Acthar® Gel (repository corticotropin injection)

Clinical Benefit to Appropriate Patients

March 27, 2019

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Acthar provides important clinical benefit to appropriate patients

- Acthar Gel (Acthar) offers a **important treatment option for appropriate patients**
- There are **limited alternatives to Acthar as a later line treatment**
  - Providers and patients choose Acthar when patients do not respond to or cannot tolerate other therapies and the unmet medical need remains
- Multiple indications **supported by decades of clinical experience, published literature and clinical trials**
  - Acthar's **safety profile has been demonstrated and established** over many years
- The **FDA has repeatedly affirmed Acthar's beneficial effects**, as recently as 2010

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Acthar is a clinically beneficial treatment option for patients with persistent unmet need

- Acthar is FDA-approved to treat a number of serious, often rare, conditions for which there are very limited or no treatment options available
- For Infantile Spasms, Acthar is considered as a first-line therapy [a-d]
- For patients with other serious medical conditions, Acthar is often prescribed as a later-line treatment when an alternative therapeutic option is needed
  - e.g., MS relapse, NARCOMS research survey demonstrated 30% of patients experienced no change or worsening of relapses symptoms post-IVMP therapy[1]
  - Published clinical data of Acthar use in multiple therapeutic areas[2-15] demonstrates that patients typically utilized multiple therapies prior to Acthar

NARCOMS-North America Research Committee on Multiple Sclerosis; IVMP-intravenous methylprednisolone

a.Go C.Y. et al. Evidence-based guideline update: Medical treatment of infantile spasms: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society – Neurology, 2012;78:1974-1980. b Stafstrom CE et al. Treatment of IS insights from clinical & basic science perspectives - J Child Neurol 2011 26(11) 1411-1421 c. Barram TZ et al. High-dose Corticotropin (ACTH) Versus Prednisone for Infantile Spasms: A Prospective, Randomized, Blinded Study – Pediatrics 1996;97(3):375-379. d .Knupp K.G. et al. Response to Treatment in a Prospective National Infantile Spasms Cohort – Ann Neurol 2016;79:475-484

1. Nickerson M, et al, BMC Neurol. 2013;13:119. 2. Bomback AS, et al. *Am J Nephrol.* 2012;36:58-67. 3. Hladunewich MA, et al. *Nephrol Dial Transplant*. 2014;29:1570-1577. 4**.** Hogan J, et al. *Clin J Am Soc Nephrol.* 2013;8:2072-2081. 5. Filippone EJ, et al. *Int Med Case Rep J*. 2016;9:125-133. 6. Bomback AS, et al. *Drug Des Devel Ther*. 2011;5:147-153. 7. Madan A, et al. *BMC Nephrology*. 2016;17:34. 8. Tumlin JA, et al. *Kidney Int*. 2017;2:924-932. 9. Levine T. *Drug Des Devel Ther.* 2012;6:133-139. 10. Patel A, et al. *Case Rep Rheumatol*. 2016 11. Levine T, et al. *J Neurol Disord*. 2016;4(5):1-6. 12. Aggarwal R, et al. *Ann Rheum Dis*. 2017;Dec 13. Baughman RP, et al. *Lung.* 2017; 14 Baughman RP, et al. *Respir Med*. 2016;110:66-72. 15 Gillis T et al. Rheum 2017 Jul 19;9:131-138

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Significant data generated to support value of Acthar in appropriate patients

- Over **300** published abstracts and papers describing Acthar's use[1]
- **18** health economics and outcomes research (HEOR) studies and **8** company-sponsored clinical studies as of 2017
- **>110** abstracts and manuscripts published and **40+** investigator-initiated research programs funded since acquiring Acthar in 2014
- **Nearly $400 million** invested in Acthar since 2014, upon Mallinckrodt acquisition of Acthar

[1]http://www.mallinckrodt.com/research/medical-affairs

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

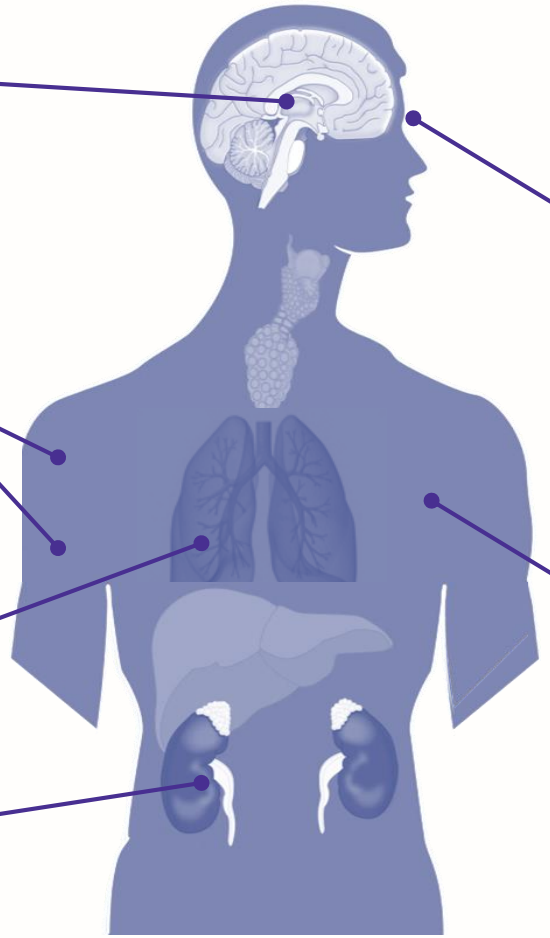
FDA-approved in 19 debilitating diseases/conditions; currently marketed in only 10 indications*

Neurology
- **Infantile spasms (IS)***
- **Multiple sclerosis (MS) flares in adults***

Rheumatology
Multiple organs (including muscle and joint):
- **Lupus***
- **Dermatomyositis/polymyositis (DM/PM)***
- **Rheumatoid arthritis (RA) 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

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Health economic and outcomes research data reinforces value of Acthar in appropriate patients

Research Priorities

- Demonstrate value in real world settings

Key Findings

- Reduced HCRU*
- Economic benefits
- Decreased medication use (corticosteroids)

*HCRU-health care resource utilization

Highlights of Recent Data Presentations

Advances in Therapy 2017; 34(8): 1775-1790.

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

Journal of Medical Economics 2017; 20(11): 1170-1177.

- **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 decreased**

Rheumatology and Therapy 2017; 4(2): 465-474.

- **RA, SLE, DM/PM, PsA**[6]: After Acthar initiation, **medical resource use significantly reduced**

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1 Systemic Lupus Erythematosus
2 Rheumatoid Arthritis
3 Dermatomyositis/Polymyositis
4 Intravenous Immunoglobulin
5 Multiple Sclerosis
6 Psoriatic Arthritis

FDA has Repeatedly Affirmed Acthar's Beneficial Effects

- The FDA reviewed the evidence addressing the indicated uses of Acthar on three separate occasions (1977, 1978, 2010) and affirmed that the product is safe and effective for the labeled indications
  - Acthar was first approved as a new drug based upon demonstration of safety. In 1962, Congress amended the FD&CA* to create the Drug Efficacy Study Implementation (DESI) review.
  - DESI review of Acthar was initiated in 1971 and finalized in 1977
    - FDA concluded the medication was effective for 52 indications
  - With exception of adding the indication for treatment of acute exacerbations of multiple sclerosis in adults in 1978, the list of FDA-approved indications remained largely unchanged until 2010.
  - In 2010, the indication of treatment of infantile spasms (IS) was added to the label.
    - The FDA reassessed the evidence in support of each of the product's then-approved indications, and specifically maintained its approval for 19 indications, including IS.

*Food Drug & Cosmetic Act

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Acthar® Gel Overview

(repository corticotropin injection)

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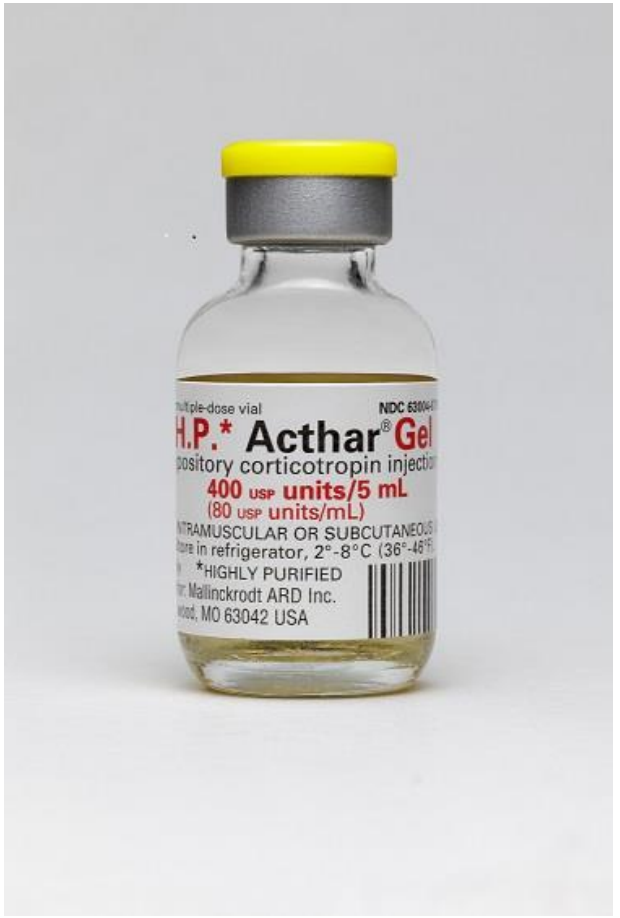
Acthar product information

Acthar Gel (repository corticotropin injection)

- Injectable peptide complex derived from porcine pituitary glands
- Contains ACTH
- Typically used in patients with moderate-to-severe disease requiring an alternative therapy
- In 16% gelatin, Acthar demonstrates prolonged release after intramuscular or subcutaneous injection
- Available as a 5 mL multi-dose vial containing 80 U/mL (400 U/vi)
- Can be administered by self-injection



Key therapeutic areas

- Neurology: IS, MS relapse
- Nephrology: Proteinuria of nephrotic syndrome
- Rheumatology: DM/PM, RA, lupus, psoriatic arthritis flares, ankylosing spondylitis flares
- Pulmonology: Symptomatic sarcoidosis
- Ophthalmology: Uveitis

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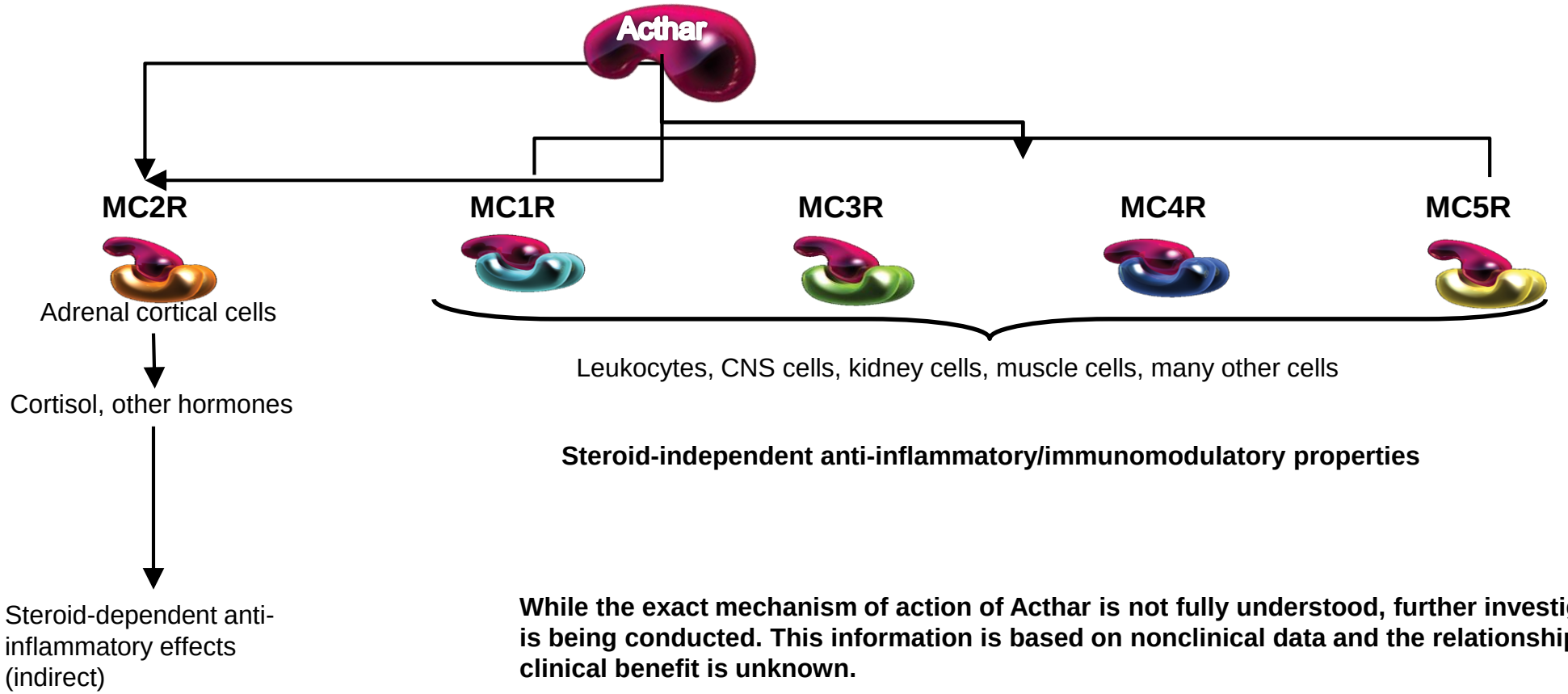
Reference: Acthar Gel Package Insert.

Acthar binds to MCRs*, potentially providing a different way to impact various cells



While the exact mechanism of action of Acthar is not fully understood, further investigation is being conducted. This information is based on nonclinical data and the relationship to clinical benefit is unknown.

*MCRs – melanocortin receptors

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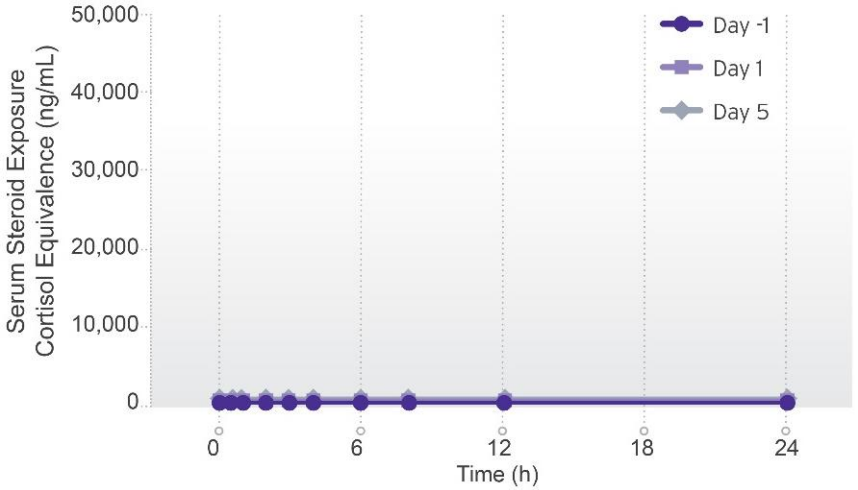
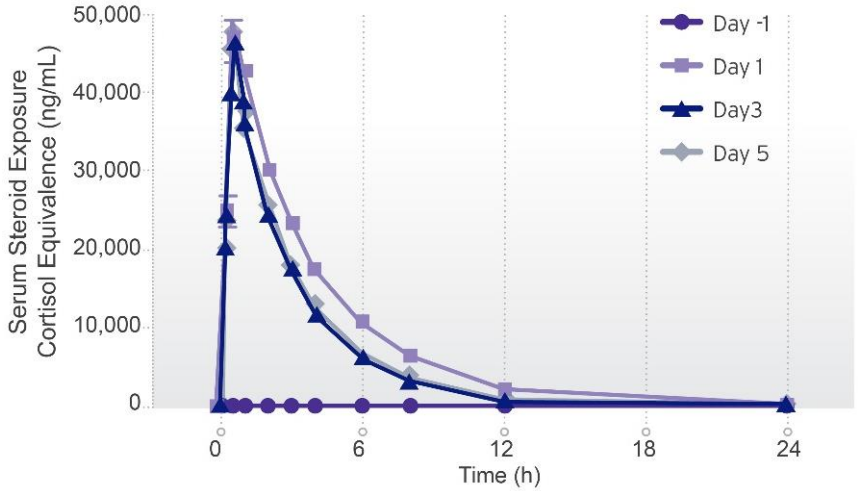
Pharmacodynamics distinguishes acthar from corticosteroids

Corticosteroids and Acthar differ in total steroid exposure[1]

A study of 18 healthy subjects showed total steroid exposure to be significantly lower with Acthar versus intravenous methylprednisolone (IVMP)*†



Acthar AUEC=3,641 h*ng/mL



IVMP AUEC=133,310 h*ng/mL

*Study was conducted in healthy volunteers and should not be used to draw comparisons between medications. The impact of these findings on clinical outcomes or safety evaluations is unknown. Although some differences in the pharmacodynamic outcomes and safety assessments were noticed in this healthy subject crossover study (N=18), the extrapolation and relevance to patient population clinical outcomes remain to be investigated.

†Total serum cortisol equivalent exposure was statistically greater for IVMP than for Acthar on day 5 ($P<0.001$). Total steroid exposure (based on cortisol equivalence) = AUEC cortisol + (MP AUC*Potency Factor of 5).

AUC=area under the curve; AUEC=area under the effect curve; IVMP=intravenous methylprednisolone.

Common adverse reactions for Acthar are similar to those of corticosteroids and include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain.

Reference: 1. Lal R, et al. *J Clin Pharmacol*. 2016;56(2):195-202.

Please see Important Safety Information later in this presentation and full Prescribing Information.

MS Relapse Treatments and Relapse Resolution: Retrospective Study Results from a US Health Plan

Tara Nazareth[1], Manasi Datar[2], Rich Sheer[2], Tzy-Chyi Yu[1], Phil Schwab[2]

1. Mallinckrodt Pharmaceuticals, Bedminster, NJ;
2. Comprehensive Health Insights (CHI), Humana, Louisville, KY

This study was funded by Mallinckrodt Pharmaceuticals

7th Joint ECTRIMS – ACTRIMS | Paris, France October 25-28, 2017 | Poster P809

Introduction

- MS affects an estimated 400,000 people in the United States (U.S.) and 2.5 million people worldwide[1]
- MS is characterized by relapses, which may indicate disease progression[2]
  - Relapses have a high cost burden and adversely impact health-related quality of life and functional ability
- Corticosteroids [CS; oral (OCS) and intravenous methylprednisolone (IVMP)] are considered first-line treatment[3]; OCS are often used first due to convenience
  - Other options which may be considered include repository corticotropin injection (RCI - Acthar Gel, approved in the U.S.), plasmapheresis (PMP; procedure), and intravenous immunoglobulin (IVIG; not approved in the US for MS relapses). Limited data supports IVIG's efficacy[3]
- Little information exists on the real-world use of relapse treatments and their effectiveness beyond CS
  - Relapse methodology using claims data does not usually account for inter-related events

1. Hersh CM, Fox RJ. Multiple sclerosis. http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/neurology/multiple_sclerosis/. Accessed August 20, 2017. **2.** Oleen-Burkey M, et al. *Patient.* 2012;5(1):57-69. **3.** National Multiple Sclerosis Society. Relapse management. http://www.nationalmssociety.org/For-Professionals/Clinical-Care/Managing-MS/Relapse-Management. Accessed on August 20, 2017.

Introduction (continued) and Objective

- We evaluate relapse episodes and unresolved relapses to do so: 1) 'relapse episode' uses a standardized 30-day[1] window to inter-relate relapse events, 2) 'unresolved relapse' uses a subsequent event occurring within 30 days[1] of a prior event to inter-relate relapse events
  - These may be used to infer lack of resolution and treatment effectiveness
- Humana, a US health and wellness company, has a coverage policy which requires experience of an acute MS relapse, and contraindications or intolerance to CS, in order to receive second-line relapse treatment
  - CS trial and failure is not required

Objective[2]:

- To evaluate the prevalence of MS relapse, use of relapse treatments, and rate of unresolved relapse per treatment. Unresolved relapses were not evaluated when the index treatment was OCS or IVMP

CS, corticosteroids; IVMP, intravenous methylprednisolone; MS, multiple sclerosis; OCS, oral corticosteroids; US, United States.

1. National Multiple Sclerosis Society. Relapse management. http://www.nationalmssociety.org/For-Professionals/Clinical-Care/Managing-MS/Relapse-Management. Accessed on August 20, 2017. **2.** Nazareth T, et al. Presented at 7th Joint ECTRIMS – ACTRIMS. October 25-28, 2017; Paris, France: Poster P809.

Methods

Study Design[1]:

- Retrospective, observational, cohort study (unrestricted enrollment)
- Study period: January 1, 2008 to July 31, 2015
- Patients ages >18 and < 90 years*

Key Definitions & Measures[1]:

- MS relapse event = inpatient admission or outpatient claim with a diagnosis of MS (ICD-9-CM code 340.xx) followed by receipt of a relapse therapy or procedure (OCS, IVMP, RCI, PMP, or IVIG) within 30 days[2]
- OCS = oral forms of dexamethasone, methylprednisolone, prednisolone, and prednisone; IVMP = intravenous methylprednisolone

*In compliance with Humana privacy requirements.

IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; MS, multiple sclerosis; OCS, oral corticosteroids; PMP, plasmapheresis; RCI, repository corticotropin injection.

References: 1. Nazareth T, et al. Presented at 7th Joint ECTRIMS – ACTRIMS. October 25-28, 2017; Paris, France: Poster P809. **2.** Ollendorf DA, et al. *Journal of Managed Care Pharmacy.* 2002;8(6):469-476.

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Methods (continued)

Key Definitions & Measures (continued):

- The relapse event date was designated the date of treatment
- The first relapse event observed = index relapse event; its date = index date
- A relapse episode comprised all relapse events (i.e., 1 or more) occurring within 30 days of the first relapse event
- A relapse event was called an ‘unresolved relapse’ event if the next relapse occurred within 30 days (and ‘new’ if it occurred >30 days) of the prior event

Data Source:

- Humana provides Medicare Advantage, stand-alone prescription drug plan, and commercial health insurance across the US
- Humana Commercial and Medicare Advantage administrative claims data, comprised of integrated medical, pharmacy, and eligibility files, were used
- This study was approved by the Schulman Institutional Review Board

US, United States.

Reference: Nazareth T, et al. Presented at 7th Joint ECTRIMS – ACTRIMS. October 25-28, 2017; Paris, France: Poster P809.

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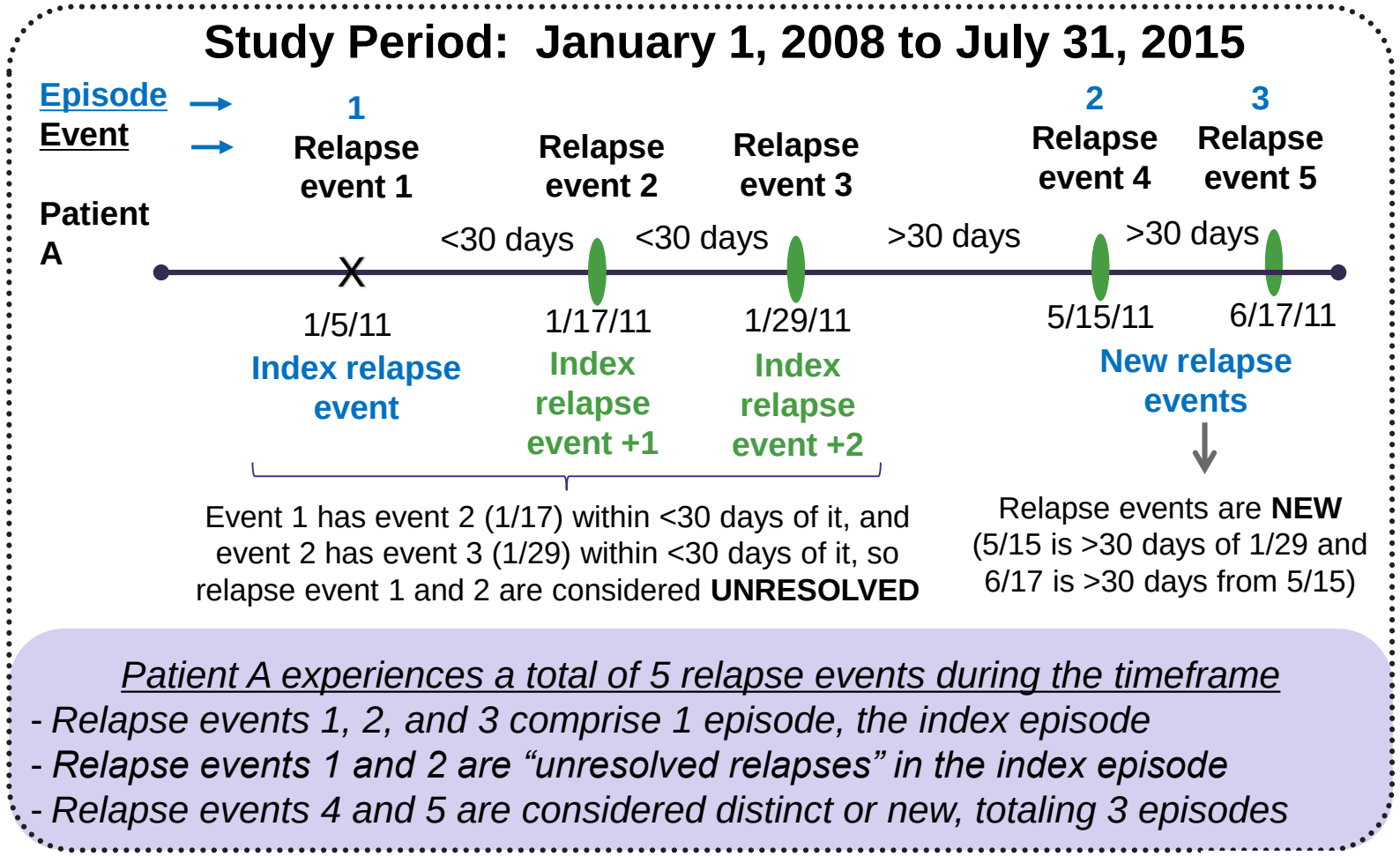
Methods (continued)

Key Relapse Definitions



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Methods (continued)

Analysis:

- Comprehensive Health Insights managed all data and conducted all analyses using SAS Enterprise Guide 7.1
- The annualized rate of relapse episodes were calculated in addition to treatments used for relapse episodes and total unresolved relapses
- Subsequent relapse episodes were calculated and the number and distribution of unresolved relapse events within the index relapse episode was assessed
- Counts below 10 had to be suppressed or combined*

*In compliance with Humana privacy requirements.

Nazareth T, et al. Presented at 7th Joint ECTRIMS – ACTRIMS. October 25-28, 2017; Paris, France: Poster P809.

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Limitations

- Administrative claims data often lack clinical detail, such as disease severity, reason for prescription, etc.
- Relapses were identified based on treatment-seeking behavior using an established claims-based algorithm[2]; treatment received outside a healthcare visit was not addressed
- Index relapse events were first observed, but perhaps not the actual first events; however, unresolved relapses evaluate subsequent (vs. prior) relapses
- Unrestricted enrollment could underestimate unresolved relapses. Analyses should be repeated with fixed enrollment*
- PMP and IVIG may be administered as courses of therapy, i.e., multiple administrations, which would lead to an underestimation of relapse resolution*

*Nazareth T, Sheer R, Datar M, Schwab P, Yu TC. Relapse resolution and HCRU in patients with MS: A retrospective study of relapse therapy alternatives to corticosteroids. Presented at 7th Joint ECTRIMS - ACTRIMS event, Paris, France, October 25-28, 2017. ePoster EP1425.

IVIG, intravenous immunoglobulin; PMP, plasmapheresis.

1. Nazareth T, et al. Presented at 7th Joint ECTRIMS – ACTRIMS. October 25-28, 2017; Paris, France: Poster P809.

2. Ollendorf DA, et al. *Journal of Managed Care Pharmacy.* 2002;8(6):469-476.

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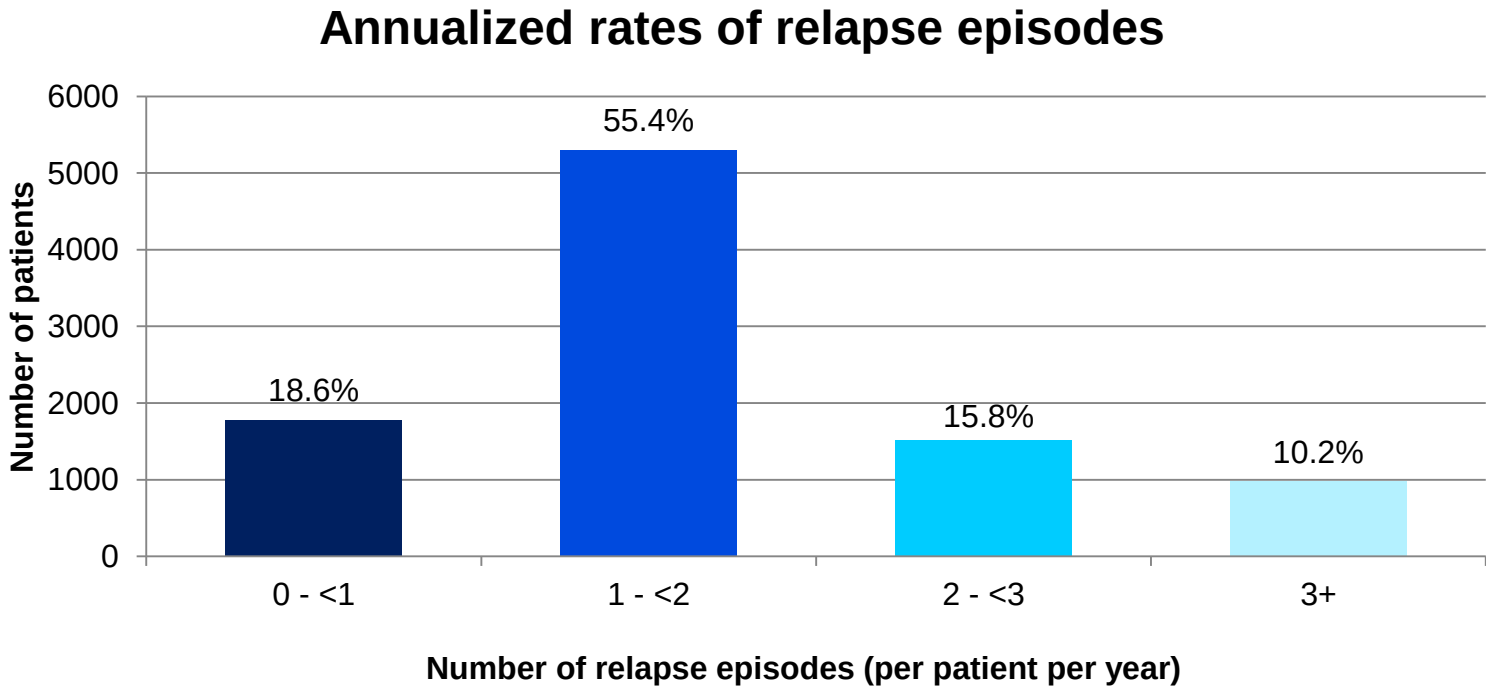
Results: Annualized Rates of Relapse Episodes

- 9,574 patients with relapse episodes and 25,162 relapse episodes were identified
  - The mean ± SD follow-up time per patient was 2.7 ± 2.1 years
- The majority of patients (74.0%) had <2 relapse episodes and 26.0% had ≥2 relapses per year



SD, standard deviation.

Nazareth T, et al. Presented at 7th Joint ECTRIMS – ACTRIMS. October 25-28, 2017; Paris, France: Poster P809.

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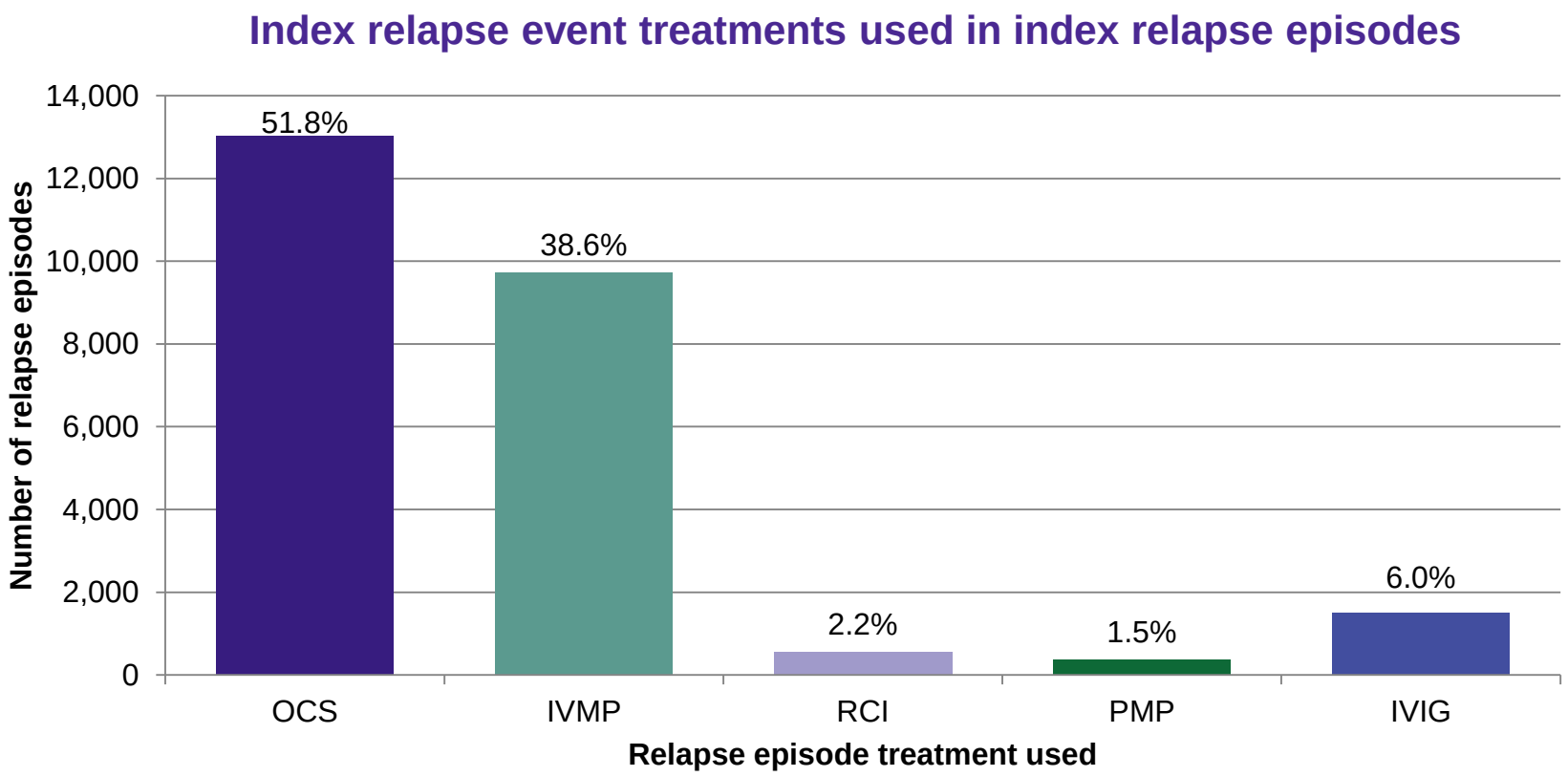
Results: Treatments used for relapse episodes

- CS were used to treat 90.4% of index relapse events (OCS 51.8%, IVMP 38.6%) within the index relapse episode



CS, corticosteroids; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; OCS, oral corticosteroids; PMP, plasmapheresis; RCI, repository corticotropin injection.

Reference: Nazareth T, et al. Presented at 7th Joint ECTRIMS – ACTRIMS. October 25-28, 2017; Paris, France: Poster P809.

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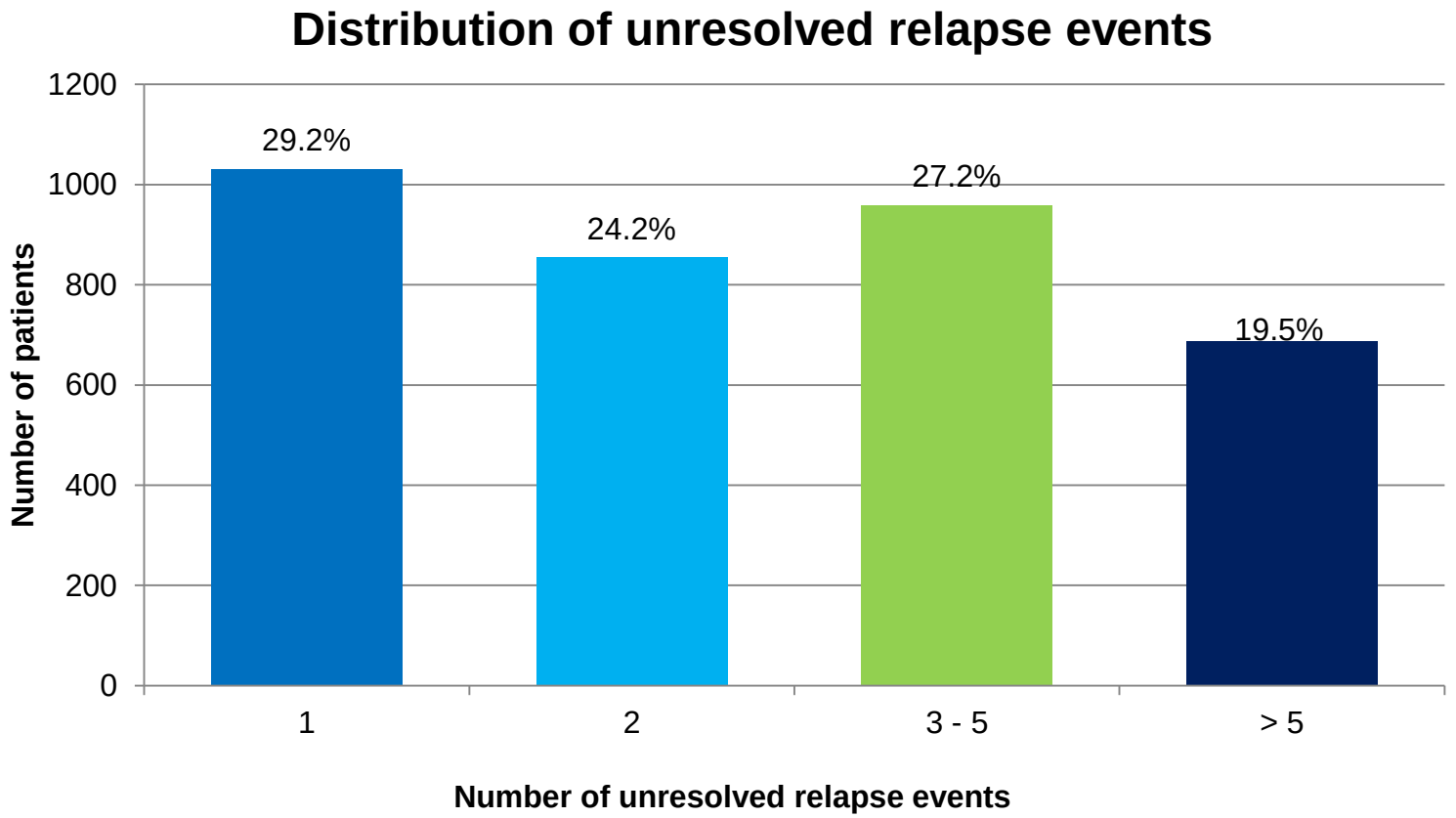
Results: Distribution of Unresolved Relapse Events

- Of patients experiencing relapse episodes, 36.9% (n=3,532) of patients had ≥1 unresolved relapse event, for a total 16,707 unresolved relapse events during the study period [mean (SD) = 4.7 (8.9) unresolved relapse events per patient]



SD, standard deviation.

Nazareth T, et al. Presented at 7th Joint ECTRIMS – ACTRIMS. October 25-28, 2017; Paris, France: Poster P809.

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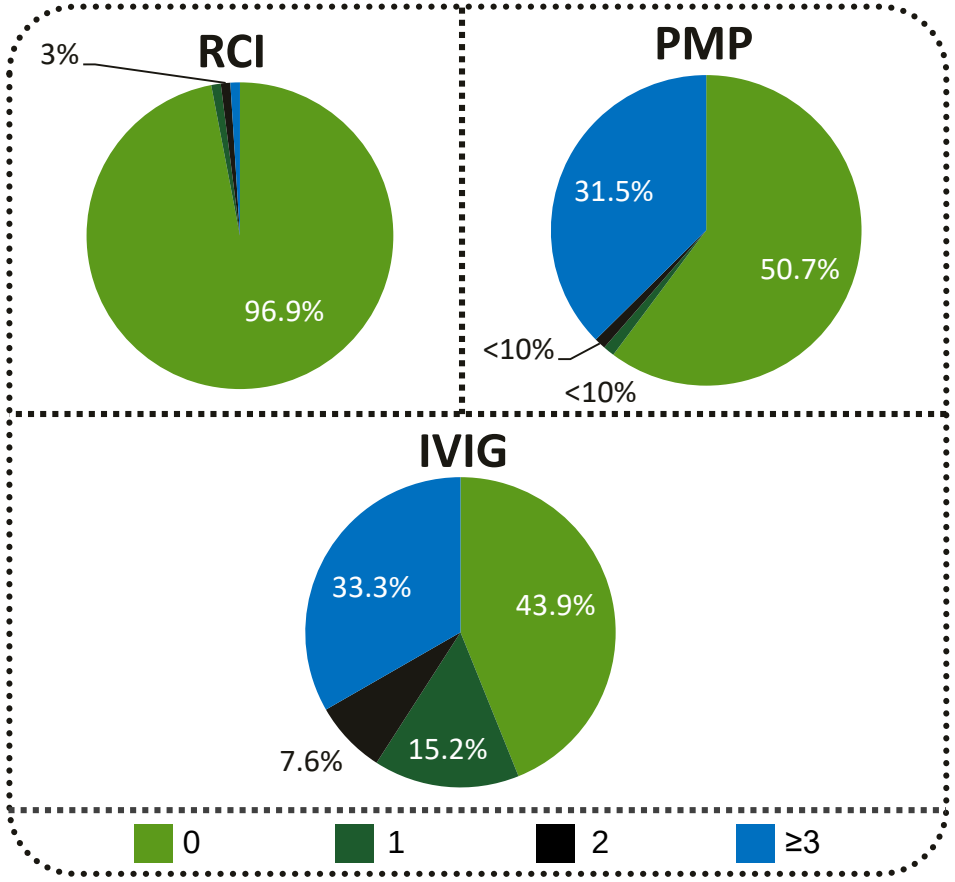
Results: Unresolved relapse events in the index episode

- When treated with RCI, 96.9% of patients had 0 unresolved relapses
- When treated with PMP and IVIG, 50.7% and 43.9% of patients, respectively, had 0 unresolved relapses
- The distribution of unresolved relapses (1, 2, ≥3) remained lowest with RCI

Unresolved relapses in the index episode analyses



*Further analyses will address this (Nazareth T, et al. Presented at 7th Joint ECTRIMS – ACTRIMS. October 25-28, 2017; Paris, France: e-Poster EP1425.)
IVIG, intravenous immunoglobulin; PMP, plasmapheresis; RCI, repository corticotropin injection.
Reference: Nazareth T, et al. Presented at 7th Joint ECTRIMS – ACTRIMS. October 25-28, 2017; Paris, France: Poster P809.

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Key Findings

- Study results provide current insight into existing challenges with MS relapse
- 26% of patients with MS experienced 2 or more relapse episodes per year
- Over 1/3 of patients experienced ≥1 unresolved relapse event, requiring additional relapse treatment beyond the initial treatment received
- Based on index relapse episode analyses, we found unresolved relapse rates differed by treatment. Patients receiving RCI had the lowest unresolved relapse rate; 96.9% (RCI), 43.9% (IVIG), and 50.7% (PMP) experienced 0 unresolved relapses
- Robust management of MS relapse should reflect timely resolution with appropriate treatment to minimize patient burden

IVIG, intravenous immunoglobulin; MS, multiple sclerosis; PMP, plasmapheresis; RCI, repository corticotropin injection.

Nazareth T, et al. Presented at 7th Joint ECTRIMS – ACTRIMS. October 25-28, 2017; Paris, France: Poster P809.

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Importance of treating MS relapses

Incomplete Recovery from MS Relapses is Associated with Disability:

- 42% of patients maintained residual deficit as measured by EDSS at ≥30 days post-exacerbations[1]
- The residual from exacerbation does not diminish with time[1]
- Acute exacerbations of MS have a measurable and sustained effect on accrued impairment and disability in MS[1]
- 49.4% of patients had a residual increase in disability post-relapse of at least 0.5 EDSS points[2]
  - 32.7% had an increase of at least 1 point[2]
- Acute relapses are commonly associated with objective worsening of disability in majority of patients with MS[2]
  - Recovery is incomplete in approximately half of patients[2]

Effective Relapse Treatment Improves Chances of More Complete Recovery:

- The longer the length of time a lesion enhances, the greater the risk for development of a persistent black hole[3,4]

References: 1. *Lublin FD, et al. Neurology. 2003;61:1528-1532 2. Hirst C, et al. J Neurol. 255:280-287*
3. *Naismith RT et al., Neurology. 2010;74:1694-701* 4. *Bagnato et al., Brain. 2003;126:1782-1789.*

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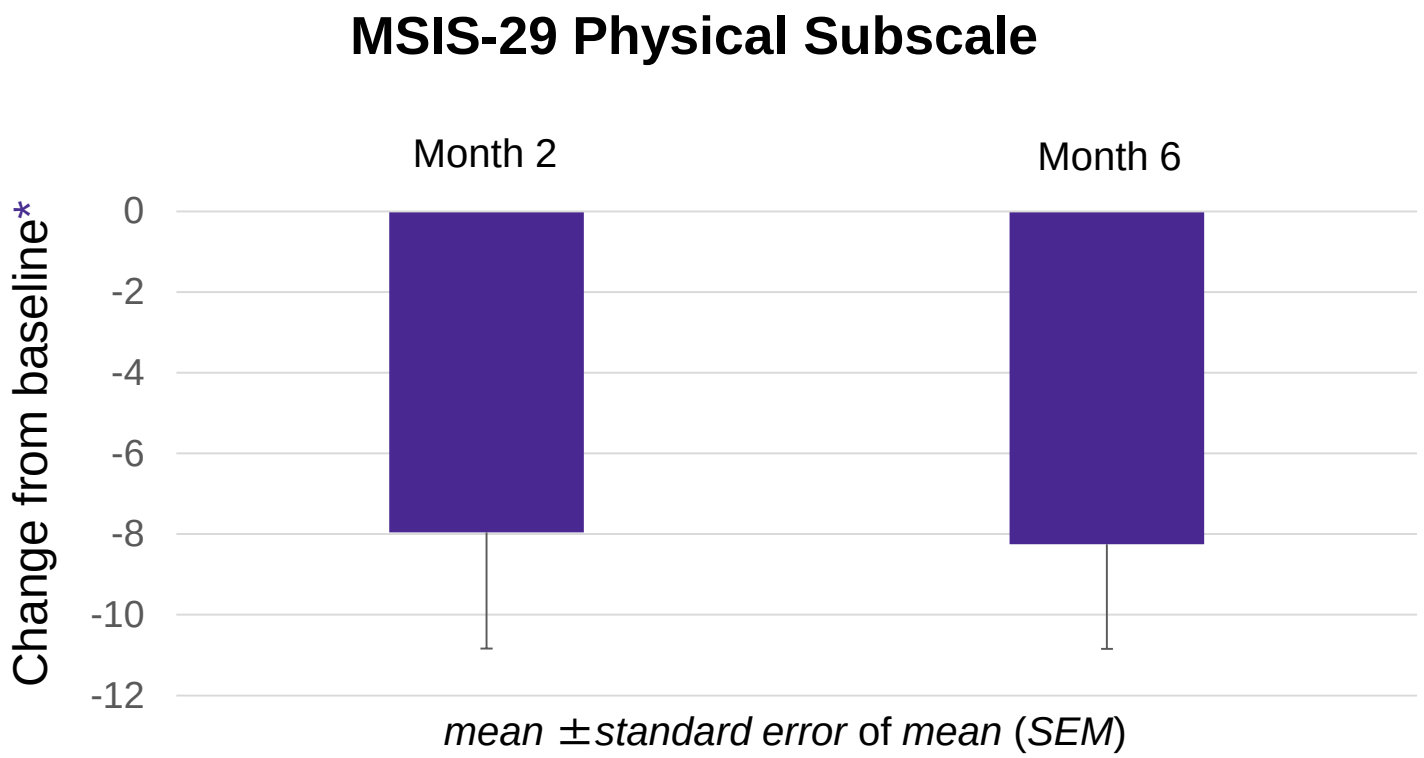
Acthar MS Relapse Registry: Enrolled over 100 patients, preliminary results show clinically meaningful improvements

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]

Data on File

[1]Costelloe et al. 2007

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Proteinuria in Nephrotic Syndrome

Acthar is indicated to induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus.

Contraindications

- Acthar should never be administered intravenously.
- Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar.
- Acthar is contraindicated where congenital infections are suspected in infants.
- Acthar is contraindicated in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency, adrenocortical hyperfunction or sensitivity to proteins of porcine origins.

Acthar has clinical experience across various etiologies of nephrotic syndrome

Dataset	Journal	Type of Dataset	N
Bomback, et al 2012[1]	Am J Nephrol	Prospective open-label trial	15
Hladunewich, et al 2014[2]	Nephrol Dial Transplant	Prospective randomized trial	20
Hogan, et al 2013[3]	Clin J Am Soc Nephrol	Combined prospective trial and retrospective review	24[a]
Filippone, et al 2016[4]	Int Med Case Rep J	Retrospective case series	13
Bomback, et al 2011[5]	Drug Des Devel Ther	Retrospective case series	21
Madan, et al 2016[6]	BMC Nephrology	Retrospective case series	40
Tumlin, et al 2017[7]	Kidney Int	Prospective observational study	22

[a] Included 4 patients from previous datasets—1 patient from 2011 dataset and 3 patients from 2012 trial; the Hogan dataset includes longer follow-up data for these patients. [b] No biopsy performed.

These datasets are subject to limitations. The data combine retrospective observational data with prospective data of patients who were not randomly assigned to therapy. There was no comparison group for interpretation of safety and efficacy findings with Acthar. Most patients were on multiple therapies during Acthar treatment, and the clinical outcomes may not be solely attributable to Acthar.

References: 1. Bomback AS, et al. *Am J Nephrol.* 2012;36:58-67. **2.** Hladunewich MA, et al. *Nephrol Dial Transplant*. 2014;29:1570-1577. **3.** Hogan J, et al. *Clin J Am Soc Nephrol.* 2013;8:2072-2081. **4.** Filippone EJ, et al. *Int Med Case Rep J*. 2016;9:125-133. **5.** Bomback AS, et al. *Drug Des Devel Ther*. 2011;5:147-153. **6.** Madan A, et al. *BMC Nephrology*. 2016;17:34. doi: 10.1186/s12882-0241-7. **7.** Tumlin JA, et al. *Kidney Int*. 2017;2:924-932.

Please see Important Safety Information later in this presentation and full Prescribing Information.

Nephrotic syndrome is one of the principal presentations of glomerular disease

Reflects the pathophysiologic effects of urinary losses of large quantities of protein	Persistent marked proteinuria is a requirement (>3.5 g/day in an adult; >50 mg/kg or >40 mg/hr/m^2 in a child)

Other characteristics	Hypoalbuminemia
	Edema
	Hyperlipidemia
	Lipiduria

Terminology	Albuminuria	Proteinuria
Physiologic range proteinuria	<20 mg/day (15 µg/min)	<150 mg/day
Nephrotic range proteinuria	N/A	>3.5 g/day

Healthy kidneys excrete less than 150 mg of protein/day; approximately 20 mg is albumin

References: 1. Stoycheff N et al. *Am J Kidney Dis*. 2009;54:840-849. **2.** de Seigneux S et al. *Swiss Med Wkly*. 2009;139:416-422.
3. Floege J et al. *Comprehensive Clinical Nephrology*. 2010; 193-207. **4.** Naderi AS et al. *J Am Board Fam Med.* 2008; 21: 569-574.

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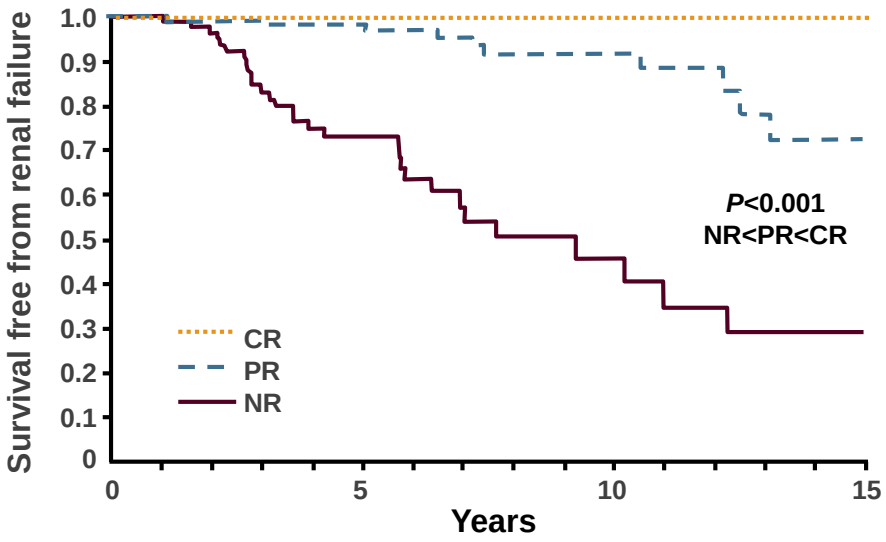
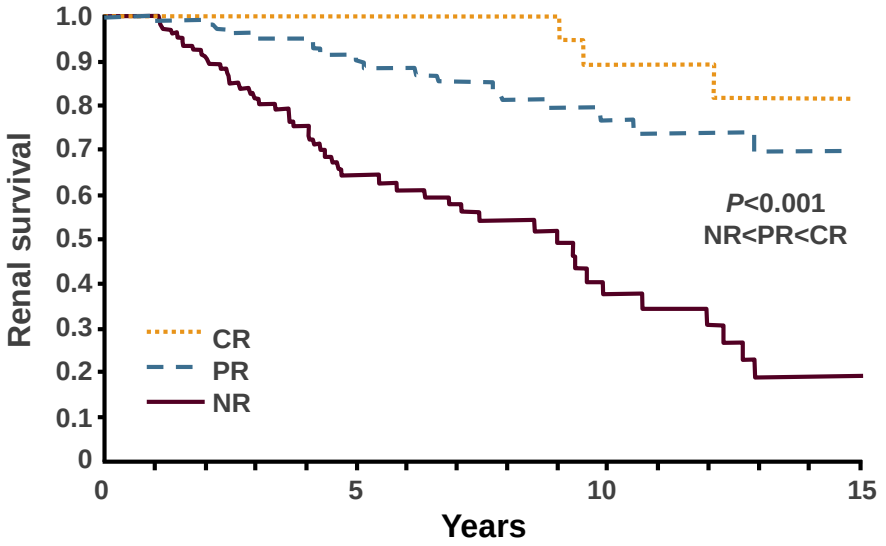
Studies demonstrate that complete and partial remission of proteinuria prolongs kidney survival

Idiopathic Membranous Nephropathy[1]



Focal Segmental Glomerulosclerosis[2]



Number of patients assessed at follow-up:

Years	0	5	10	15
CR	102	67	33	12
PR	135	74	32	9
NR	106	34	9	4

0	5	10	15
55	40	16	8
117	62	27	11
108	43	13	5

CR, complete remission: proteinuria ≤300 mg/day; NR, no remission; PR, partial remission: proteinuria <3500 mg/day plus a 50% reduction from peak value.

1. Adapted with permission from Troyanov S, et al. *Kidney Int*. 2004;66:1199-1205.
2. Adapted with permission from Troyanov S, et al. *J Am Soc Nephrol*. 2005;16:1061-1068.

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Hladunewich 2014: Determining the dose and effectiveness of Acthar in iMN nephropathy

	Hladunewich 2014
Type of Dataset	Prospective randomized trial
# of Patients	20
Endpoints	Changes in the measures of nephrotic syndrome including improvements in proteinuria, serum albumin and cholesterol profile as well as documented side effects and toxicity
Dosage	▪ 1:1 block randomization to either 40 or 80 units twice weekly; patients received twice weekly dosing starting Week 5 ▪ Crossover patients: patients receiving 40 unit dose who did not demonstrate significant improvement in urine protein by Day 91 were offered a dose increase to 80 units 2x/wk for an additional 12 weeks (Mayo Clinic only)

Efficacy	▪ Mean proteinuria (entire cohort) improved significantly from 9.1 g/day at baseline to:
	  ▪ 6.2 g/day at completion of Acthar therapy ($P<0.05$)
	  ▪ 3.9 g/day at 1 year follow-up ($P<0.001$)
	▪ 50% (10/20) had >50% reduction in urine protein at completion of Acthar therapy
	▪ 65% (13/20) had >50% reduction in urine protein at 1 year follow-up

Safety	The two most common adverse effects were hyperglycemia (13 patients) and skin changes (7 patients). See study description for full adverse events information

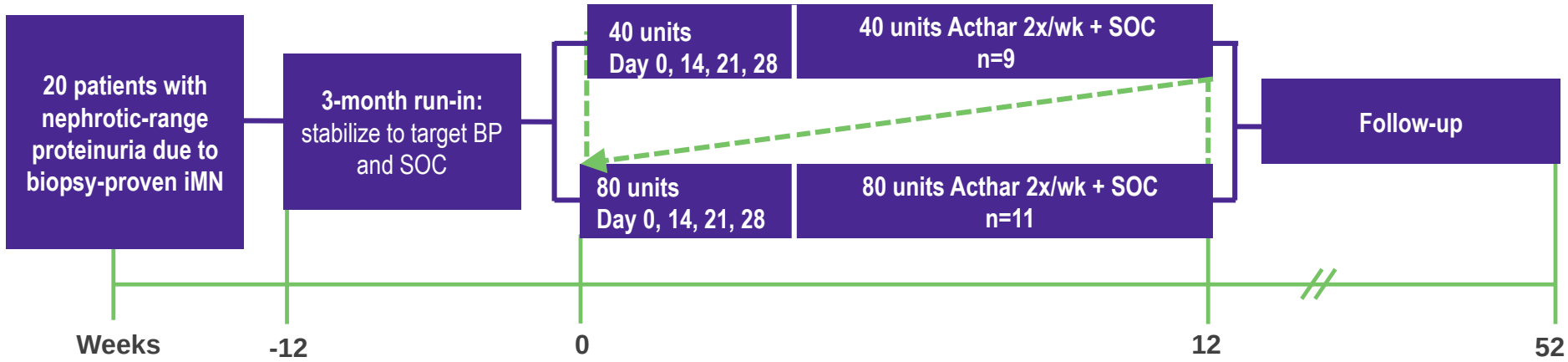
Reference: Hladunewich MA et al. *Nephrol. Dial Transplant*. 2014; 0:1-8.

Please see Important Safety Information later in this presentation and full Prescribing Information.

Hladunewich 2014 study: Determining the dose and effectiveness of Acthar Gel in iMN nephropathy

Objective

- Describe the findings from a Phase Ib/II pilot study using Acthar in patients with iMN



Study Design

- Study performed at Mayo Clinic and University of Toronto
- Standard of care (SOC): maximum tolerated/FDA-approved RAS blockade to target BP (<130/75 mm Hg); statins to maximum recommended dose; dietary counseling to maintain a low-salt diet (2-3 g/day) and a dietary protein intake of 0.8 g/kg ideal body weight/day of high-quality protein
- 1:1 block randomization to either 40 or 80 units twice weekly; patients received twice weekly dosing starting Week 5
- Crossover patients: patients receiving 40 unit dose who did not demonstrate significant improvement in urine protein by Day 91 were offered a dose increase to 80 units 2x/wk for an additional 12 weeks (Mayo Clinic only)

Please see Important Safety Information later in this presentation and full Prescribing Information.

Source: Hladunewich MA et al. *Nephrol. Dial Transplant*. 2014; 0:1-8.

Hladunewich 2014 study: Determining the dose and effectiveness of Acthar Gel in iMN nephropathy

Study Design (cont'd)

- Primary outcome measures
  - Changes in the measures of nephrotic syndrome including improvements in proteinuria, serum albumin, and cholesterol profile
  - Documented side effects and toxicity
- Secondary endpoints
  - Proportion of patients achieving complete remission, partial remission, or no response
- Additional measures
  - Cortisol, blood glucose, and anti-PLA_2R
  - 24-hour proteinuria, eGFR, and blood pressure monitored throughout the study

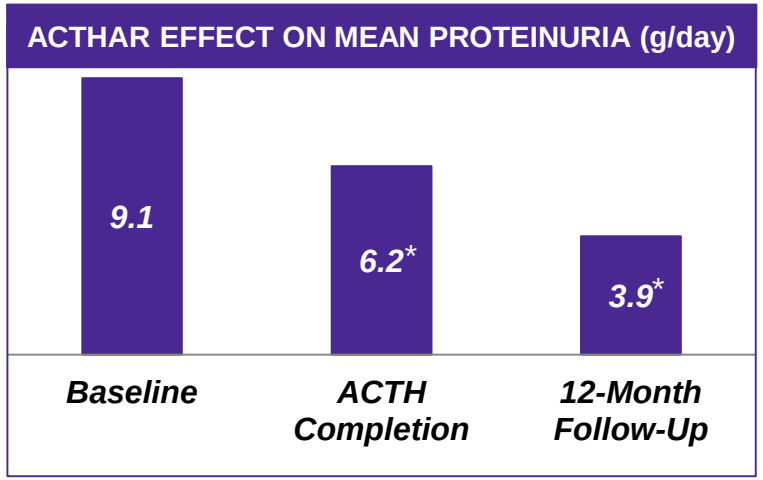
Source: Hladunewich MA et al. *Nephrol. Dial Transplant*. 2014; 0:1-8.

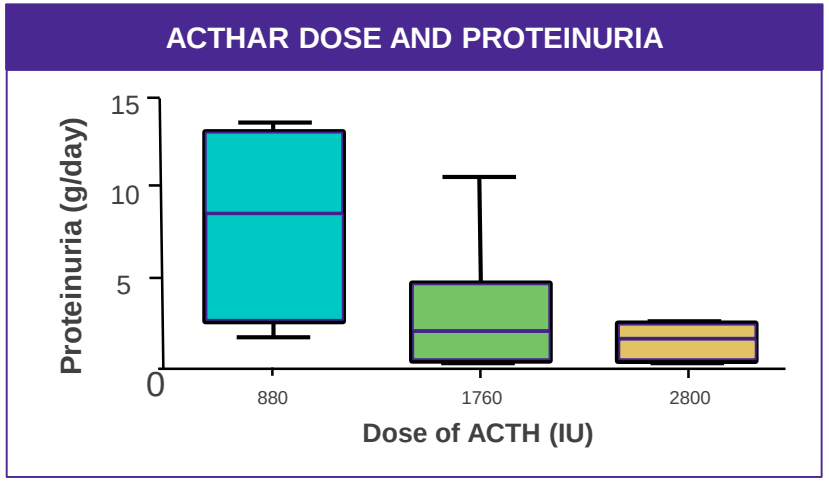
Please see Important Safety Information later in this presentation and full Prescribing Information.

Hladunewich 2014: Determining the dose and effectiveness of Acthar in iMN nephropathy (continued)

Results:

- Mean proteinuria (entire cohort) improved significantly from 9.1 g/day at baseline to:
  - 6.2 g/day at completion of Acthar therapy (*P*<0.05)
  - 3.9 g/day at 1 year follow-up (*P*<0.001)
- 50% (10/20) had >50% reduction in urine protein at completion of Acthar therapy
- 65% (13/20) had >50% reduction in urine protein at 1 year follow-up
- Proteinuria was inversely related to cumulative Acthar dose and the trend of this relationship was statistically significant (R=0.53, *P*<0.05)





Reference: Hladunewich MA et al. *Nephrol. Dial Transplant*. 2014; 0:1-8.

Please see Important Safety Information later in this presentation and full Prescribing Information.

Hladunewich 2014: Determining the dose and effectiveness of Acthar in iMN nephropathy (continued)

Adverse effects	Number of patients (%)
Cushingoid appearance	3 (15)
Weight gain (≤7 kg)	5 (25)
Transient worsening of edema or bloating	3 (15)
Skin changes (acne, flushing, or bronzing)	7 (35)
Psychological (irritability, depression, or improved mood)	6 (30)
Transient insomnia	6 (30)
Bruising at injection site	5 (25)
Hyperglycemia	13 (65)
Transient blood glucose increase ≥130 mg/dL	5 (25)

Tremulousness (n=3), hoarseness (n=2), dizziness (n=5), muscle aches or pain (n=5), headaches (n=5), GI symptoms (n=7), blurred vision (n=2), and generalized weakness or fatigue (n=9) were also described throughout the year of follow-up, but were not in all cases clearly related to the therapy

Reference: Hladunewich MA et al. *Nephrol. Dial Transplant*. 2014; 0:1-8.

Please see Important Safety Information later in this presentation and full Prescribing Information.

Hladunewich 2014 study: Determining the dose and effectiveness of Acthar in iMN nephropathy (cont'd)

Clinical data limitations

- Results may not be fully representative of outcomes in the overall patient population
- No comparison or control group
- Patients were receiving standard of care medications (e.g., RAS blockade, statins) in addition to Acthar.
- The clinical outcomes may not be solely attributable to Acthar.
- Acthar dosing regimens and duration varied and these limitations should be taken into consideration when interpreting results.

Source: Hladunewich MA et al. *Nephrol. Dial Transplant*. 2014; 0:1-8.

Dermatomyositis and Polymyositis

Acthar is indicated during an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus, systemic dermatomyositis (polymyositis)

Contraindications

- Acthar should never be administered intravenously.
- Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar.
- Acthar is contraindicated where congenital infections are suspected in infants.
- Acthar is contraindicated in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency, adrenocortical hyperfunction or sensitivity to proteins of porcine origins.

Efficacy and Safety of Adrenocorticotropic Hormone Gel (Acthar) in Refractory Dermatomyositis and Polymyositis

A 2-site, open-label trial of patients diagnosed with DM or PM who were refractory to first- and second-line therapies (N=11)

Aggarwal R, Marder G, Koontz DC, et al. *Ann Rheum Dis*. Published Online First: 13 December 2017. doi: 10.1136/annrheumdis-2017-212047

Acthar® Gel (repository corticotropin injection) is indicated during an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus, systemic dermatomyositis (polymyositis)

Please see Important Safety Information later in this presentation and full Prescribing Information.

Dermatomyositis and Polymyositis – background

- Idiopathic inflammatory myopathies are a group of systemic autoimmune muscle disorders characterized by inflammation of skeletal muscle
- Dermatomyositis (DM) and polymyositis (PM) are among the most common idiopathic inflammatory myopathies
- Many patients with DM/PM either require high doses of glucocorticoids with significant side effects or are refractory to conventional immunosuppressive drugs

Reference: Aggarwal R et al. *Ann Rheum Dis.* 2017 Dec 13. doi: 10.1136/annrheumdis-2017-212047.

Please see Important Safety Information later in this presentation and full Prescribing Information.

Study objectives and design and patient overview

Study Objectives

- Proof-of-concept study to evaluate the efficacy, safety, tolerability, and steroid-sparing effect of Acthar in patients with refractory DM and PM

Patient Overview

- 11 patients with DM (n=6) or PM (n=5) were enrolled
- 82% of the cohort possessed ≥1 myositis-associated autoantibody

Study Design

- 24-week, 2-site, prospective, open-label study
- Patients were evaluated every 4 weeks for a total of 7 visits

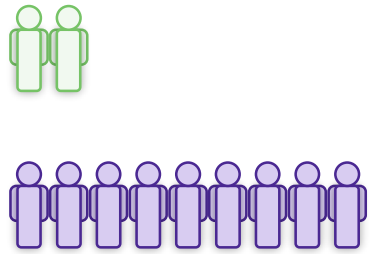
Average age

49 years

(range, 27-75 years)

Male (n=2)

Female (n=9)



Reference: Aggarwal R et al. *Ann Rheum Dis.* 2017 Dec 13. doi: 10.1136/annrheumdis-2017-212047.

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Treatment

Treatment

- Acthar was self-administered 80 U 2X/week via subcutaneous injection from week 0 through week 24
- All 11 patients had previously failed glucocorticoids and a mean of 2.6 additional immunosuppressive agents before the trial

10 of 11 patients[a]
completed treatment through
week 24

- All 11 patients were also being treated with stable doses of ≥1 other commonly used therapy for DM or PM, including:
  - Prednisone (n=11; mean baseline dose, 19.5 mg)
  - Methotrexate (n=5)
  - Azathioprine (n=3)
  - Mycophenolate mofetil (n=5)
  - Tacrolimus (n=1)
  - Cyclosporine (n=5)
  - Hydroxychloroquine (n=2)
- Patients were receiving a stable dose of these medications for ≥8 weeks pre-trial and were maintained during Acthar treatment, except for decreases in prednisone dosing

[a]Patient discontinued due to heart block unrelated to study drug.

Reference: Aggarwal R et al. *Ann Rheum Dis.* 2017 Dec 13. doi: 10.1136/annrheumdis-2017-212047.

Clinical Experience in Dermatomyositis and Polymyositis

Primary Endpoint Measure

- International Myositis Assessment and Clinical Studies Group (IMACS) definition of improvement (DOI)
  - 3 of any of the 6 core set measures (CSM) improved by ≥20%, with no more than 2 CSM worsening by ≥25%[a]
- Primary endpoint was also evaluated on a subset of patients with severe muscle weakness (≤ 125/150 of MMT at baseline), as well as moderate to severe cutaneous DM rashes (≥ 2.5/10 cutaneous VAS score at baseline)

Secondary Endpoint Measure

- Frequency and type of adverse events (AEs) and serious adverse events (SAEs)
  - Measured by detailed questionnaires, patient reports, and study withdrawal due to study drug side effects or tolerability problems
- Additional secondary endpoints included:
  - Change in individual CSM from baseline
  - Time to DOI from baseline
  - 2016 ACR/EULAR myositis response criteria
  - Change in glucocorticoid dose from baseline

[a] Worsening measure cannot include manual muscle testing (MMT).

Reference: Aggarwal R et al. *Ann Rheum Dis.* 2017 Dec 13. doi: 10.1136/annrheumdis-2017-212047.

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Clinical Experience in Dermatomyositis and Polymyositis (continued)

Primary Endpoint: 70% of Patients Met the DOI After Treatment With Acthar

- 7 of 10 patients completing the study met the IMACS DOI by a median of 8 weeks (interquartile range [IQR]= 4 to 20 weeks)
- DM and PM patients did not differ in their response to treatment

Secondary Endpoints

- 90% of patients met the secondary outcome measure of minimal improvement using the new 2016 ACR/EULAR myositis response criteria, but 2 patients had significant worsening before the 24-week period
- Median (IQR) total improvement score[a] was 52.5 (30-65) at 24 weeks with 40%, 30%, and 20% of patients achieving minimal, moderate, and major improvement, respectively

Study Limitations

- Results are based on 10 patients who completed the study. This study may not be fully representative of outcomes in the overall patient population. All patients were on multiple therapies; therefore the clinical outcomes may not be solely attributable to Acthar. Acthar has not been formally studied in combination with other treatments

[a]Metric derived from the 2016 ACR/EULAR myositis response criteria, which corresponds to magnitude of improvement.

Reference: Aggarwal R et al. *Ann Rheum Dis.* 2017 Dec 13. doi: 10.1136/annrheumdis-2017-212047.

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Clinical Experience in Dermatomyositis and Polymyositis
Safety Findings

Summary of Adverse Events (AEs)	n
Injection site bruising	4
Hyperglycemia	3
Insomnia	2
Calcinosis	2
Infection (sinusitis and URI)	2
Hypertension	2
Diarrhea	1
Anxiety	1
Depression	1
Agitation	1
Herpes pneumonitis	1
Sinus tachycardia	1
High cholesterol	1

Safety Results

- 5 serious AEs (SAEs) were reported in 3 patients:
  - Herpes zoster infection
  - Disseminated Herpes zoster infection
  - Avascular necrosis
  - Chest pain
  - Heart block (not related to study drug)
- 22 AEs were reported in 8 patients:
  - Most were mild to moderate in severity
- No patient developed microalbuminuria or cushingoid features
- No significant increase in mean weight from baseline
- None of the AEs required long-term dose interruption or dose reduction were considered mild
- No patient discontinued treatment due to AEs
- Mean (SD) glycosylated hemoglobin A1c (HbA1c) did not change over 24 weeks
- No significant changes in white blood cell count, hemoglobin, platelet count, sedimentation rates, serum creatinine, or blood glucose

Select Important Safety Information

Adverse Reactions: Common adverse reactions for Acthar are similar to those of corticosteroids and include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite, and weight gain.

Reference: Aggarwal R et al. *Ann Rheum Dis.* 2017 Dec 13. doi: 10.1136/annrheumdis-2017-212047.

Please see Important Safety Information later in this presentation and full Prescribing Information.

Chronic Pulmonary Sarcoidosis

Acthar is indicated for symptomatic sarcoidosis

Contraindications

- Acthar should never be administered intravenously.
- Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar.
- Acthar is contraindicated where congenital infections are suspected in infants.
- Acthar is contraindicated in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency, adrenocortical hyperfunction or sensitivity to proteins of porcine origins.

Please see Important Safety Information later in this presentation and full Prescribing Information.

Repository Corticotropin (Acthar) for Chronic Pulmonary Sarcoidosis

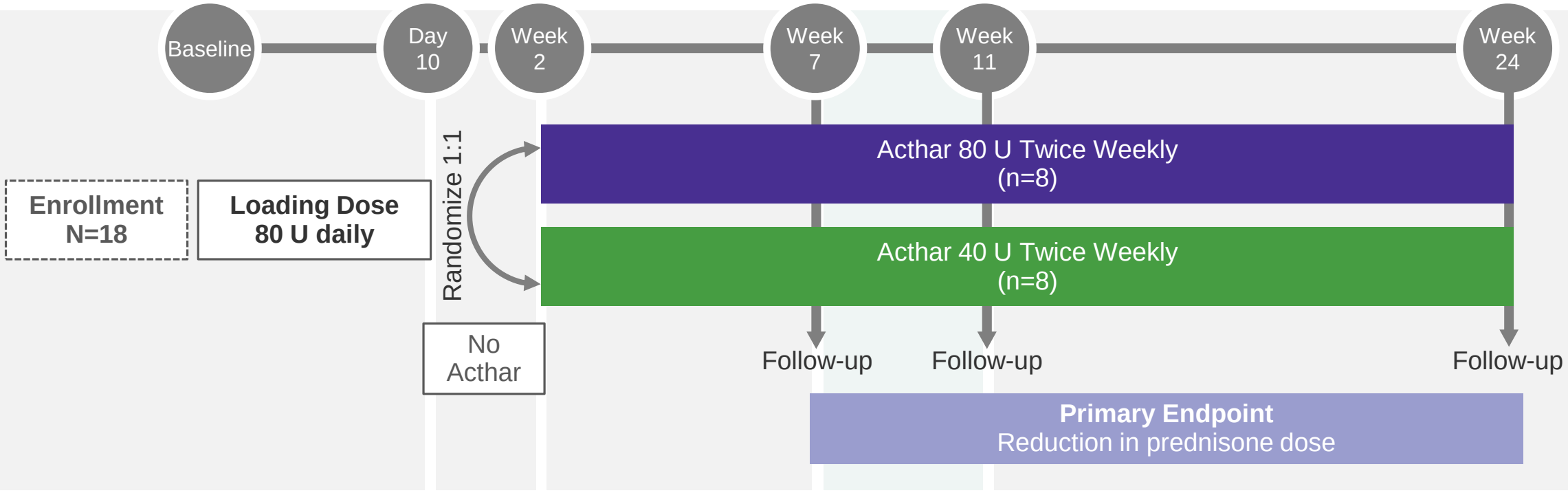
A Prospective, Pilot Study Examining the Use of Acthar Gel in Patients With Advanced Pulmonary Sarcoidosis

Baughman et al. *Lung.* 2017; 195(3):313-322

Acthar® Gel (repository corticotropin injection) is indicated for symptomatic sarcoidosis

Please see Important Safety Information later in this presentation and Full Prescribing Information.

A prospective, single-blind, pilot study examining the use of Acthar in patients with advanced pulmonary sarcoidosis[a]



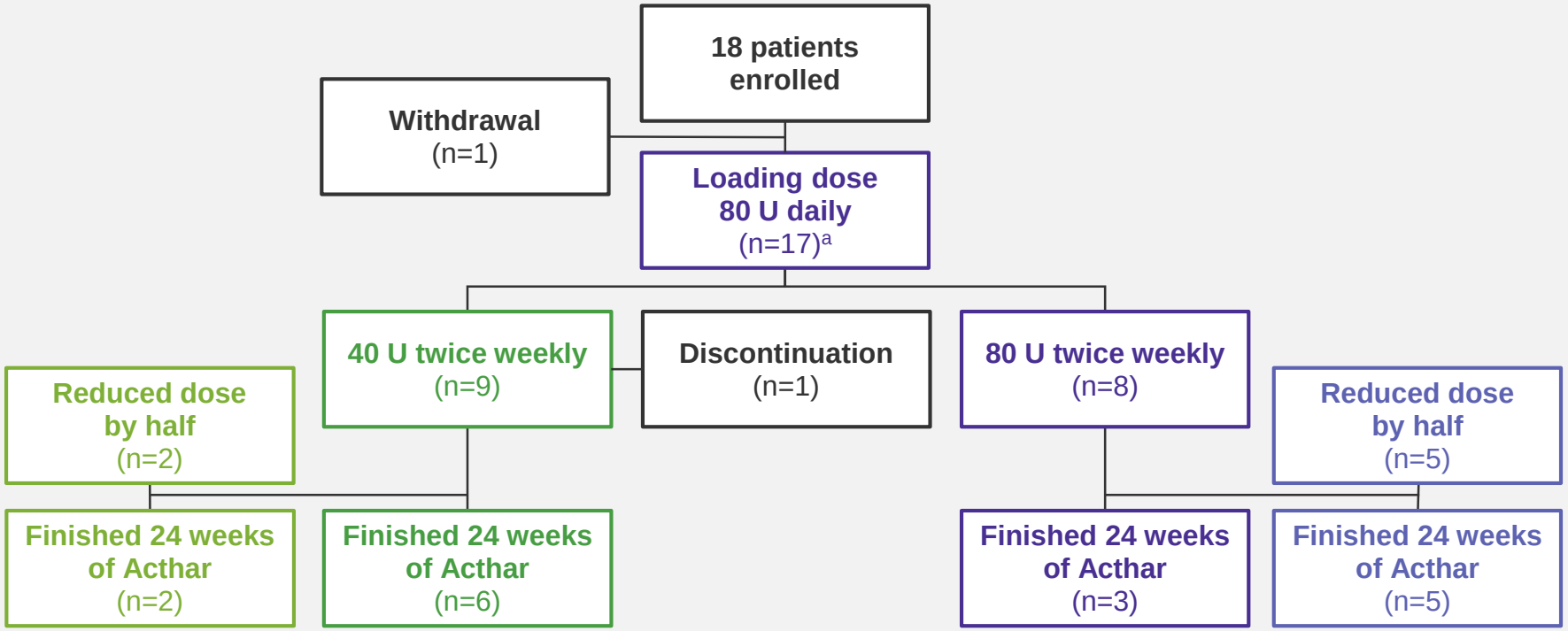
Patients had the flexibility to reduce their dose by half due to perceived problems with drug treatment

[a]**The efficacy and safety results discussed may not be representative of the overall symptomatic sarcoidosis patient population. Patients may have been on multiple medications. The clinical outcomes for the patients discussed may not be solely attributable to Acthar.**

Reference: Baughman et al. *Lung.* 2017; 195(3):313-322

Please see Important Safety Information later in this presentation and full Prescribing Information.

Study flow



Due to the study's small population size,
no comparisons can be made between the 40 and 80 U doses by week 24

[a]5 patients stopped the loading schedule at days 7 through 9 due to toxicity.

Reference: Baughman et al. *Lung.* 2017; 195(3):313-322

Please see Important Safety Information later in this presentation and full Prescribing Information.

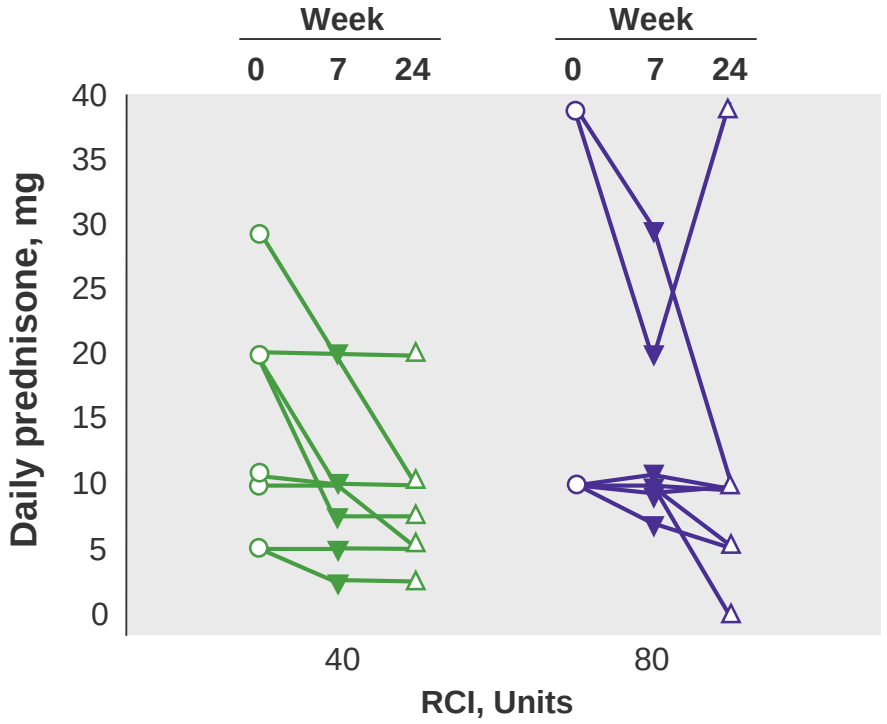
Study limitations according to the author[a]

- Results are based on a single-blind, prospective, pilot study of 18 patients and may not be fully representative of outcomes in the overall patient population
- Due to the absence of a placebo group, it is unclear if reduction in prednisone dose is due to the effect of repeat study visits and effort to reduce prednisone
- The small number of patients limits ability to comment on the effect of Acthar on pulmonary function
- Results of specific dosing are unclear
  - This was a small, pilot study
  - It is unclear whether a loading dose is necessary or how it may have affected the results
  - Patients had the flexibility to halve their doses based on perceived problems with Acthar

[a]The efficacy and safety results discussed may not be representative of the overall symptomatic sarcoidosis patient population. Patients may be on multiple medications. The clinical outcomes for the patients discussed may not be solely attributable to Acthar.

Reference: Baughman et al. *Lung.* 2017; 195(3):313-322

Reduction in prednisone dose over 24 weeks from a prospective, single-blind study



- There was a significant reduction in prednisone dosage at 7 and 24 weeks, **irrespective of Acthar dose** (*P*=0.0156 and *P*=0.0078, respectively)[a]
- There was no significant difference between the 40 and 80 U treatment groups at week 7

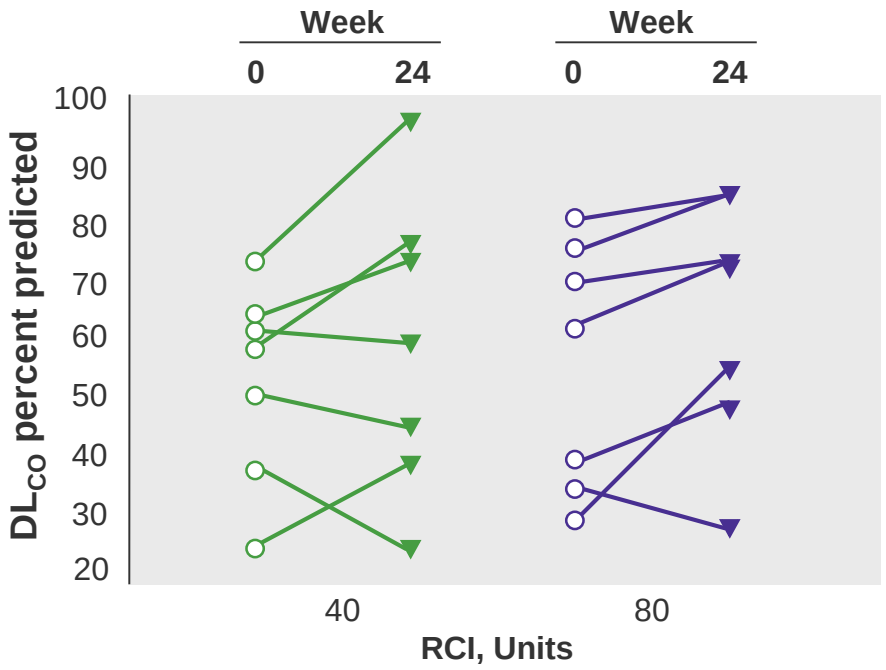
[a]Results are based on a single-blind, prospective study of 18 patients and may not be fully representative of outcomes in the overall patient population. Due to the absence of a placebo group, it is unclear if reduction in prednisone dose is due to the effect of repeat study visits and effort to reduce prednisone.

Reference: Baughman et al. *Lung.* 2017; 195(3):313-322

Please see Important Safety Information later in this presentation and full Prescribing Information.

Increase in diffusing capacity of the lungs at week 24 from a prospective, single-blind study

DL_{CO} % Predicted at Weeks 0 and 24 (n=14)



- There was a significant increase in DL_{CO} % predicted after 24 weeks of therapy, irrespective of Acthar dose (*P*=0.0419)[a]
- There was no significant difference in FVC or FEV-1[a]
- Five patients had a 5% or greater increase of the absolute FVC % predicted[a]

[a]Results are based on a single-blind, prospective study of 18 patients and may not be fully representative of outcomes in the overall patient population. Due to the absence of a placebo group, it is unclear if reduction in prednisone dose is due to the effect of repeat study visits and effort to reduce prednisone.

Reference: Baughman et al. *Lung.* 2017; 195(3):313-322

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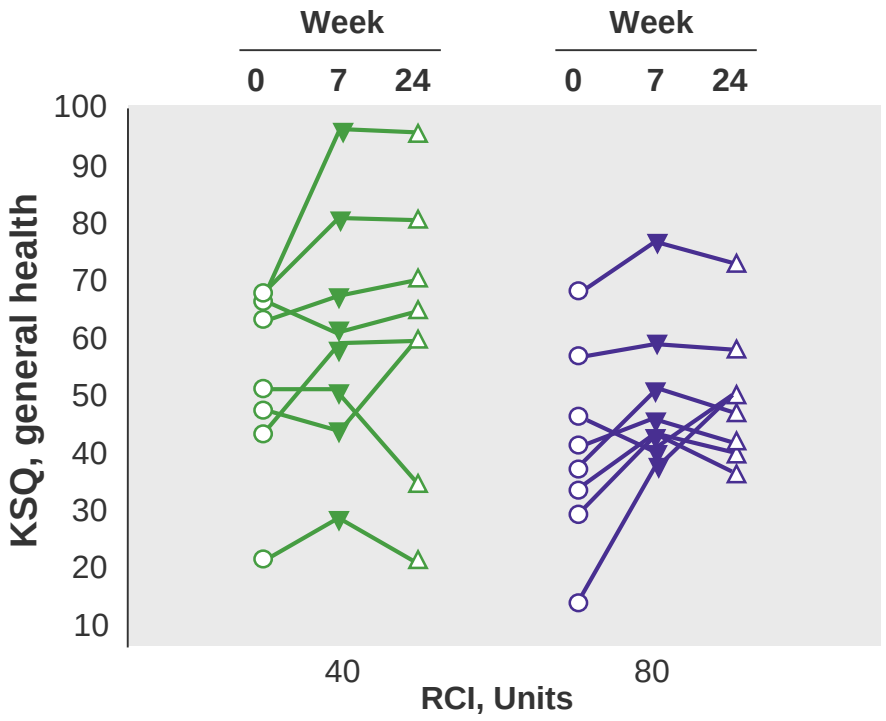
Increase in king's sarcoidosis questionnaire over time from a prospective, single-blind study

KSQ General Health Score Over Time[1]



- The King's Sarcoidosis Questionnaire consists of a general health status module and organ-specific modules that are scored using a 7-point Likert scale[2]
  - Higher scores indicate a better health status, with a maximum score of 100
- Overall, there was a significant rise in KSQ general health score at weeks 7 and 24 (*P*=0.0043 and *P*=0.0084, respectively)[1]
- There was no significant difference between the 40 and 80 U treatment groups at week 7[1]

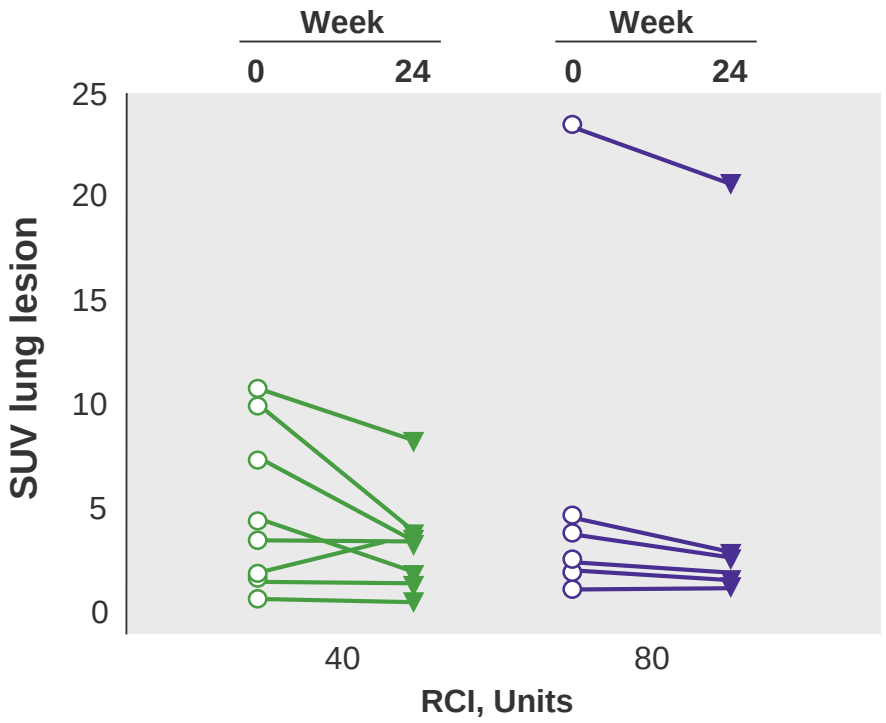
KSQ, King's Sarcoidosis Questionnaire.

Reference: Baughman et al. *Lung.* 2017; 195(3):313-322 2. Patel et al. *Thorax.* 2013;68:57.

Please see Important Safety Information later in this presentation and full Prescribing Information.

Reduction in SUV of highest lung lesion over 24 weeks from a prospective, single-blind study

Reduction in SUV of Lung Lesion (n=15)



- There was a significant reduction in the SUV of the highest lung lesion after 24 weeks of therapy, irrespective of Acthar dose (*P*=0.0085)
- This improvement in SUV occurred despite the reduction of prednisone dose

SUV, standard uptake value.

Reference: Baughman et al. *Lung.* 2017; 195(3):313-322

Please see Important Safety Information later in this presentation and full Prescribing Information.

Adverse events from a prospective, single-blind study

- The most common adverse events were anxiety and fluid retention, many of which occurred on the day of drug administration
  - Jitteriness (n=6)
  - Headache (n=1)
  - Edema (n=2)
  - Nausea (n=1)
- 8 patients complained of ≥1 of the following:
- 5 patients stopped the loading dose at days 7-9 due to toxicity
- There was no significant difference in the reported prednisone toxicity, including changes in moodiness, appetite, or bruising

Reference: Baughman et al. *Lung.* 2017; 195(3):313-322

Adverse events from a prospective, single-blind study (cont'd)

- Over the 24 weeks of the study, there was no significant change in weight
- 6 patients had an elevated HbA_{1C} at the time of study entry
  - None of the patients' HbA_{1C} fell into normal range by the end of the study
- There were no changes in the patients' diabetic or hypertensive medications during the course of the study

Reference: Baughman et al. *Lung.* 2017; 195(3):313-322

Please see Important Safety Information later in this presentation and full Prescribing Information.

Study summary: Prospective, single-blind pilot trial

- This was a prospective, single-blind, pilot study assessing the prednisone-sparing effect of Acthar
- Acthar therapy was associated with a significant reduction in prednisone dose and significant improvement in DL_{CO}
- There was no significant difference in reduction of prednisone dosage between the 40 and 80 U treatment groups at week 7
- There was a significant improvement in patient-reported outcomes, including lung health and reduction of fatigue
- The most common adverse events were anxiety and fluid retention, many of which occurred on the day of drug administration
- The results of specific dosing are unclear due to the study's small population size, the unknown effects of the loading dose on the results, and the dose of Acthar being halved without knowing exactly when it was halved during treatment regimen

Reference: Baughman et al. *Lung.* 2017; 195(3):313-322

Mallinckrodt's Acthar Gel Investments Since 2014 Acquisition

Please see Important Safety Information later in this presentation and Full Prescribing Information.

Since Acquiring Acthar, Mallinckrodt Has Initiated Numerous Clinical Trials

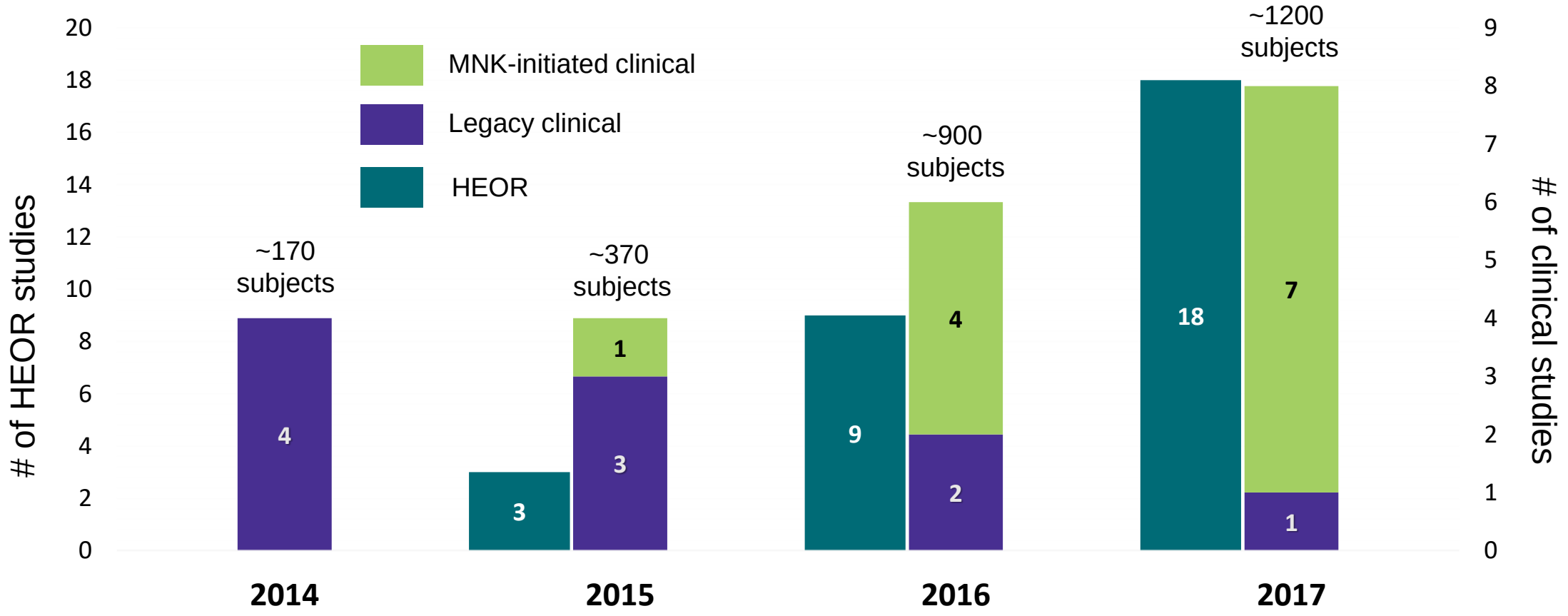
Design / Primary Objectives	Patients	Status	LPLV[5]	Data
FSGS[1]: Phase 4, randomized withdrawal study in Idiopathic FSGS subjects with treatment-resistant or treatment-intolerant proteinuria				
• Part 1: 24 weeks (open label), to evaluate induction of remission • Part 2: 24 weeks (placebo-controlled, double-blind, randomized withdrawal), to evaluate maintenance therapy	~240	▶ Ongoing	1H2021	2H2021
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	~160	▶ Ongoing	2H2019	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	2H2019	2H2019
Sarcoidosis: Phase 4, pilot, double-blind, placebo-controlled study in subjects with pulmonary sarcoidosis				
• Double-blind, placebo-controlled parallel group, 24-week treatment	~100	▶ Ongoing	2H2019	1H2021
Uveitis: Phase 4, multi-center, multiple-dose, open-label ophthalmology study in subjects with uveitis				
• 36 weeks (open label) followed by 2-week taper with additional 2-week further taper	~30	▶ Ongoing	2H2020	1H2021
Amyotrophic lateral sclerosis (ALS) is not an approved use.				
ALS: Phase 2, double-blind, placebo-controlled study in subjects with ALS				
• Double-blind, placebo-controlled parallel group, 36-week treatment	~210	▶ Ongoing	2H2019	1H2020

1. Focal Segmental Glomerulosclerosis; 2. Systemic Lupus Erythematosus; 3. Multiple Sclerosis; 4. Rheumatoid Arthritis; 5. Last Patient Last Visit

Please see Important Safety Information on slides 61-63 and full Prescribing Information.

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

Data generation and dissemination have increased for Acthar



- >110 abstracts and manuscripts published since acquisition
- >40 Investigator-Initiated Research programs funded by Mallinckrodt

Please see Important Safety Information later in this presentation and full Prescribing Information.

Summary: Acthar provides important clinical benefit to appropriate patients

- Acthar offers an **important treatment option for appropriate patients**
- There are **limited alternatives to Acthar as a later line treatment**
  - Providers and patients choose Acthar when patients do not respond to or cannot tolerate other therapies and the unmet medical need remains
- Multiple indications **supported by decades of clinical experience, published literature and clinical trials**
  - Acthar's **safety profile has been demonstrated and established** over many years
- The **FDA has repeatedly affirmed Acthar's beneficial effects**, as recently as 2010

Please see Important Safety Information later in this presentation and full Prescribing Information.

IMPORTANT SAFETY INFORMATION

Contraindications

- Acthar should never be administered intravenously
- Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar
- Acthar is contraindicated where congenital infections are suspected in infants
- Acthar is contraindicated in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency, adrenocortical hyperfunction or sensitivity to proteins of porcine origins

Warnings and Precautions

- The adverse effects of Acthar are related primarily to its steroidogenic effects
- Acthar may increase susceptibility to new infection or reactivation of latent infections
- Suppression of the hypothalamic-pituitary-axis (HPA) may occur following prolonged therapy with the potential for adrenal insufficiency after withdrawal of the medication. Adrenal insufficiency may be minimized by tapering of the dose when discontinuing treatment. During recovery of the adrenal gland patients should be protected from the stress (e.g. trauma or surgery) by the use of corticosteroids. Monitor patients for effects of HPA suppression after stopping treatment
- Cushing's syndrome may occur during therapy but generally resolves after therapy is stopped. Monitor patients for signs and symptoms

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions (continued)

- Acthar can cause elevation of blood pressure, salt and water retention, and hypokalemia. Blood pressure, sodium and potassium levels may need to be monitored
- Acthar often acts by masking symptoms of other diseases/disorders. Monitor patients carefully during and for a period following discontinuation of therapy
- Acthar can cause GI bleeding and gastric ulcer. There is also an increased risk for perforation in patients with certain gastrointestinal disorders. Monitor for signs of bleeding
- Acthar may be associated with central nervous system effects ranging from euphoria, insomnia, irritability, mood swings, personality changes, and severe depression, and psychosis. Existing conditions may be aggravated
- Patients with comorbid disease may have that disease worsened. Caution should be used when prescribing Acthar in patients with diabetes and myasthenia gravis
- Prolonged use of Acthar may produce cataracts, glaucoma and secondary ocular infections. Monitor for signs and symptoms
- Acthar is immunogenic and prolonged administration of Acthar may increase the risk of hypersensitivity reactions. Neutralizing antibodies with chronic administration may lead to loss of endogenous ACTH activity
- There is an enhanced effect in patients with hypothyroidism and in those with cirrhosis of the liver

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions (continued)

- Long-term use may have negative effects on growth and physical development in children. Monitor pediatric patients.
- Decrease in bone density may occur. Bone density should be monitored for patients on long-term therapy.
- Pregnancy Class C: Acthar has been shown to have an embryocidal effect and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Adverse Reactions

- Common adverse reactions for Acthar are similar to those of corticosteroids and include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain
- Specific adverse reactions reported in IS clinical trials in infants and children under 2 years of age included: infection, hypertension, irritability, Cushingoid symptoms, constipation, diarrhea, vomiting, pyrexia, weight gain, increased appetite, decreased appetite, nasal congestion, acne, rash, and cardiac hypertrophy. Convulsions were also reported, but these may actually be occurring because some IS patients progress to other forms of seizures and IS sometimes mask other seizures, which become visible once the clinical spasms from IS resolve**.**
- **Other adverse events reported are included in the full Prescribing Information.**

Please see full Prescribing Information for additional Important Safety Information.

Thank you