Mallinckrodt Provides Update on Phase 4 Data H.P. Acthar® Gel (Repository Corticotropin Injection) Clinical Trial in Patients with Rheumatoid Arthritis (RA)

February 5, 2019

-- Open-label phase of study completed; primary end point results consistent¹ with prior reports (n=116) that showed 61% of patients with persistently active RA reported in the open-label period achieved low disease activity at 12 weeks --

-- Open-label phase results (n=259) presentation planned for mid-2019, with full study results targeted for research meeting later in the year --

STAINES-UPON-THAMES, United Kingdom, Feb. 5, 2019 /PRNewswire/ -- Mallinckrodt plc (NYSE: MNK), a leading global specialty pharmaceutical company, has completed the open-label phase of the ongoing Phase 4, multicenter study assessing the efficacy and safety of H.P. Acthar® Gel in patients with persistently active rheumatoid arthritis (RA) who were previously treated with disease-modifying anti-rheumatic drugs (DMARDs) and corticosteroids.

H.P. Acthar Gel is U.S. Food and Drug Administration (FDA)-approved as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in RA including juvenile RA (selected cases may require low-dose maintenance therapy).

Primary end point results observed from the 100% patient enrollment (n=259) point in the study's open-label phase are consistent¹ with those observed at the 25% and 50% milestone assessments. As most recently reported relative to 50% patient enrollment data (n=116) – where primary end point results showed 61% of the 100 patients with persistently active RA who completed the open-label period achieved low disease activity (LDA) at 12 weeks – H.P. Acthar Gel continued to produce reduction in joint disease activity in patients whose disease was uncontrolled on prednisone and DMARDs. The company intends to present full open-label phase findings by mid-2019.

"We are pleased with the insights gleaned thus far into the clinical utility of H.P. Acthar Gel in patients with persistently active rheumatoid arthritis who were previously treated with disease-modifying drugs and corticosteroids," said Steven Romano, M.D., Executive Vice President and Chief Scientific Officer at Mallinckrodt. "Mallinckrodt remains committed to the ongoing study of H.P. Acthar Gel in rheumatology – building on the decades of clinical experience for the product – and continuing to meet the needs of the rheumatology community. We look forward to presenting the RA trial data at conferences later this year."

The controlled, double-blind phase of the study is ongoing with completion expected in the first quarter of 2019, and full results targeted for presentation at a research meeting later this year.

About the Study
The study is a Phase 4, multicenter, two-part study assessing the efficacy and safety of H.P. Acthar Gel in adult subjects with rheumatoid arthritis with persistently active disease who were previously treated with DMARDs and corticosteroids. The primary endpoint of the study is the proportion of patients reaching LDA at 12 weeks.

Part 1 of the study was an open-label period. After 12 weeks of treatment with H.P. Acthar Gel, subjects were evaluated for treatment response using the DAS28-ESR². At the interim analysis completed at the midway point of study enrollment (n=116), 14 patients had withdrawn and two patients were still active in Part 1. The most common adverse events (AEs) reported at the midway point – a secondary endpoint – were headache (10), urinary tract infection (4), hyperglycemia (3) and pharyngitis (3). Two patients reported serious AEs (chest pain and pneumonia).

The trial is now fully enrolled with 259 patients with persistently active RA who were previously treated with corticosteroids and conventional synthetic and/or biologic DMARDs.

Study Limitations
- Data previously reported were from a pre-planned 50% data review of the open-label phase of an ongoing study. The 50% interim analysis was for 116 patients in a larger 2-part study with no comparator arm in Part 1. Because it was an interim report, significance tests were not conducted, and therefore P values are not reported. Full results of this 2-part study may vary from the interim analysis.³,⁴
Sample bias may exist since this was an open-label phase of an ongoing study, and patients were aware that they were receiving H.P. Acthar Gel.\(^3\)

Examiner bias may also exist as the patient had to reach low disease activity in order to enter the second phase of the study.\(^3\)

The results cannot be solely attributed to H.P. Acthar Gel since patients were on different medications at the start of the trial and no washout periods were undertaken. H.P. Acthar Gel has not been formally studied in combination with other treatments.\(^3\)

Find more information about the study [here](https://clinicaltrials.gov) on the ClinicalTrials.gov website.

**About Rheumatoid Arthritis**
RA is an autoimmune disease. It is a chronic condition that causes pain, stiffness, and swelling of the joints—all symptoms caused by inflammation.\(^6\)

An estimated 1.5 million U.S. adults are living with RA.\(^6\) Treatment is aimed at stopping inflammation to put the disease in remission and relieve symptoms.\(^7\) Nonsteroidal anti-inflammatory drugs are used to ease symptoms whereas corticosteroids, disease-modifying anti-rheumatic drugs and biologics are used to slow down the disease activity.

**H.P. Acthar Gel (repository corticotropin injection) Indications**
H.P. Acthar Gel is an injectable drug approved by the FDA for the treatment of 19 indications. Of these, today the majority of Acthar 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)
- 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 H.P. 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
- 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 that develops, manufactures, markets and distributes specialty pharmaceutical products and therapies. 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. To learn more about Mallinckrodt, visit [www.mallinckrodt.com](http://www.mallinckrodt.com).

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**CAUTIONARY STATEMENTS RELATED TO FORWARD-LOOKING STATEMENTS**

This release includes forward-looking statements concerning H.P. Acthar Gel including expectations with regard to the study described in this release. 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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1. Data on file, Mallinckrodt, 2019
2. DAS28-ESR=Disease Activity Score with 28 joint count and Erythrocyte Sedimentation Rate


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