Mallinckrodt Achieves 50 Percent Enrollment for Phase 2B Trial Investigating the Use of Acthar® Gel (Repository Corticotropin Injection) in Amyotrophic Lateral Sclerosis (ALS)

June 24, 2019

STAINES-UPON-THAMES, United Kingdom, June 24, 2019 /PRNewswire/ -- Mallinckrodt plc (NYSE: MNK), a leading global specialty biopharmaceutical company, today confirmed it has achieved 50 percent patient enrollment in the company's Phase 2B study designed to assess the efficacy and safety of Acthar® Gel (repository corticotropin injection) as an investigational treatment for amyotrophic lateral sclerosis (ALS).

The U.S. Food and Drug Administration (FDA) previously granted the company's request for a Fast Track designation and orphan status for its Acthar Gel Investigational New Drug application in patients with ALS. The drug is not FDA-approved for the ALS indication. Please see Important Safety Information for Acthar Gel below.

"ALS is a rare and incurable disorder that impacts patients from all walks of life," said **Todd Levine, M.D., Medical Director of Honor Health Neurology and adjunct Professor of Neurology at Kansas University**. "The community looks forward to learning more from this research aimed at further understanding the disease and potential new treatments for ALS."

Mallinckrodt's Phase 2B study of Acthar Gel in ALS patients is investigating a potential new indication for the product. The company is also studying Acthar Gel in a number of Phase 4 randomized, placebo-controlled, blinded clinical trials in approved indications for the drug.

"We are very pleased to reach this milestone in our important study of Acthar Gel in ALS patients," said **Steven Romano, M.D., Executive Vice President and Chief Scientific Officer at Mallinckrodt**. "We embarked on this multi-center, double blind, placebo-controlled trial to evaluate the effects of the therapy on established measures of disease symptoms and progression, and look forward to assessing the potential clinical value Acthar Gel may bring to patients with this devastating disease."

About the PENNANT Trial
The Phase 2B clinical study is titled "A Multicenter, Double Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Acthar Gel in the Treatment of Subjects with Amyotrophic Lateral Sclerosis." The study will enroll patients ages 18 to 75 with ALS and symptom onset (defined as first muscle weakness or dysarthria) ≤ two years prior to the screening visit. Subjects will be randomized on a 2:1 basis to receive subcutaneous (SC) Acthar Gel 0.2 mL (16 units) daily or SC matching placebo 0.2 mL daily for 36 weeks.

The efficacy of Acthar Gel will be assessed using standard measures of functional decline, including change from baseline in the ALS Functional Rating Scale-Revised, assessed after 36 weeks of therapy. Approximately 210 patients will be enrolled across multiple sites.

Find more information about the PENNANT trial here on the ClinicalTrials.gov website. The study is expected to be completed by late 2020, with topline results in the first quarter of 2021.

About ALS
ALS is a progressive neurodegenerative disease that affects motor neuron cells in the brain and the spinal cord. Motor neurons reach from the brain and the spinal cord to the muscles throughout the body. The progressive degeneration of the motor neurons in ALS eventually leads to their demise and when the motor neurons die, voluntary and involuntary muscle movement is lost. With the progressive loss of motor neurons, people with ALS may lose the ability to speak, eat, move and breathe.

There is increasing evidence that neuro-inflammation accompanies the death of motor neurons in ALS. Several inflammatory events that appear to accompany disease progression in ALS might be amenable to pharmacologic interventions as a component of disease management, and research in the field is investigating new approaches to implement an anti-inflammatory strategy for treating ALS[1].

Acthar Gel (repository corticotropin injection) Indications
Acthar Gel is an injectable drug approved by the FDA for the treatment of 19 indications. Of these, today the majority of Acthar Gel use is in these indications:

- Adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)

- The treatment of symptomatic sarcoidosis
- Monotherapy for the treatment of infantile spasms in infants and children under 2 years of age
- Treatment during an exacerbation or as maintenance therapy in selected cases of systemic lupus erythematosus
- 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)
- 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.

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 with regard to Acthar Gel including expectations specific to this Phase 2B study, as well as its potential impact on patients. 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: clinical trial results; 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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[1] The ALS Association, Our Research, Focus Areas, Disease Mechanisms. http://www.alsa.org/research/focus-areas/disease-mechanisms/ Accessed June 17, 2019.

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