Mallinckrodt Announces Publication of Data on Acthar® Gel (Repository Corticotropin Injection) from its Randomized, Double-Blind, Placebo-Controlled Phase 4 Study in Rheumatoid Arthritis (RA) in Rheumatology and Therapy

April 15, 2020

-- The two-part multicenter study of 259 enrolled subjects showed >60 percent of patients achieved low disease activity (LDA) at week 12 with open-label therapy, an effect that was maintained in a proportion of patients with 12 additional weeks of treatment in the double-blind phase --

STAINES-UPON-THAMES, United Kingdom, April 15, 2020 /PRNewswire/ -- Mallinckrodt plc (NYSE: MNK), a global biopharmaceutical company, today announced the publication of findings from its randomized, placebo-controlled, double-blind Phase 4 study to assess the safety and efficacy of Acthar® Gel (repository corticotropin injection, or RCI) in patients with persistently active rheumatoid arthritis (RA) despite treatment with stable background disease-modifying antirheumatic drugs (DMARDs) and low-dose glucocorticoids. Results of the study were recently published online in *Rheumatology and Therapy*, an open access peer-review journal. Preliminary findings from the study were presented at the European Congress of Rheumatology 2019 (EULAR) held in June.

Acthar Gel is a naturally sourced complex mixture of adrenocorticotropic hormone analogs and other pituitary peptides. Acthar Gel is approved by the U.S. Food and Drug Administration (FDA) 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).[1] Please see Important Safety Information for Acthar Gel below.

The study, titled "Repository Corticotropin Injection for Active Rheumatoid Arthritis Despite Aggressive Treatment: A Randomized Controlled Withdrawal Trial," enrolled 259 adult patients (≥18 years of age) with RA who were treated at 60 centers in four countries between Nov. 7, 2016, and Feb. 13, 2019. Results of the study showed that Acthar Gel demonstrated the potential for effectiveness in achieving low disease activity (LDA) as assessed by DAS28-ESR[2] in patients with active RA despite current treatment with low-dose glucocorticoids and one or two DMARDs.

"The results of this study suggest that there could be a reasonable risk-benefit for the short-term use of RCI over six months in appropriate patients with persistently active RA despite concurrent use of DMARDs and low-dose glucocorticoids. Many patients achieved LDA by three months with the response persisting for an additional three months in a majority of patients whether discontinuing or continuing RCI. The adverse event profile was similar in patients who continued and discontinued RCI,[i]" said **Dr. Roy Fleischmann, Co-Medical Director of the Metroplex Clinical Research Center and Clinical Professor of Medicine at the University of Texas Southwestern Medical Center in Dallas and the study's lead author**.

"Rheumatoid arthritis is a common autoimmune disease that can damage bone and joints and greatly impact daily functioning for patients. The goal of treatment is remission or low disease activity, but for a subset of underserved patients with debilitating RA who don't achieve remission or LDA with standard therapy, additional options are greatly needed," said **Tunde Otulana, M.D., Senior Vice President and Chief Medical Officer at Mallinckrodt**. "We are encouraged by the results of this study that demonstrate Acthar Gel can be considered for appropriate patients in this persistently active population, and we're grateful to the patients, their families and clinicians who participated in the study."

Key Findings[3]:

Open-label Period

- At week 12, 163 patients (62.9 percent, 95 percent Confidence Interval 57.3–69.1 percent) achieved DAS28-ESR <3.2, the study's primary endpoint (p<0.0001).
- The mean DAS28-ESR over time from baseline to week 12 decreased by 2.75 (standard deviations (SD) 1.45, p<0.001) from a mean baseline of 6.3.
- At week 12, 169 patients (65.3 percent) reached LDA as defined by the Clinical Disease Activity Index (CDAI, score ≤10), a composite measure of disease activity in patients with RA (p<0.001).
- The proportion of patients (N=259) who achieved ACR 20, 50, and 70 response criteria[ii] at week 12 were as follows: 83.0 percent (n=215) achieved ACR20, 62.5 percent (n=162) achieved ACR50, and 30.1 percent (n=78) achieved ACR70 (all p<0.0001).
- 49 patients (18.9 percent) achieved DAS28-ESR < 2.6 (remission) at week 12.
- Significant decreases from baseline in the number of tender and swollen joints were observed.
- In terms of patient-reported outcomes (PROs) at week 12, significant improvements from baseline in Health Assessment Questionnaire – Disability Index (HAQ-DI) and Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scores were observed, as well as significant decreases from baseline in the percentages of work time missed, impairment

while working, overall work impairment, and activity impairment, as assessed via the Work Productivity and Activity Impairment (WPAI) questionnaire.
- Bone turnover markers, an exploratory endpoint, were stable during the open-label period. At week 12, significant decreases in levels of cartilage degeneration markers CTX-II ($p<0.01$) and CTX-II CRT ($p<0.001$), as well as the bone formation marker PINP ($p<0.01$) were observed, and bone degeneration markers CTX and CTX-I showed no significant changes with Acthar Gel treatment in this population. The clinical relevance of these data are unknown as bone density assessments were not taken during this study.
- During the open-label period, 98 patients (37.8 percent) reported adverse events (AEs), the most common were urinary tract infection (3.9 percent, n=10), headache (3.5 percent, n=9) and pharyngitis (2.7 percent, n=7). Three patients experienced serious AEs.

Randomized, Placebo-Controlled, Blinded, Withdrawal Period

- LDA as assessed by DAS28-ESR was maintained at week 24 in 47 of 77 (61.0 percent) of patients treated with Acthar Gel versus 32 of 76 (42.1 percent) of patients treated with placebo ($p=0.019$).
- Mean DAS28-ESR over time during the double-blind period did not differ significantly between the Acthar Gel and placebo groups.
- Mean time to disease activity flare during weeks 12 through 24 was 6.5 weeks (SD 2.61 weeks) for the placebo group and 8.2 weeks (SD 2.92 weeks) for the Acthar Gel-treated group.
- At week 24, 66 patients (85.7 percent) treated with Acthar Gel and 50 patients (65.8 percent) in the placebo group maintained LDA, as defined by CDAI scores ≤ 10 ($p=0.004$).
- At week 24, ACR20 response achieved during the open-label period was maintained through the double-blind period in the Acthar Gel (91 percent, n=77) and placebo (84 percent, n=76) groups. ACR50 and ACR70 responses evaluated post hoc at week 24 of the double-blind period were seen in 75 percent and 47 percent, respectively, of patients treated with Acthar Gel and 70 percent and 42 percent of patients who had discontinued Acthar Gel therapy.
- At week 24, 23 patients (29.9 percent) treated with Acthar Gel and 23 patients (30.3 percent treated with placebo achieved DAS28-ESR remission ($p=0.828$) in this population with previously highly active RA.
- As an exploratory endpoint, C-reactive protein values were noted to be 12.1 µg/mL at baseline, 14.3 µg/mL at week 12 and 16.4 µg/mL at week 24 for the Acthar Gel group, and 21.8 µg/mL and baseline, 16.9 µg/mL at week 12 and 20.0 µg/mL at week 24 for the placebo group.
- The mean number of tender and swollen joints as derived for the calculation of the DAS28-ESR remained decreased during the double-blind period, with no significant differences between the Acthar Gel and placebo groups noted.
- In terms of PROs, improvements on the HAQ-DI, FACIT-F, and WPAI that were noted during the open-label period were generally maintained in the Acthar Gel and placebo groups throughout the double-blind period. There were no significant differences between the Acthar Gel and placebo groups on these metrics.
- Levels of the osteoclast differentiation marker sRANKL significantly increased from baseline to week 12 and week 24 (both $p<0.05$) in the Acthar Gel group, but not in the placebo group. All other bone turnover markers remained stable.
- 25 patients (32.5 percent) from the Acthar Gel group and 31 patients (40.3 percent) in the placebo group reported AEs during the double-blind period, the most common being: headache (6.5 percent both groups, n=5), hypertension (3.9 percent, n=3 RCI; 0 placebo), hyperglycemia (3.9 percent, n=3 RCI; 2.6 percent, n=2 placebo) and diarrhea (1.3 percent, n=1 RCI; 3.9 percent, n=3 placebo).

Methods[3]:

- The study was a Phase 4, multicenter, two-part clinical study assessing the efficacy and safety of Acthar Gel in adult patients with RA with persistently active disease who were previously treated with low-dose glucocorticoids and nonbiologic and/or biologic DMARDs. The primary endpoint of the study was the proportion of patients reaching LDA at 12 weeks.
- Part 1 of the study was an open-label period (259 patients were enrolled and 235 completed part 1). Patients were assessed at baseline and at weeks 4, 8 and 12.
- After 12 weeks of treatment with Acthar Gel, patients were evaluated for treatment response using the DAS28-ESR. Participants who achieved LDA as defined by DAS28-ESR <3.2 at week 12 in part 1 entered part 2, a double-blind withdrawal period. Patients who did not achieve LDA at week 12 were discontinued from further study participation.
- 154 patients entered part 2 of the study (77 in each treatment group) and 127 patients completed part 2 of the study (Acthar Gel, n=71; placebo, n=56).
- In part 2, patients were randomized in a 1:1 ratio to receive either Acthar Gel 1 ml (80 U) or matching placebo twice weekly for an additional 12 weeks.

Study Limitations[3]:

- All patients were aware that they were being treated with Acthar Gel during the open-label period. This may have led to higher responses to treatment.

- Sample bias may exist, limiting the extrapolation of the results to the general population:
  - >80 percent of study participants were of Hispanic or Latino ethnicity
  - Patients with other rheumatic autoimmune diseases, clinically significant infections, or malignancies were excluded from the study
- The results may not be solely attributed to Acthar Gel because patients were on different stable background medications at the start of the trial, and there were no washout periods. Acthar Gel has not been formally studied in combination with other treatments.

The study was funded by Mallinckrodt.

About Rheumatoid Arthritis

RA is an autoimmune disease. It is a chronic condition that causes pain, stiffness, and swelling of the joints—all symptoms and signs caused by inflammation.[4] An estimated 1.5 million U.S. adults are living with RA.[5] Treatment is aimed at stopping inflammation to put the disease in remission and relieve symptoms.[6] Nonsteroidal anti-inflammatory drugs are used to ease symptoms whereas glucocorticoids, and non-biologic and biologic DMARDs are used to slow down the disease activity.[6]

INDICATIONS

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

- Treatment during an exacerbation or as maintenance therapy in selected cases of systemic lupus erythematosus
- Treatment during an exacerbation or as maintenance therapy in selected cases of dermatomyositis (polymyositis)
- 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); ankylosing spondylitis
- Adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in psoriatic arthritis
- The treatment of symptomatic sarcoidosis

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 origin

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-adrenal (HPA) axis 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 to 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 masks 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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References

[i] AEs reported in ≥1.5% of patients in part 1 or in either group in part 2.
[ii] ACR20=American College of Rheumatology 20% improvement; ACR50=American College of Rheumatology 50% improvement; ACR70=American

College of Rheumatology 70% improvement

[1] Acthar® Gel (repository corticotropin injection) [prescribing information]. Mallinckrodt ARD LLC.

[2] Disease Activity Score 28-joint count Erythrocyte Sedimentation Rate.

[3] Fleischmann R, Furst DE, Connolly-Strong E, Liu J, Zhu J, Brasington R. *Rheumatol Ther (2020).* https://doi.org/10.1007/s40744-020-00199-3.

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[5] Arthritis Foundation. What is Rheumatoid Arthritis? Available at: http://www.arthritis.org/about-arthritis/types/rheumatoid-arthritis/what-is-rheumatoid-arthritis.php. Accessed April 1, 2020.

[6] Arthritis Foundation. Rheumatoid Arthritis Treatment. Available at: http://www.arthritis.org/about-arthritis/types/rheumatoid-arthritis/treatment.php. Accessed April 1, 2020.

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