanin IHC[5] Staining



This marker of podocyte health may be useful in differentiating the MOA of Acthar versus steroids

Abstract accepted for publication ASN[4] November 2017

1 Mechanism of Action
2 Focal Segmental Glomerulosclerosis
3 Puromycine Aminonucleoside Nephrosis
4 American Society of Nephrology
5 Immunohistochemistry

Alternative presentation for H.P. Acthar Gel delivery will modernize administration, address unmet needs

Most Acthar patients have injection experience from other therapies

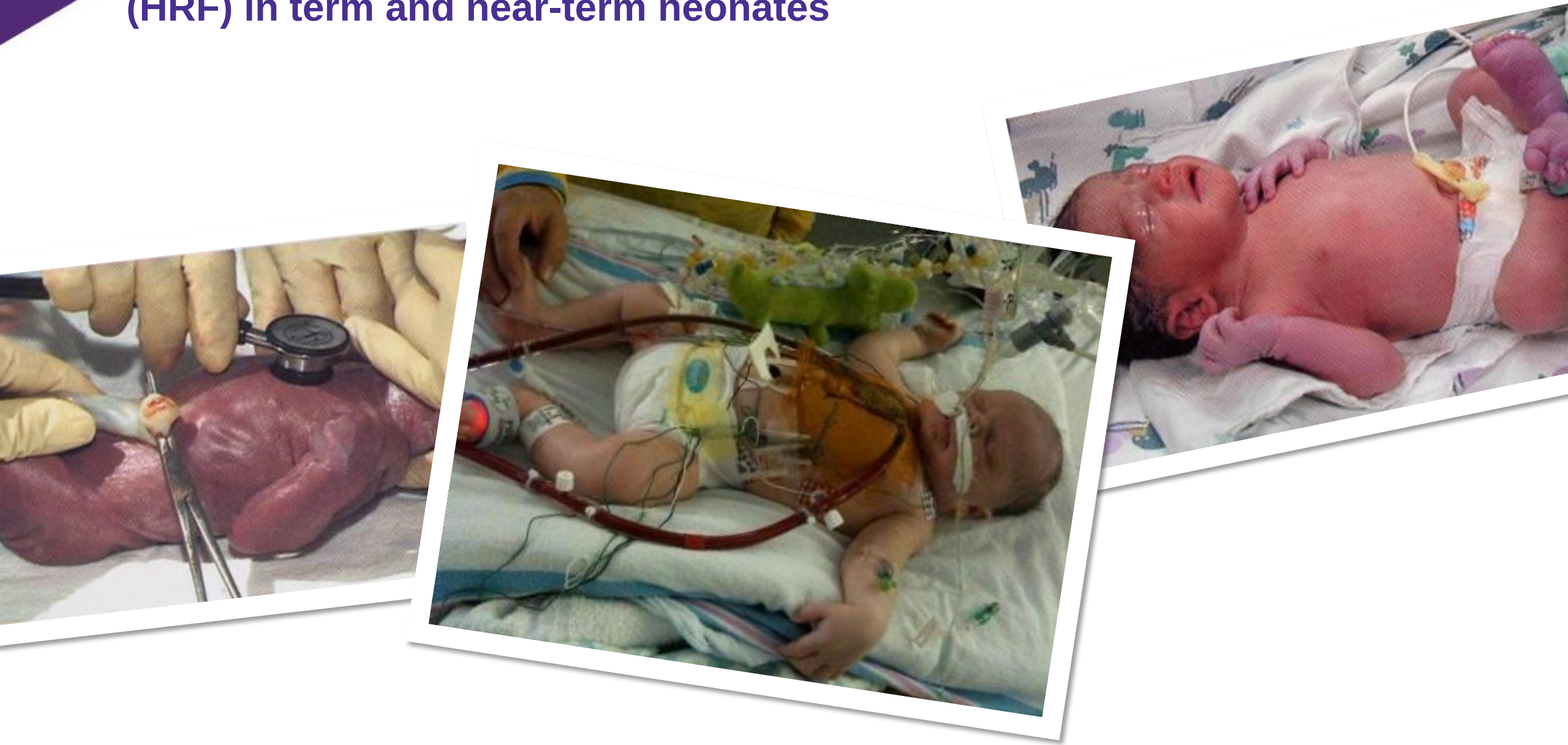
Delivery device selected

- Design modification to available, manual injection device
  - Prefilled syringe with desired dose
  - User controls injection rate
  - Provides feedback when dose delivered
- Compatible with connected health applications and technology
- Projected FDA submission: 2H2020

LAUNCH TARGET: 2H2021

- Select Key Brands – Approved Indications
  - **H.P. Acthar® Gel**
  - **INOMAX®**
- Development Pipeline

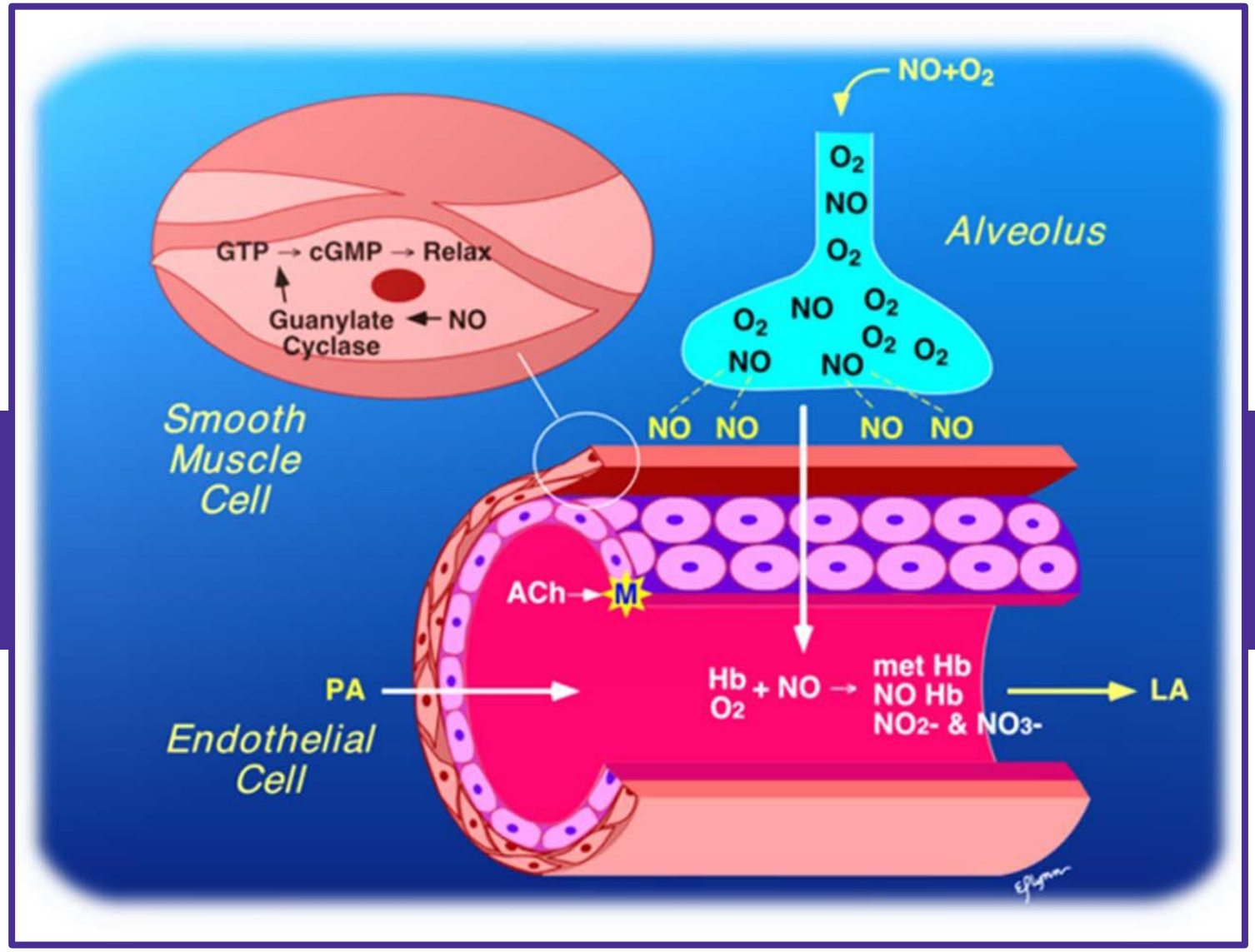
INOMAX: Leading treatment for Hypoxic Respiratory Failure (HRF) in term and near-term neonates



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



Prospective registry study established to evaluate INOMAX in premature infants

Assess effectiveness of iNO[1] in premature neonates with pulmonary hypertension (PH)

- Prospective, two cohort[2] registry
- Multicenter, 60 U.S. sites
- 150 subjects

Objectives

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

Endpoints

Measures being evaluated:

- *Meets ECMO[3] criteria*
- *All cause mortality*
- *Respiratory response*
- *Days on ventilation and in ICU*
- *Acute response*

1 Inhaled Nitric Oxide
2 Cohorts: Premature and Term/Near-Term
3 Extracorporeal Membrane Oxygenation

- Select Key Brands – Approved Indications
  - **H.P. Acthar® Gel**
  - **INOMAX®**
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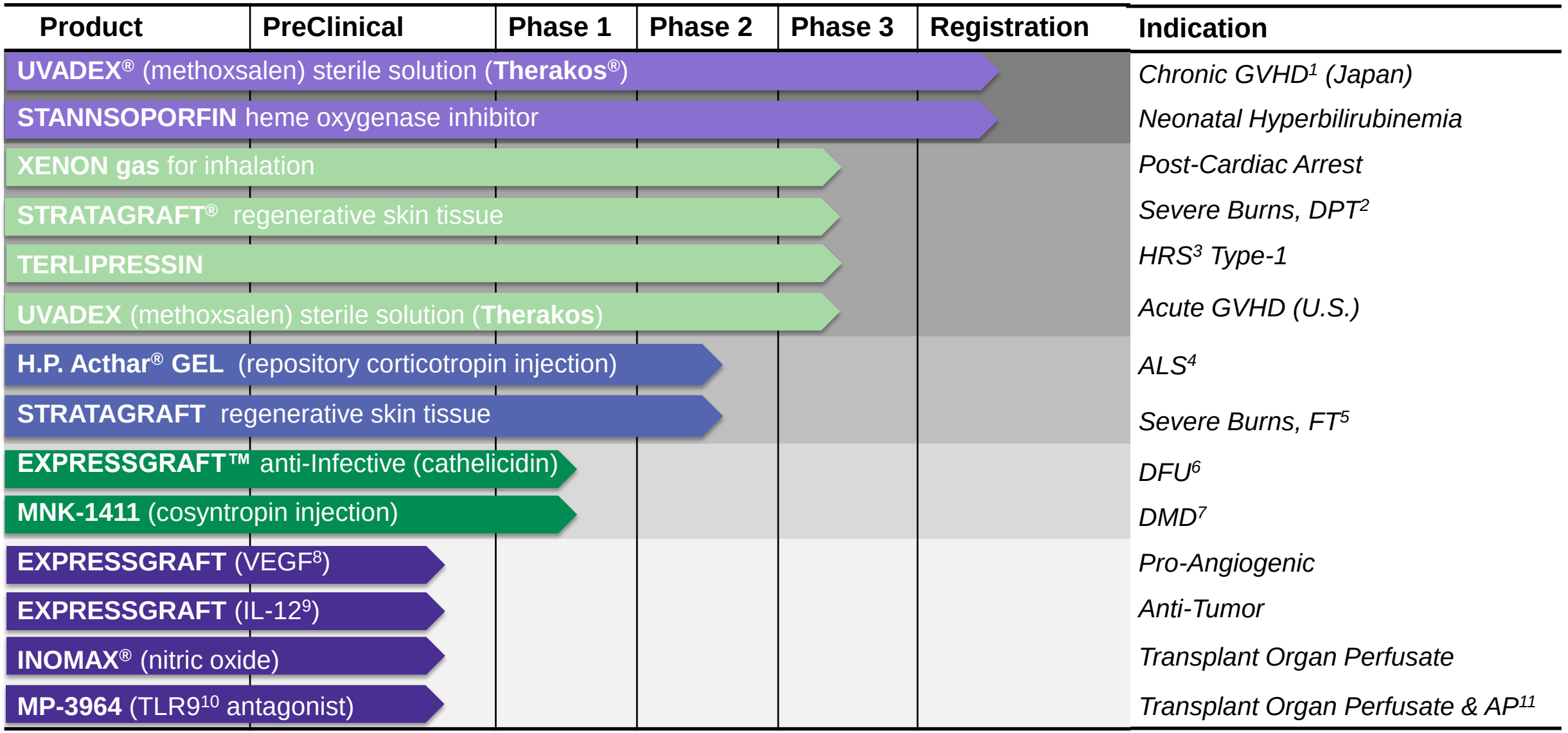
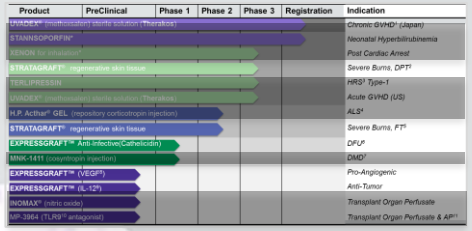
Expanding Specialty Brands pipeline will provide long-term organic growth



1 Graft vs Host Disease
2 Deep Partial Thickness
3 Hepatorenal Syndrome,
4 Amyotrophic Lateral Sclerosis
5 Full Thickness
6 Diabetic Foot Ulcers
7 Duchenne Muscular Dystrophy
8 Vascular Endothelial Growth Factor
9 Interleukin
10: Toll-like Receptor
11: Acute Pancreatitis

Development Pipeline



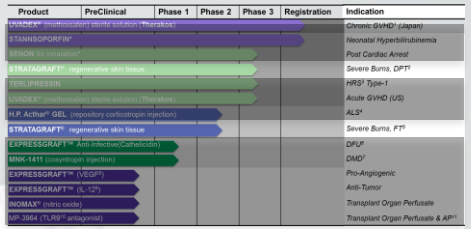
- StrataGraft
- ExpressGraft
- Therakos
- Stannsoporfin
- Terlipressin
- Xenon
- H.P. Acthar Gel
- MNK-1411
- INOMAX
- MP-3964

Mallinckrodt Pharmaceuticals:

Dr. Lynn Allen-Hoffmann
SVP, Regenerative Medicine

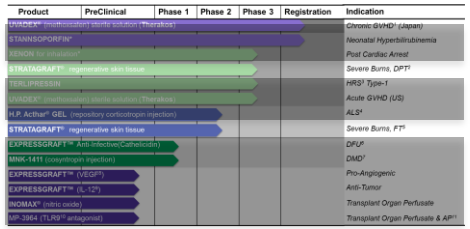
Mallinckrodt Pharmaceuticals

Development Pipeline

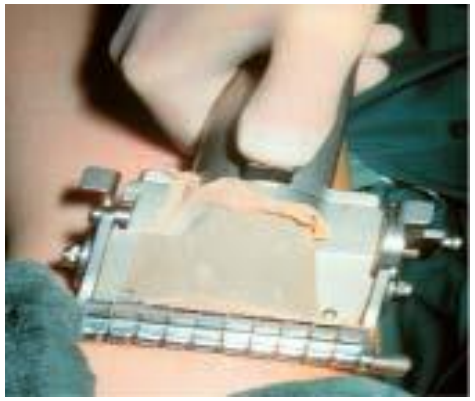


- StrataGraft
- ExpressGraft
- Therakos
- Stannsoporfin
- Terlipressin
- Xenon
- H.P. Acthar Gel
- MNK-1411
- INOMAX
- MP-3964

Regenerative Medicine: StrataGraft has potential to be standard of care for severe burn patients



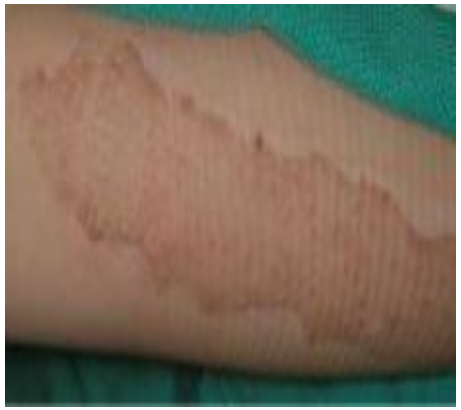
Human Skin Autografting: Current Standard of Care for 2nd/3rd Degree Burns



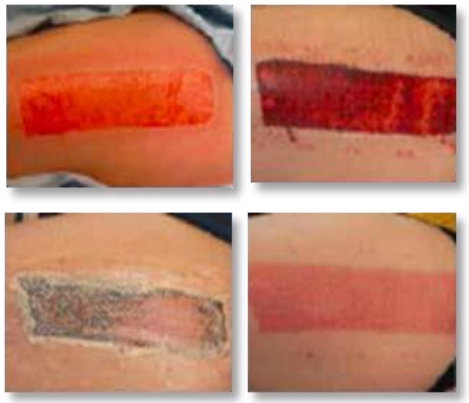
Harvest skin with dermatome

Current burn management requires autograft and has negative patient impact:

- Painful harvesting of donor skin creates new wound
- Causes extensive scarring
- Multiplies infection risk
- Results in multiple treatments and surgeries, and hospitalizations of variable, unknown length



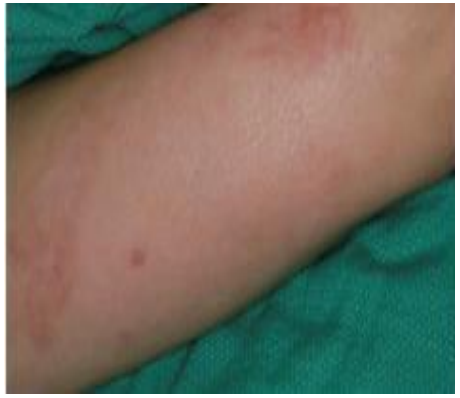
Autograft (3 months)



Donor sites

StrataGraft has potential to:

- Eliminate painful donor site, reduce short- and long-term care
- Result in fast coverage and closure
- Reduce rate of contracture and scarring
- Simplify surgical procedure and shorten surgical time
- Eliminate multiple surgeries and reduce costs

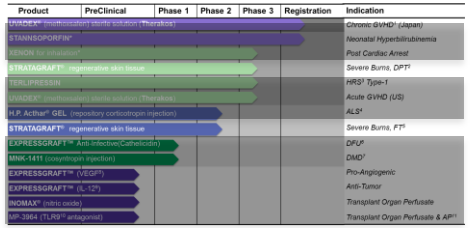


StrataGraft (3 months)

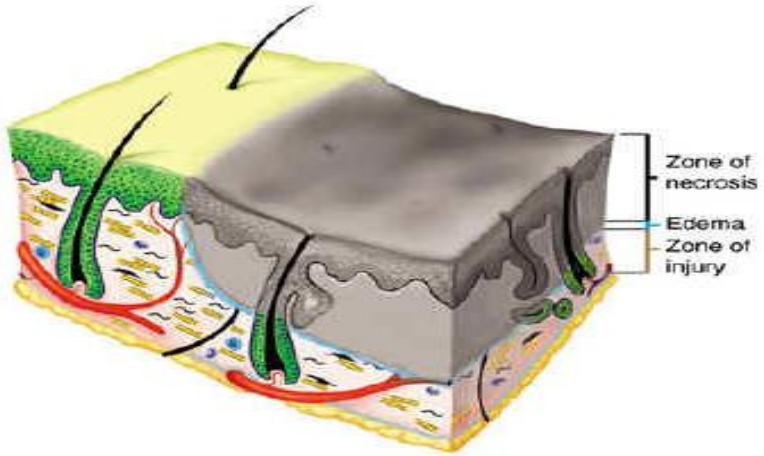
Sources: American Burn Association, STRATA2011 clinical trial

StrataGraft among first products designated a Regenerative Medicine Advanced Therapy (RMAT) by the FDA under the 21st Century Cures Act provisions

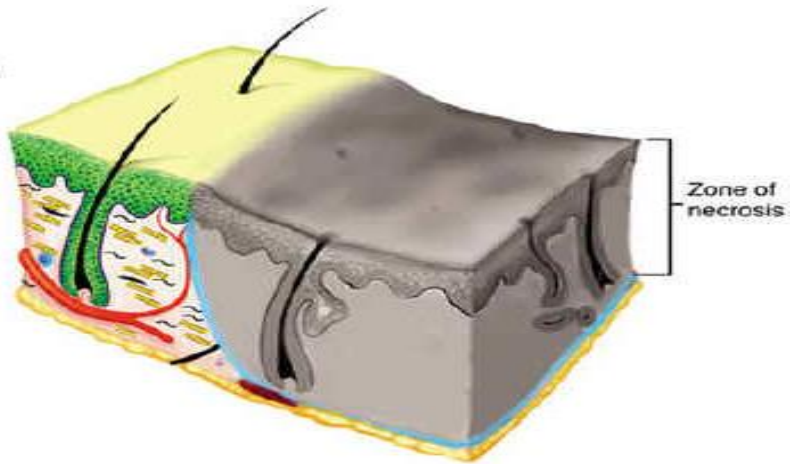
StrataGraft Phase 2 and 3 studies initiated in complex skin defects resulting from severe burns



- Complex skin defects typically contain both full thickness (FT) and deep partial thickness (DPT) components



DPT (Phase 3)

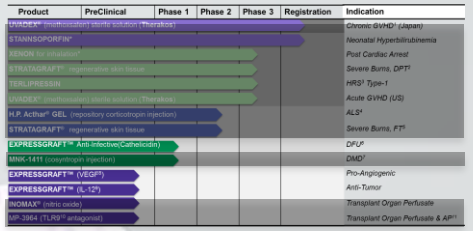


FT (Phase 2)

- Clinical management of FT and DPT is similar as both are excised and autografted
  - FT requires autografts
  - DPT needs autografts to reduce scarring and improve functional outcome

DATA AVAILABLE (DPT): 1H2020 **DATA AVAILABLE (FT): 2H2019**

Development Pipeline



- StrataGraft
- ExpressGraft
- Therakos
- Stannsoporfin
- Terlipressin
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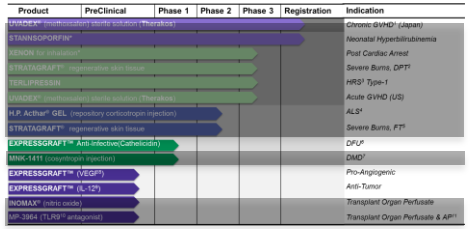
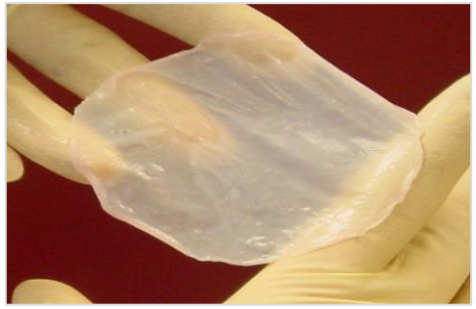
- H.P. Acthar Gel
- MNK-1411
- INOMAX
- MP-3964

Regenerative Medicine: ExpressGraft is skin-substitute technology platform with potential to alter wound treatment paradigm



Genetically enhanced tissue for elevated wound healing

- World's first genetically enhanced tissue pipeline



- Engineered skin substitutes expressing therapeutic proteins to help accelerate healing
  - Anti-infective
  - Pro-angiogenic
  - Anti-protease
  - Anti-tumorigenic
  - Long shelf life, frozen or dried
- Research and development through competitive federal grants

ExpressGraft pipeline of products

Anti-infective factors (Cathelicidin)
- Host defense peptides (HDPs)
- Important in epithelial healing

Angiogenesis factors (VEGF[1])
- Balances vascularization
- Important in ischemic patients

Protease inhibitors
- Chronic ulcers are proteolytic
- Inhibits degradation of GFs[2], etc.

Anti-Tumor (IL-12)
- Fights tumor recurrence
- Used following Moh's surgery

EpiReady
- Dried antimicrobial skin
- Field use

DATA AVAILABLE: 2H2019

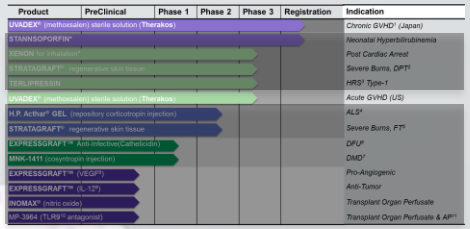
1 Vascular Endothelial Growth Factor
2 Growth Factors

Mallinckrodt Pharmaceuticals:

Dr. Steve Romano
EVP and Chief Scientific Officer

Mallinckrodt
Pharmaceuticals

Development Pipeline



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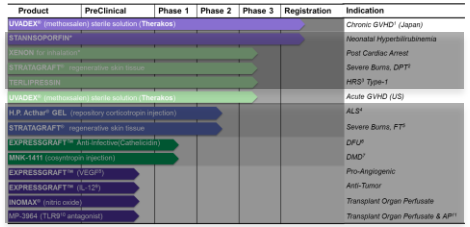
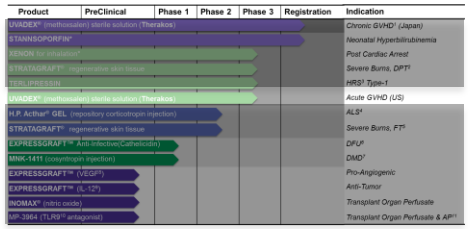
Therakos: Key Programs



- U.S. Phase 3 aGVHD[1] pediatric study
- cGVHD[2] Japan submission
- Supporting large investigator initiated research in Lung BOS[3]

1 acute Graft vs Host Disease
2 chronic Graft vs Host Disease
3 bronchiolitis obliterans syndrome

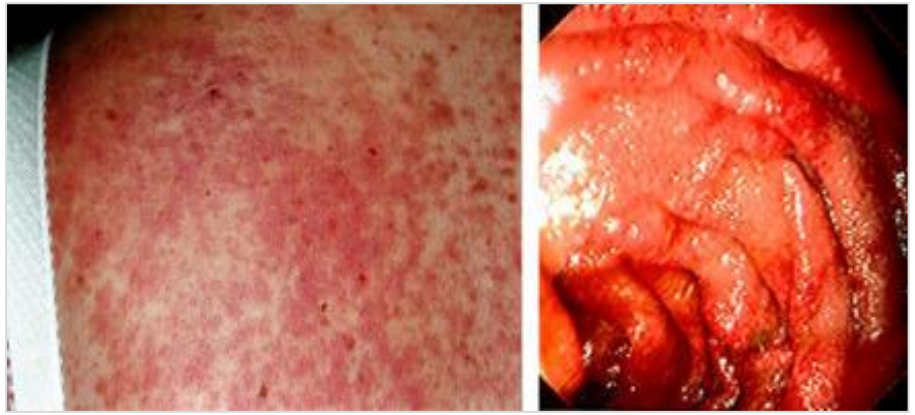
Therakos being evaluated in pediatric patients for treatment of acute Graft vs Host Disease (aGVHD)



acute Graft vs Host Disease[1]

- Severe inflammatory complication of allogeneic (donor) HCT[2] developing 4-100 days post-transplant
- Prevalence: 1-9 per 100,000; Incidence: 30-50% post Allo-HCT[3]
- Annually, 6,800 patients undergo donor HCT, with majority experiencing manifestations of aGVHD
- Characterized by generalized patchy skin rash, sickness, weight loss, loss of appetite, watery diarrhea, severe abdominal pain, bloody diarrhea and jaundice (liver)
- No approved treatments; ~50% of patients will not have a sustained, response to first line-therapy with steroids
- Significant cause of morbidity and mortality in allogeneic HCT recipients
- Survival is poor in SR[4] aGVHD (~15% in 2 years)

Clinical appearance of aGVHD involving the skin and upper intestinal mucosa

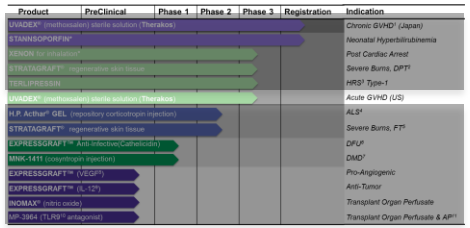


Left panel: Diffuse erythematous maculopapular rash typical of aGVHD. **Right panel:** Endoscopic view of edematous, reddened, gastrointestinal mucosa seen in a patient with aGVHD.

Source: Riddell SR, Appelbaum FR - PLoS Med. (2007)

1 Holtan SG, Pasquini M, Weisdorf DJ. Acute Graft-Versus-Host Disease: A Bench-to-Bedside Update. *Blood.* 2014;124(3):363-373
2 Hematopoietic Cell Transplantation 3 allogenic HCT 4 steroid-refractory

Therakos: aGVHD[1] 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-D
  - 12 weeks of ECP[2] study treatment:
    - Weeks 1-4: 3 treatments per week
    - Weeks 5-12: 2 treatments per week

Primary Efficacy Endpoint

ECP Efficacy

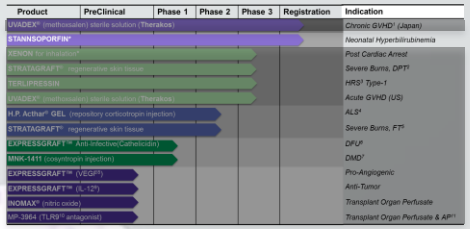
Proportion of patients who achieve overall response after four weeks (day 28) of ECP treatment

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

1 acute Graft vs Host Disease
2 Extracorporeal Photopheresis

DATA AVAILABLE: 1H2020

Development Pipeline



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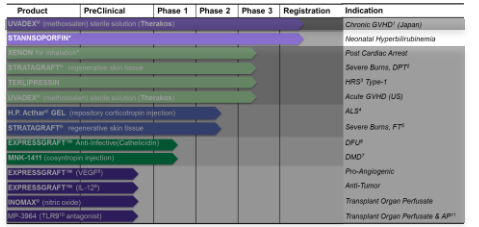
Severe jaundice can threaten the lives of infants



DISEASE OVERVIEW[1,2]

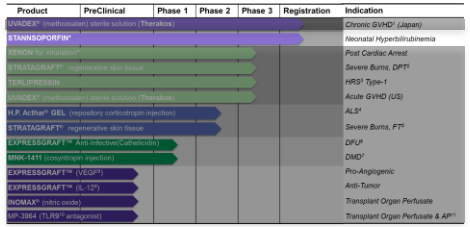
- **Jaundice** in infants is common and usually self-limiting
- Jaundice caused by excess bilirubin in blood (hyperbilirubinemia); bilirubin is formed during normal breakdown of hemoglobin (hemolysis)
- In some newborns hemolysis occurs at a greater rate, potentially reaching **severe bilirubin levels**
- In the brain bilirubin can cause **acute encephalopathy** syndrome
  - **Symptoms include** poor feeding, shrill cry, muscle rigidity, markedly arched back with neck hyperextended backwards, seizures, and stupor or coma
  - **Complications** can include hearing loss or even death
  - Unresolved, can progress to **kernicterus**, a rare condition associated with severe and permanent brain damage
- AAP[3] guidelines[4] recommend assessing all newborns for **hyperbilirubinemia** risk prior to discharge from hospital

CURRENT TREATMENT OPTIONS

- Phototherapy is standard of care to reduce bilirubin levels; may not address severe cases
- In some severe cases, HCPs[5] must resort to invasive options, including blood exchange transfusion or, less often, IVIG[6]
- No treatments currently indicated for severe condition; high unmet need for severe and refractory patients

1 http://www.mayoclinic.org/diseases-conditions/infant-jaundice/basics/complications/con-20019637 Accessed July 20, 2017
2 https://medlineplus.gov/ency/article/007309.htm Accessed July 20, 2017
3 American Academy of Pediatrics
4 http://pediatrics.aappublications.org/content/114/1/297
5 Healthcare Professionals
6 Intravenous immunoglobulin

Stannsoporfin reduces severe jaundice through novel mechanism of action



Bilirubin forms from breakdown of hemoglobin in red blood cells

Hemoglobin

Heme is a component of hemoglobin

Heme

Heme oxygenase enzyme catalyzes heme breakdown to produce biliverdin

Biliverdin

Biliverdin reductase enzyme acts on biliverdin to create bilirubin

Bilirubin

Stannsoporfin reduces bilirubin production by inhibiting heme oxygenase

STANNSOPORFIN

Hemoglobin

Heme

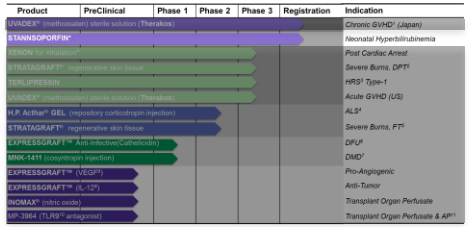
Heme Oxygenase

Biliverdin

Bilirubin

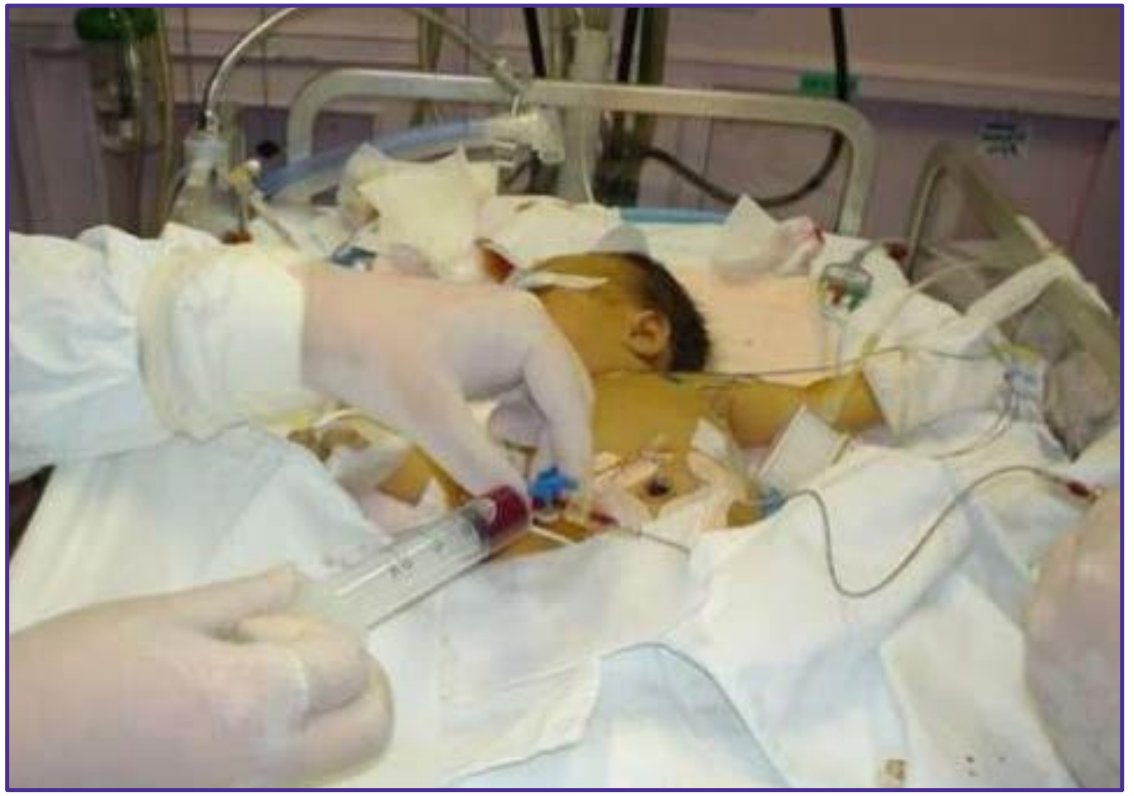
Source: Mallinckrodt's evaluation of clinical trials

Stannsoporfin has potential to provide unique therapeutic benefits vs. other treatment options



Demonstrates robust effect in inhibiting bilirubin production via novel mechanism of action; other treatment options focus on increased bilirubin removal which is less effective in severe jaundice

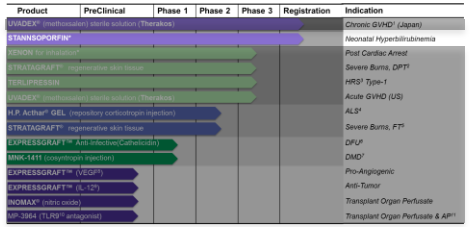
- **May reduce potential** of advancing to bilirubin levels requiring more intrusive therapies
- **Potentially decreases incidence** of readmission
- **May lower risks associated with other treatments** (e.g., bilirubin rebound) and prolonged/severe bilirubin elevation, which can impact central nervous system development
- **Exhibits favorable** safety/tolerability profile
- **Administered conveniently** by single, intramuscular injection vs. more invasive, complex and lengthy treatment options beyond phototherapy

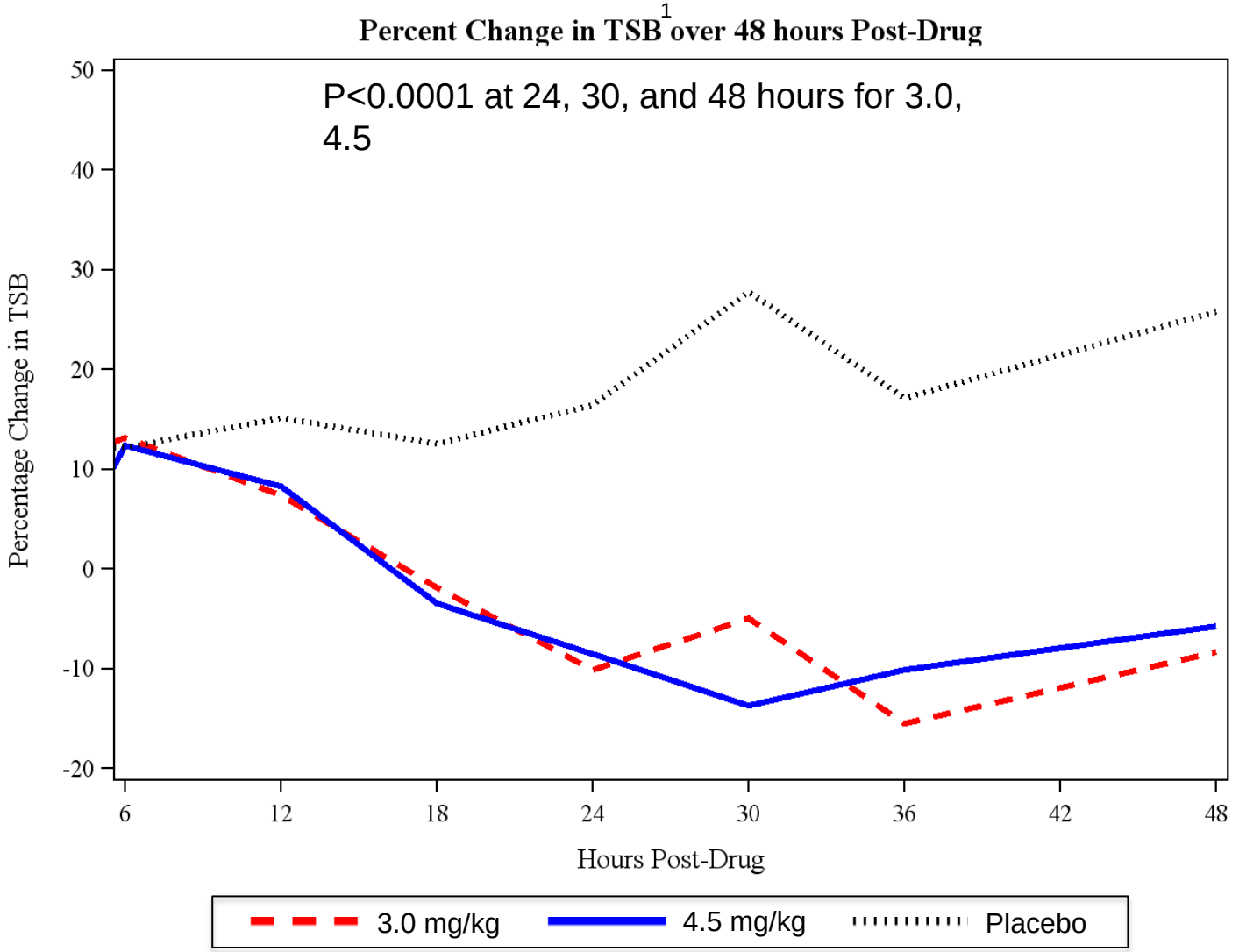


Stannsoporfin is expected to significantly improve lives of infants

Source: Mallinckrodt's evaluation of clinical trials

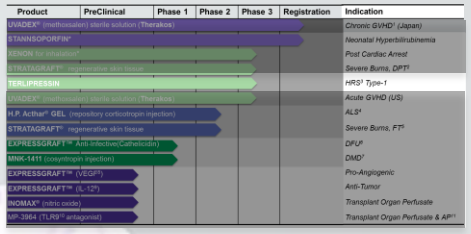
Phase 2b pivotal trial results: Stannsoporfin in combination with phototherapy was superior to phototherapy alone





1 total serum bilirubin

Development Pipeline



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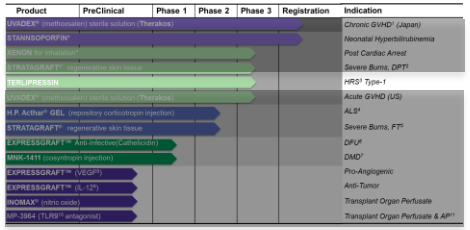
Terlipressin: A vasopressin analog, is the global standard of care for HRS Type-1, a rare life-threatening condition

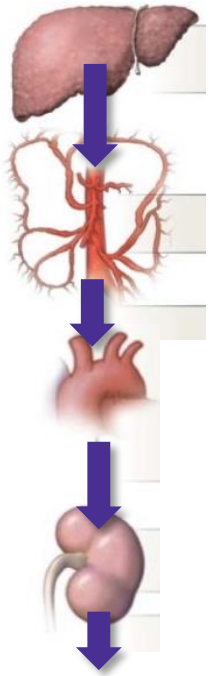


Ongoing Phase 3 U.S. development program

- Hepatorenal Syndrome Type 1 (HRS-1) is a rare, life-threatening complication of cirrhosis of the liver
- Affects from 10,000 to as many as 30,000 patients in U.S.[1-4]; high mortality rates
- Condition leads to multi-organ failure including acute kidney failure[5,6]
- Kidneys appear structurally normal on diagnostic imaging[5,6]
- Survival improves with early diagnosis and treatment[5,6]

Pathophysiology of HRS

Decompensated Cirrhosis

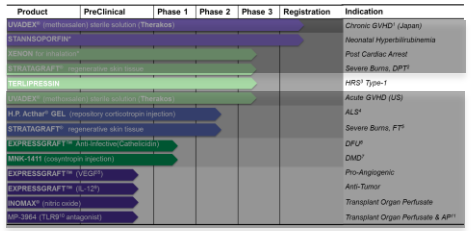


- Disease progression
- Severe portal hypertension
- Bacterial translocation
- Severe splanchnic arterial vasodilatation
- Markedly reduced effective arterial blood volume
- Increased cardiac output and plasma volume insufficient to normalize arterial blood volume
- Activation of sodium-retaining and vasoconstrictor systems
- Sodium and water retention and ascites formation
- Further activation of vasoconstrictor systems
- Impairment in cardiac output

Renal failure

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
4Gines 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

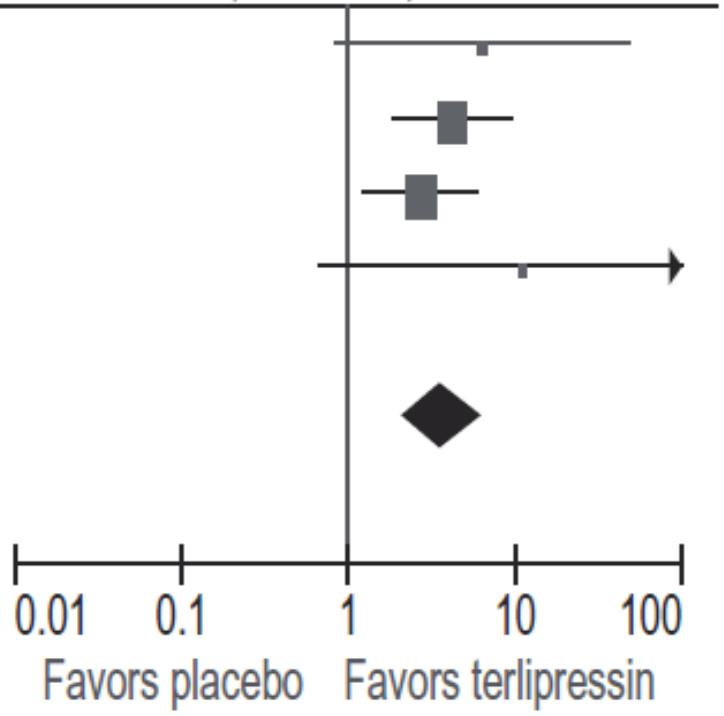
Subjects treated with terlipressin plus albumin had greater incidence of HRS reversal than albumin alone



Study or Subgroup	Terlipressin Events	Total	Placebo Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Marta 2008	6	17	1	18	7.0%	6.35 (0.85, 47.44)
Neri 2008	21	26	5	26	43.2%	4.20 (1.87, 9.44)
Sanyal 2008	19	56	7	56	46.2%	2.71 (1.24, 5.94)
Solanki 2003	5	12	0	12	3.6%	11.00 (0.67, 179.29)
Total (95% CI)		111		112	100.0%	3.66 (2.15, 6.23)
Total events	51	46%	13	11.6%		

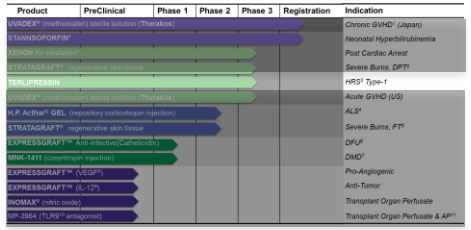
Heterogeneity: $Tau^2 = 0.00$; $\chi^2 = 1.59$, d.f. = 3 ($P = 0.66$); $I^2 = 0\%$

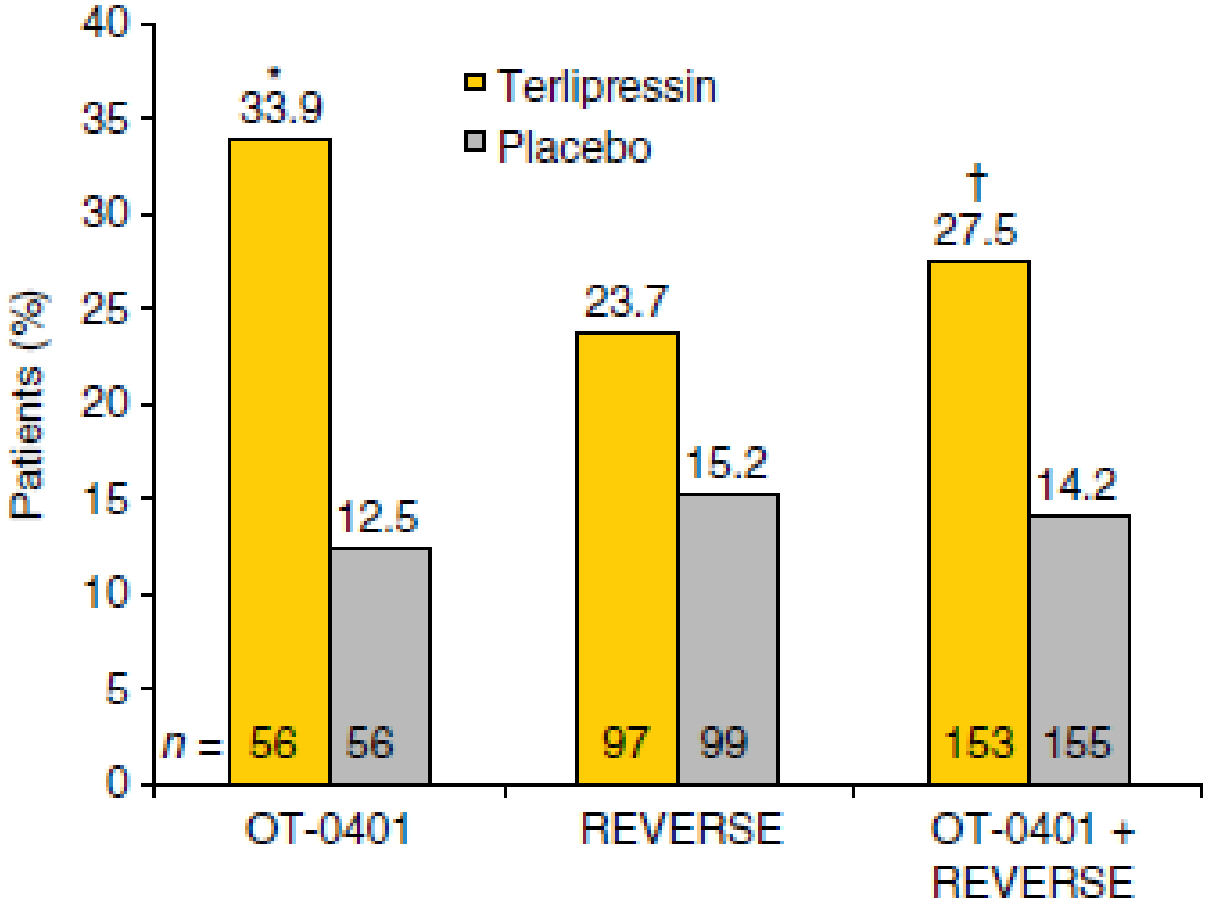
Test for overall effect: $Z = 4.78$ ($P < 0.00001$)



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

Terlipressin use led to greater incidence of HRS reversal in previous U.S. clinical trials

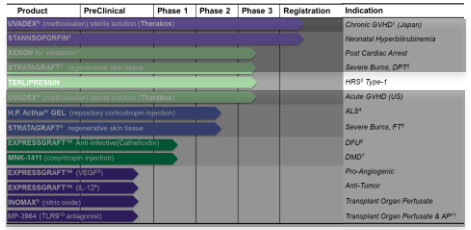




P: 0.008 vs. Placebo and ┼P: 0.004 vs. Placebo

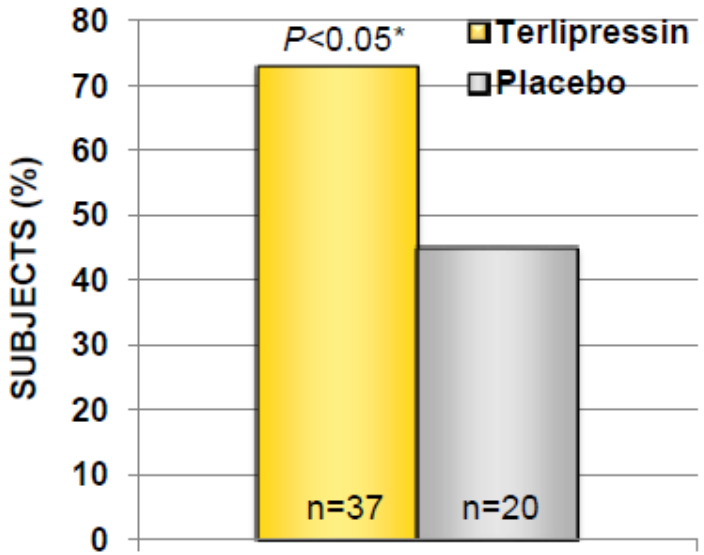
Source: Sanyal A.J et al. Journal of APT 2017

HRS reversal in terlipressin-treated subjects can lead to better survival and clinical outcomes



Survival at Day 90 without need for dialysis

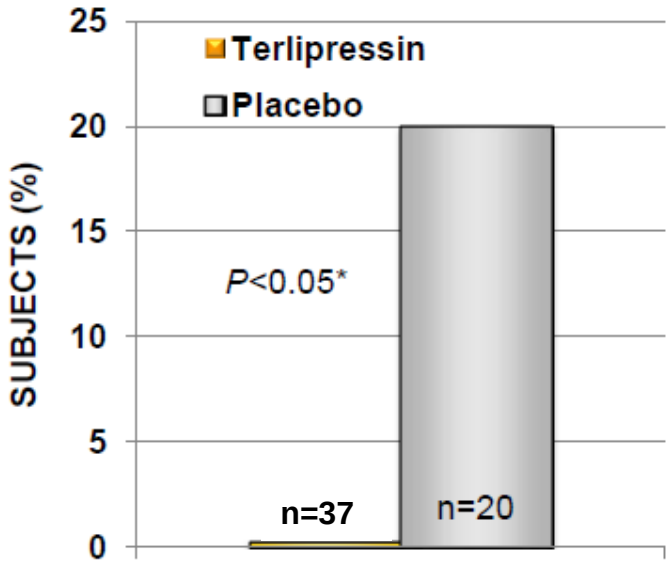
Subjects with CHRSR[1], alive, without RRT[2], Day 90



*Fisher's exact test.

Incidence of dialysis in subjects with confirmed HRS reversal, terlipressin vs Pbo at Day 90

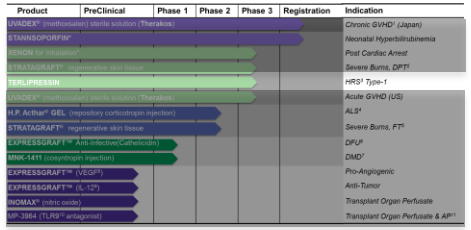
Incidence of RRT, subjects with CHRSR, alive at Day 90



No subject with CHRSR in the terlipressin group, alive at Day 90, received RRT

1 confirmed HRS reversal
2 renal replacement therapy
Source: Boyer TD. AASLD 2014- REVERSE Data Presentation

Terlipressin: HRS[1] 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
  - 300 subjects
  - Multicenter, 25-45 sites

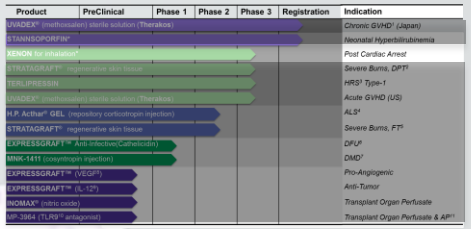
Primary Efficacy Endpoint

Confirm HRS reversal
% of subjects with SCr[2] ≤ 1.5 mg/dL on treatment by / before Day 14 or discharge

1 Hepatorenal Syndrome
2 serum creatinine
3 interim analysis target 1H2018

DATA AVAILABLE: 1H2020[3] **LAUNCH: 2H2020**

Development Pipeline



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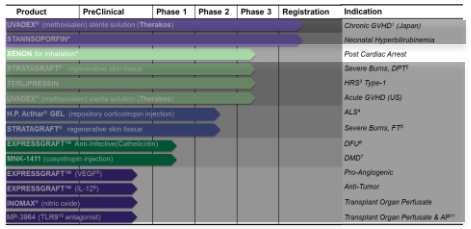
Xenon gas for inhalation's unique mechanism of action may contribute to lowering neuronal cell death, primary cause of disability and death in resuscitated cardiac arrest patients



Xenon[1] is a noble gas that has been used safely as an inhaled therapy in several studies to date

Cardiac arrest interrupts blood flow to the brain

↓

Negative cascade opens calcium channels

⊘

⇧ Ca^{2+}[4] flow into cells causes neuronal cell death

Over-activation of calcium channels is known to cause neuronal damage and cell death[2]

Xenon binds to NMDA[3] receptors through **a unique glycine-binding mechanism** to regulate Ca^{2+} flow through the channel

Reduced neuronal cell death expected to reduce time in coma, lower mortality rates, and improve cognitive and motor functions

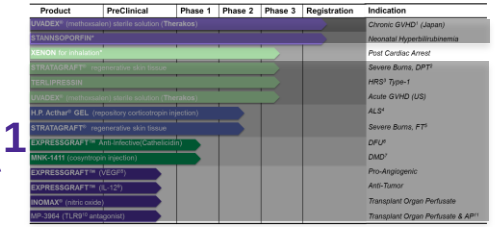
Improvements in functional abilities can lower the cost of patient care

Drug Delivery System

- Pharmaceutical-grade xenon gas for inhalation delivered into breathing circuit through a proprietary delivery device
- Planned for use with TTM[5] in hospital ER and ICU

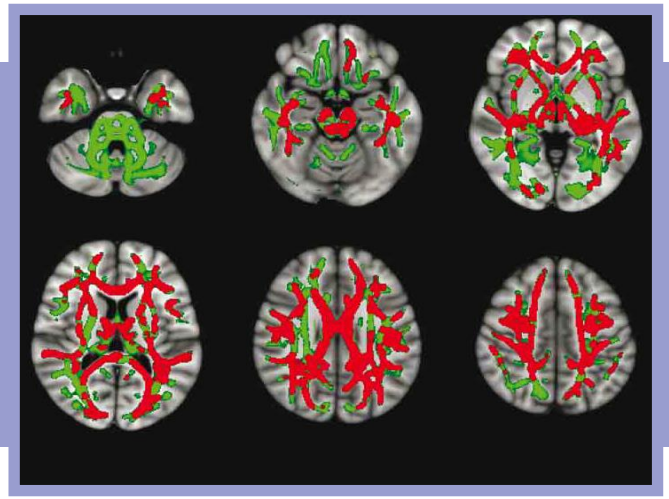
1 Dickinson and Franks Critical Care 2010, 14:229
2 Luo et al, Front Biol. 2011 Dec; 6(6): 468–476
3 N-methyl-D-aspartate
4 Calcium ions
5 Targeted Temperature Management

Pharmaceutical-grade xenon gas for inhalation showed clear reduction of brain damage in Phase 2 trial published in JAMA[1]



Phase 2 Results

- Xenon gas for inhalation associated with less brain damage on primary neuroimaging endpoint measured using MRI[2] (p=0.006)
- Reduction in mortality was not statistically significant (p=0.053) and there was no difference in neurological outcomes at 6 months in the overall population
- However, post-hoc analysis of patients resuscitated in ≤ 30 minutes[3] who received xenon gas for inhalation showed improved 60-day mortality and better modified Rankin Scores* (lower mortality rates and improved cognitive and motor functions)



Patient Population: 110 comatose OHCA[4] patients resuscitated with return of spontaneous circulation (RoSC) within 45 minutes

Treatment: Xenon + TTM[5] vs. TTM-alone

Method: MRI used to measure biomarker – Global Fractional Anisotropy – that shows differences in the diffusion of water in white matter tracts of the brain; more diffusion = more damage

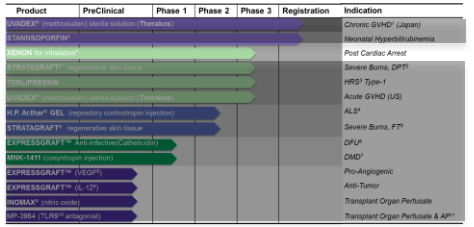
Brain damage biomarker exhibited the best independent predictive value for mortality at 6 months

Red – significantly worse damage in TTM-alone vs. xenon + TTM group
Green – no difference between groups

* See Appendix

1 Laitio et al. JAMA 2016 (Journal of the American Medical Association)
2 Magnetic Resonance Imaging
3 Data on file; as analyzed by NeuroproteXeon
4 Out of Hospital Cardiac Arrest
5 Targeted Temperature Management

Phase 3 registration trial designed to replicate positive treatment outcomes with xenon gas for inhalation in patients resuscitated in ≤ 30 minutes

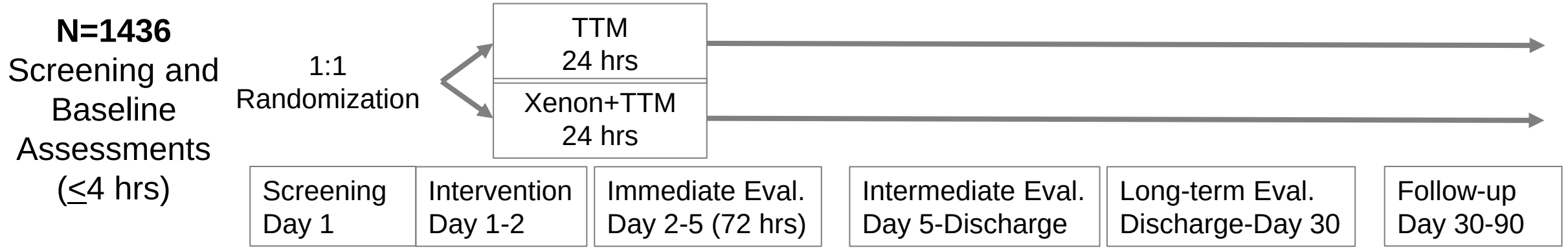


- Phase 2 patients resuscitated in ≤ 30 minutes[1] who received xenon gas for inhalation plus TTM[2] had improved 60-day mortality and good functional outcome

		TTM	%	Xenon+TTM	%	Relative Change
Functional Outcome	Good (mRS[3] 0-2)	32/50	64%	33/44*	75%	17.2%
	Poor (mRS 3-6)	18/50	36%	11/44*	25%	-30.6%
Mortality		17/50	34%	9/45**	20%	-41.2%

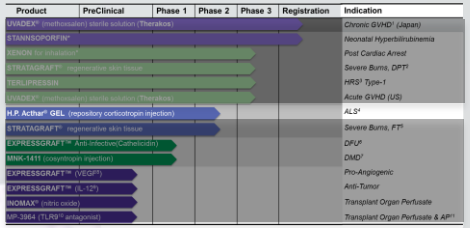
*excludes one patient with no data and one patient with mental disability who entered and exited the study with mRS[3]
** excludes one patient with no data

- Single Phase 3 registration trial – to be conducted under FDA[4] SPA[5]
  - **Primary Endpoint:** % with good functional outcome (mRS ≤ 2) on Day 30
  - **Secondary Endpoints:** % surviving on Day 30 (plus others)



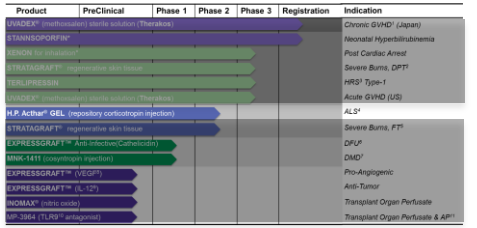
1 Data on file; as analyzed by NeuroproteXeon
2 Targeted Temperature Management
3 modified Rankin Score
4 U.S. Food and Drug Administration
5 Special Protocol Assessment

Development Pipeline



- StrataGraft
- ExpressGraft
- Therakos
- Stannsoporfin
- Terlipressin
- Xenon
- **H.P. Acthar Gel**
- MNK-1411
- INOMAX
- MP-3964

H.P. Acthar Gel being evaluated for patients with Amyotrophic Lateral Sclerosis



- ALS[1] is a progressive and fatal neurodegenerative disorder
- Characterized by muscle weakness and spasticity progressing to loss of muscle control that impacts movement, speech, swallowing and breathing
- ALS types:
  - Familial (~5-10% of patients), associated with genetic mutation
  - Sporadic (incidence 1.5-2/100,000), with no identifiable cause
- Evidence suggests a role for neuroinflammation contributing to disease progression

A majority of patients die within five years of symptom onset

Lou Gehrig

David Niven

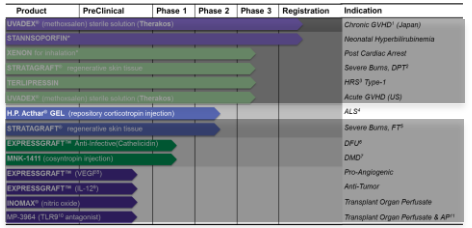
Steve Gleason

Jacob Javits

DATA AVAILABLE: 1H2020

1 Amyotrophic Lateral Sclerosis

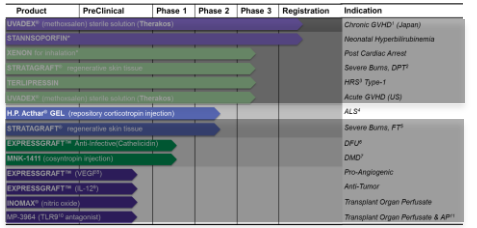
H.P. Acthar Gel: ALS Phase 2, pilot data (post-hoc case match control analysis – ALSFRS[1] total score baseline, week 8 and week 36)



ALSFRS Mean (SD)	Baseline	Week 8	Week 36
PRO-ACT Control N=106	27.2 (6.31)	26.5 (7.42)	20.9 (9.10)
Acthar Combined N=43	27.8 (5.55)	28.0 (5.41)	24.1 (8.11)

1 ALS Functional Rating Scale; Source: Post-Hoc Analyses Using PRO-ACT Database (PRO-ACT) to evaluate Repository Corticotropin Injection (RCI; H.P. Acthar® Gel) as a potential treatment for ALS, 16th Annual NEALS Meeting, October, 2017

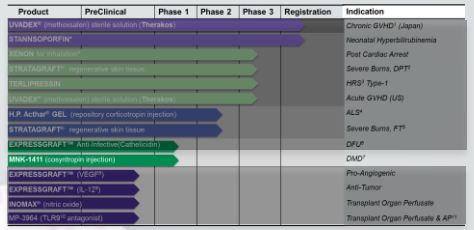
Acthar: ALS Phase 2, pilot data (post-hoc prediction algorithm summary of results)



Slope Source	N	Mean	SD	p-value (Paired T-test)
QSC01-ALS-01	21	-0.5140	0.5679	0.0855
Predicted	21	-0.7469	0.2648	

Source: Post-Hoc Analyses Using PRO-ACT Database (PRO-ACT) to evaluate Repository Corticotropin Injection (RCI; H.P. Acthar® Gel) as a potential treatment for ALS, 16th Annual NEALS Meeting, October, 2017

Development Pipeline



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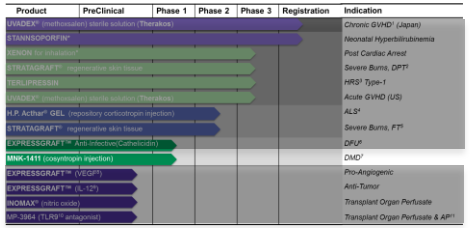
MNK-1411: Development of novel melancortin peptide expands therapeutic potential of portfolio



Long-acting (depot) formulation of synthetic ACTH[1] 1-24 analog

U.S. development and OUS commercial rights acquired from Novartis

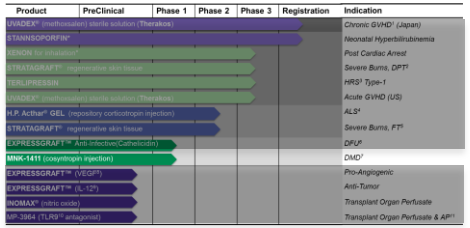
Synacthen® Depot never approved in U.S. (two short-acting ACTH 1-24 products marketed for diagnostic use)

Distinct binding and functional profile at melanocortin receptors

Cortisol production differs vs H.P. Acthar Gel

1 adrenocorticotropic hormone

MNK-1411 being evaluated for patients with Duchenne Muscular Dystrophy (DMD)

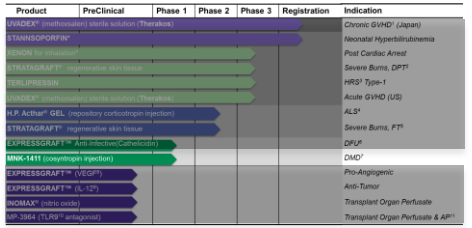


DMD

- Inherited X-linked, muscle-wasting disorder
- Characterized by progressive loss of mobility, pulmonary insufficiency, cardiomyopathy and premature death
- Worldwide prevalence ~4.78 cases per 100,000 (~15,000 in U.S.)
- Granted FDA Fast Track[1] and Orphan Designation
- Limited existing FDA-approved therapies
- Standard of care includes corticosteroids
- Melanocortin receptors associated with skeletal muscle and certain immune components may be relevant, in addition to melanocortin-mediated steroidogenic effects

1 The FDA Fast Track designation is a process designed to facilitate the development and expedite the review of drugs that treat serious conditions and fill an unmet medical need.

MNK-1411: Phase 2 DMD study design



Evaluate efficacy of MNK-1411 in subjects 4 to 8 years old with DMD

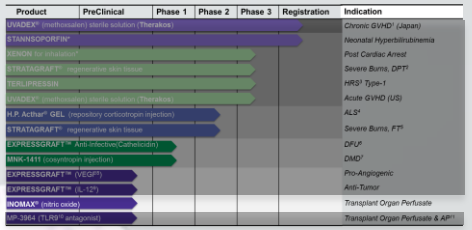
- **Phase 2, randomized, parallel group, double-blind, placebo-controlled**
  - 3 arms: 2 active doses and placebo
  - ~130 subjects
  - Multicenter, ~50 sites

Primary Efficacy Endpoint

Timed function test (TFT): 10 meter walk/run at week 24 vs baseline

DATA AVAILABLE: 1H2021

Development Pipeline



- StrataGraft
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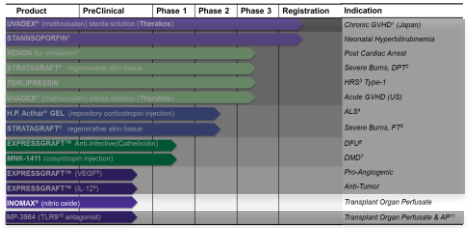
- **INOMAX**
- MP-3964

Opportunity to expand INOMAX application: Evaluating gaseous nitric oxide (gNO) in an ex-vivo human lung transplant perfusate study



Perfusion Device

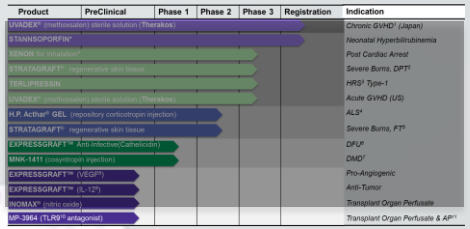
Multiple use device with integrated drug and gas delivery systems, heating systems designed to create in vivo-like circulatory environment and to monitor organ performance/improvement

***Purpose**: Demand for organs substantially outweighs supply*

***Objective**: To determine if adding gNO improves organ viability and ischemic times of marginal human lungs*

DATA AVAILABLE: 1H2018

Development Pipeline



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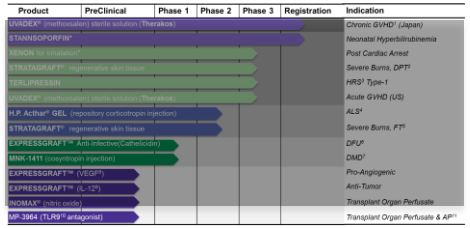
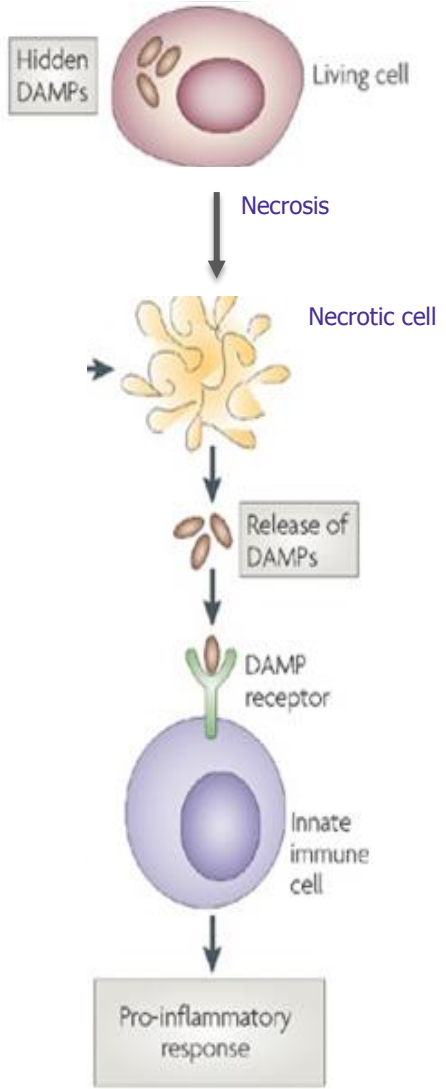
Toll-like receptors contribute to sterile inflammation

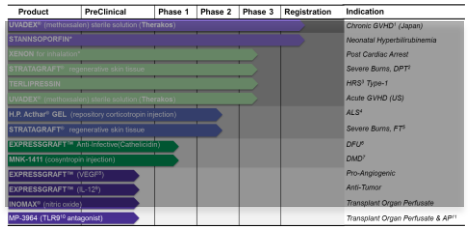


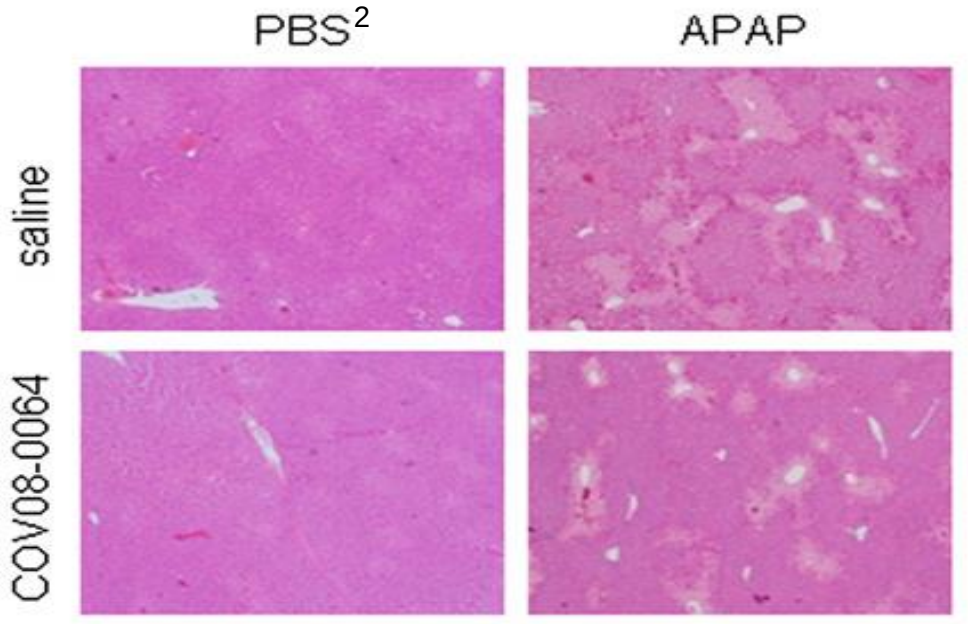
- Cell stress and necrosis release internal molecules that trigger activation of immune and tissue cells
  - Internal molecules, known as DAMPs[1], are recognized by a family of receptors (TLRs)
  - TLR9 is one of three TLRs[2] localized in endosomal compartments of immune and tissue cells
  - Binding of host DNA to TLR9 signals cells to produce cytokines which activate leukocytes and enhance inflammation without pathogens being present (sterile inflammation)
- Role of TLR9 has been established in sterile inflammatory disease models [3,4,5,6,7,8,9]

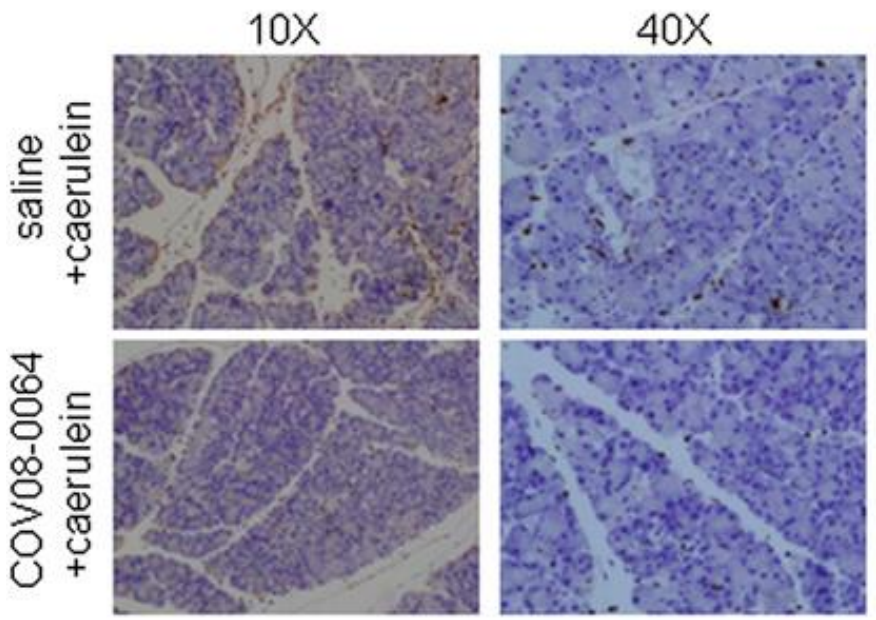


1 Damage Associated Molecular Patterns
2 Toll Like Receptor
3 Acute pancreatitis (Hoque et al., 2011, 2012)
4 Acute hepatic injury (Imaeda et al., 2009)
5 Acute kidney injury (Yasuda et al., 2008.)
6 Acute lung injury (Suresh et al 2016)
7 NASH (Garcia-Martinez et al., 2016)
8 HCC (Mohamed et al 2015)
9 Lupus (Guiducci 2010)

MP-3964[1] significantly reduced serum markers of tissue injury, and reduced tissue inflammation and damage in liver and pancreatic pre-clinical models





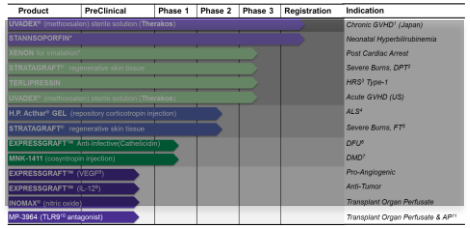


COV08-0064 pretreatment decreases liver inflammation and injury in APAP hepatotoxicity in mice

COV08-0064 co-treatment decreases pancreatic inflammation and injury in cerulein hyperstimulation induced acute pancreatitis in mice

1 formerly COV08-0064
2 phosphate buffered saline
Source: A Novel Small-Molecule Enantiomeric Analogue of Traditional (2)-Morphinans Has Specific TLR9 Antagonist Properties and Reduces Sterile Inflammation-Induced Organ Damage, Hoque et al, *J Immunol* 2013; 190:4297-4304

MP-3964 is being evaluated for the treatment of acute pancreatitis



- TLR9 has role in development of inflammation in response to damaged acinar cells in acute pancreatitis
- **MP-3964** is MNK's patented novel small molecule that inhibits TLR9 signaling and shows efficacy in animal model of pancreatitis
- Preclinical work ongoing in support of a potential IND filing

A Novel Small-Molecule Enantiomeric Analogue of Traditional (–)-Morphinans Has Specific TLR9 Antagonist Properties and Reduces Sterile Inflammation-Induced Organ Damage

Rafaz Hoque, Ahmad Farooq, Ahsan Malik, Bobby N. Trawick, David W. Berberich, Joseph P. McClurg, Karen P. Galen and Wajahat Mehal

J Immunol 2013; 190:4297-4304; Prepublished online 15 March 2013;
doi: 10.4049/jimmunol.1202184
http://www.jimmunol.org/content/190/8/4297

Progressing development and lifecycle programs: Key portfolio milestones projected for the near-term

2017

- **MNK-1411** P2 DMD study start
- **Acthar** P4 Sarcoidosis study start
- **gNO**[1] Transplant Perfusate study start
- **ExpressGraft** P1 DFU study start
- **Stannsoporfin** submission

2018

- **Xenon** P3 registration study start
- **Acthar** P4 MS study complete
- **Acthar** MS registry complete
- **gNO**[1] Transplant Perfusate study complete
- **ExpressGraft** P1 DFU study complete
- **Stannsoporfin** U.S. approval anticipated

2019

- **Acthar** P4 SLE study complete
- **Acthar** P2 ALS study complete
- **Terlipressin** P3 HRS-1 study complete
- **Therakos** P3 aGVHD study complete
- **StrataGraft** P2 FT study complete
- **StrataGraft** P3 DPT study complete
- **Xenon** P3 registration study complete and NDA submission

1 INOMAX expansion

THANK YOU

Mallinckrodt Pharmaceuticals