Data on Acthar® Gel (Repository Corticotropin Injection) Therapy in Immunoglobulin A Nephropathy (IgAN) Published in Kidney International Reports

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-- In a prospective, open-label study of 19 adult patients with biopsy-proven IgAN at high risk of progression to end-stage renal disease, treatment with Acthar Gel demonstrated a reduction in proteinuria, an effect which was sustained at 12 months --

STAINES-UPON-THAMES, United Kingdom, March 5, 2020 /PRNewswire/ -- Mallinckrodt plc (NYSE: MNK), a global biopharmaceutical company, today announced publication of findings from a prospective, open-label pilot study to assess the efficacy and safety of Acthar® Gel (repository corticotropin injection) in patients with immunoglobulin A nephropathy (IgAN) at high risk of chronic kidney disease progression.[1] The study was published in *Kidney International Reports*, the journal of the International Society of Nephrology. IgAN, also known as Berger's disease, is a kidney disease that occurs when IgA deposits build up in the kidneys, causing inflammation that damages kidney tissues[2,3]

The study, titled "An Open-Label Pilot Study of Adrenocorticotrophic Hormone in the Treatment of lgA Nephropathy at High Risk of Progression," demonstrated that treatment with Acthar Gel resulted in a significant reduction in 24-hour urinary protein (P=0.007) with a stable estimated glomerular filtration rate (eGFR) (P=0.1) – a measure of renal function – following six months of treatment with 80 units twice weekly, and an additional six-month follow up. Elevated amounts of urinary protein (>1 g/24 hours) are associated with increased risk of progression to end-stage renal disease and up to 50 percent of patients with IgAN and proteinuria will progress to end-stage renal disease within 15 years.[1] No patients discontinued the study due to side effects and there were no serious adverse events reported. Six patients were treated for infections. The most common other adverse events were injection reaction, muscle soreness, acne, hot flashes, anxiety and insomnia.[1]

Acthar® Gel (repository corticotropin injection) is indicated to induce a diuresis or a remission of proteinuria (excess protein in the urine) in nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus.[4] Please see Important Safety Information for Acthar Gel below.

"IgAN is a clinically challenging immune-mediated kidney disease in which patients are at risk of rapidly progressing to end-stage renal disease, yet there are limited therapeutic options for the reduction of proteinuria in IgAN available to physicians and patients," said **Tunde Otulana, M.D., Senior Vice President and Chief Medical Officer at Mallinckrodt**. "We are encouraged by these results and are committed to supporting additional research in this patient population with unmet needs."

Study Methods[1]

- The prospective, open-label study assessed 19 patients >18 years of age with biopsy-proven IgAN treated with Acthar Gel 80 units subcutaneously twice weekly for six months and followed patients for a total of 12 months.
- Subjects were required to have a urinary protein >1 g/24 hours despite adequate renin-angiotensin system inhibition and eGFR >30 ml/min at enrollment.
- The primary endpoint was: change in proteinuria and eGFR from baseline to 12 months. Complete response was defined as a 24-hour urinary protein <300 mg and ≤10 percent reduction in eGFR and partial response was defined as a >50 percent reduction in urinary protein and ≤25 percent reduction in eGFR.
- The primary safety endpoint was incidence of infections (pneumonia, urinary tract infections and pyelonephritis) and rate of developing diabetes.

Key Findings[1]

- The study demonstrated a significant reduction in 24-hour urinary protein from mean 2.6 to 1.3 g (P=0.007) at 12-month follow-up after being treated with Acthar Gel.
- Following treatment with Acthar Gel, patients had stable eGFR, a measure for kidney function (mean 65.5 to 61.1 ml/min, P=0.1).
- Eight patients (42 percent) achieved partial remission (PR). There were no complete remissions. Of the eight patients who achieved PR, seven had proteinuria less than 1 g at 12 months, with a median 24-hour urinary protein of 625 mg (344–1458 mg).
- Fifty-three adverse events (AEs) were reported, including six infections (two viral and four bacterial) that were treated effectively with anti-infectives. No serious AEs were reported and no patients developed hyperglycemia.

Study Limitations[1]

- Results may not be solely attributable to Acthar Gel.
- This study's small sample size and lack of a placebo group for comparison limit the ability to make associations between clinical outcomes and potential predictors.
- Due to the limited follow-up, it is not known what long-term outcomes patients experienced, including changes in eGFR, which may occur over a longer period of time.

"Patients with IgAN are at risk of renal failure progressing to end-stage renal disease," said **James A. Tumlin, M.D., FASN, Professor of Medicine at Emory University**. "There is a great need to identify effective treatment options for these patients, and it's encouraging to see new research in this area of high unmet need."

About IgA Nephropathy

Immunoglobulin A (IgA) nephropathy is one of the most common kidney diseases.[2,5] Also known as Berger's disease, IgAN is a kidney disease that occurs when the IgA deposits build up in the kidneys.[2] IgA is an antibody produced by the body's immune system.[3] Buildup of IgA antibodies results in inflammation that may hamper the kidneys' ability to filter wastes from the blood over time.[5] While IgA nephropathy often progresses slowly over many years, the course of the disease can vary in each patient. Some patients may experience blood in their urine without developing problems, some may achieve complete remission, while others develop end-stage kidney failure.[3,5] While there is no cure for IgAN, certain medications can slow its course.[3,5] IgAN can occur at any age, although the first evidence of kidney disease most frequently appears when people are in their teens to late 30s.[3] In the U.S., IgAN is twice as likely to appear in men than in women.[3] While found in people all over the world, IgAN is more common among Asians and Caucasians.[6]

Acthar® Gel (repository corticotropin injection) is indicated for:

- Treatment during an exacerbation or as maintenance therapy in selected cases of systemic lupus erythematosus
- Monotherapy for the treatment of infantile spasms in infants and children under 2 years of age
- The treatment of acute exacerbations of multiple sclerosis in adults. Controlled clinical trials have shown Acthar Gel to be effective in speeding the resolution of acute exacerbations of multiple sclerosis. However, there is no evidence that it affects the ultimate outcome or natural history of the disease
- Inducing a diuresis or a remission of proteinuria in nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus
- Treatment during an exacerbation or as maintenance therapy in selected cases of systemic dermatomyositis (polymyositis)
- The treatment of symptomatic sarcoidosis
- Adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: psoriatic arthritis, rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy), ankylosing spondylitis
- Treatment of severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation

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
- 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
- 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**.**

ABOUT MALLINCKRODT
Mallinckrodt is a global business consisting of multiple wholly owned subsidiaries that develop, manufacture, market and distribute specialty pharmaceutical products and therapies. The company's Specialty Brands reportable segment's areas of focus include autoimmune and rare diseases in specialty areas like neurology, rheumatology, nephrology, pulmonology and ophthalmology; immunotherapy and neonatal respiratory critical care therapies; analgesics and gastrointestinal products. Its Specialty Generics reportable segment includes specialty generic drugs and active pharmaceutical ingredients. To learn more about Mallinckrodt, visit www.mallinckrodt.com.

Mallinckrodt uses its website as a channel of distribution of important company information, such as press releases, investor presentations and other financial information. It also uses its website to expedite public access to time-critical information regarding the company in advance of or in lieu of distributing a press release or a filing with the U.S. Securities and Exchange Commission (SEC) disclosing the same information. Therefore, investors should look to the Investor Relations page of the website for important and time-critical information. Visitors to the website can also register to receive automatic e-mail and other notifications alerting them when new information is made available on the Investor Relations page of the website.

CAUTIONARY STATEMENTS RELATED TO FORWARD-LOOKING STATEMENTS
This release includes forward-looking statements concerning Acthar Gel including its potential impact on patients and anticipated benefits associated with its use. The statements are based on assumptions about many important factors, including the following, which could cause actual results to differ materially from those in the forward-looking statements: satisfaction of regulatory and other requirements; actions of regulatory bodies and other governmental authorities; changes in laws and regulations; issues with product quality, manufacturing or supply, or patient safety issues; and other risks identified and described in more detail in the "Risk Factors" section of Mallinckrodt's most recent Annual Report on Form 10-K and other filings with the SEC, all of which are available on its website. The forward-looking statements made herein speak only as of the date hereof and Mallinckrodt does not assume any obligation to update or revise any forward-looking statement, whether as a result of new information, future events and developments or otherwise, except as required by law.

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