

Mallinckrodt Announces Positive Open-Label Results from Phase 4 Acthar® Gel (Repository Corticotropin Injection) Clinical Trial in Rheumatoid Arthritis (RA) to be Presented at the European Congress of Rheumatology 2019 (EULAR)

- Data from a sizable (n=259) open-label part of the Phase 4 study showed 62.5 percent of patients with persistently active RA achieved low disease activity at Week 12, a robust response percentage in this more refractory patient population, and the study's primary outcome measure --
- Percentage of patients who achieved ACR 20 percent, 50 percent, and 70 percent was 79.5 percent, 62.2 percent and 31.7 percent, respectively; improvement criteria increased over time from Week 4 through Week 12 --

STAINES-UPON-THAMES, United Kingdom – May 29, 2019 – [Mallinckrodt plc](#) (NYSE: MNK), a global specialty biopharmaceutical company, is reporting data¹ from the open-label part of the Phase 4, multicenter study assessing the efficacy and safety of Acthar® Gel (repository corticotropin injection) in patients with persistently active rheumatoid arthritis (RA) who were previously treated with disease-modifying anti-rheumatic drugs (DMARDs) and corticosteroids. The data will be reported in a poster presentation on Thursday, June 13 at the European Congress of Rheumatology 2019 (EULAR), June 12-15 in Madrid.

As previously announced, both parts of the multicenter study are now complete (open-label portion, n=259; controlled, double-blind, randomized portion, n=154).

The Phase 4 study, "**A Multicenter Study Assessing the Efficacy and Safety of Repository Corticotropin Injection in Patients With Rheumatoid Arthritis: Interim Data From the Open-Label Treatment Period**" abstract can be accessed [here](#).

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).

"We are encouraged by the open-label results from this study of Acthar Gel's utility in RA and look forward to sharing the double-blind, randomized part of the study to further measure its effect against this aggressive disease," 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**. "Therapies are greatly needed for patients with RA whose disease persists, as measured by validated disease activity metrics, despite use of multiple standard treatments."

Key Findings:

- The mean Disease Activity Score 28-joint count (DAS28) – a composite index that measures disease activity in patients with RA – was 6.3 at baseline and 3.6 at Week 12.
- The primary endpoint of the study was met, the proportion of patients reaching LDA by DAS28-ESR <3.2 at 12 weeks. The open-label analysis showed there was a decrease in the mean DAS28 Erythrocyte Sedimentation Rate (DAS28-ESR) scores from baseline through Week 12, with 62.5 percent of patients who completed the open-label period achieving low disease activity (LDA <3.2) at Week 12.
- Similarly, the percentage of patients who achieved ACR 20, 50, and 70 percent criteria increased over time from Week 4 through Week 12, with 79.5 percent, 62.2 percent and 31.7 percent of

patients who completed the open-label period having achieved ACR 20, 50, and 70 responses, respectively at 12 weeks.

- An 80.3 percent improvement in patient global assessment of disease activity from baseline through Week 12 was observed.
- Adverse events observed were consistent with those in previous trials of Acthar Gel. The most common adverse events (AEs) reported were urinary tract infection (n=10), headache (n=9), and pharyngitis (n=7). Three patients reported serious AEs (chest pain, pneumonia and craniocerebral injury).
- Twenty-four subjects discontinued the open-label period of the study.

"We are pleased to have completed this important study of Acthar Gel in this underserved population of patients with RA with persistently active disease," said **Steven Romano, M.D., Executive Vice President and Chief Scientific Officer at Mallinckrodt**. "We are committed to the continued study of Acthar Gel as a therapeutic option for this potentially life-altering form of arthritis that can profoundly impact a person's health and well-being. These clinical trial results are part of our investment into a multi-year Acthar Gel evidence generation effort, and we hope this will be followed by additional data readouts in other difficult-to-manage patient subpopulations."

Study Limitations

- Sample bias may exist since this was an open-label phase of an ongoing study, and patients were aware that they were receiving Acthar Gel.²
- Examiner bias may also exist as the patient had to reach low disease activity in order to enter the second phase of the study.²
- The results cannot be solely attributed to Acthar Gel since patients were on different medications at the start of the trial and no washout periods were undertaken. Acthar Gel has not been formally studied in combination with other treatments.²

About the Study

The study was a Phase 4, multicenter, two-part study assessing the efficacy and safety of Acthar Gel in adult subjects with RA with persistently active disease who were previously treated with corticosteroids and conventional synthetic and/or biologic DMARDs. The primary endpoint of the study was the proportion of patients reaching low disease activity at 12 weeks. The secondary endpoints were (1) to assess the safety and tolerability of Acthar Gel in subjects with RA with persistently active disease and (2) the proportion of participants with low disease activity at 24 weeks.

Part 1 of the study was an open-label period (n=259). After 12 weeks of treatment with Acthar Gel, subjects were evaluated for treatment response using the DAS28-ESR1. In Part 2 of the study (n=154), participants who achieved low disease activity of DAS28-ESR <3.2 at Week 12 in Part 1 entered a double-blind period, randomized in a 1:1 ratio to receive either Acthar Gel or matching placebo for an additional 12 weeks.

Results from the controlled, double-blind phase of the study are targeted for presentation at a research meeting later this year.

Find more information about the study [here](#) 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.³ An estimated 1.5 million U.S. adults are living with

RA.⁴ Treatment is aimed at stopping inflammation to put the disease in remission and relieve symptoms.⁵ 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.

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 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 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 consisting of multiple wholly owned subsidiaries that develop, manufacture, market and distribute specialty pharmaceutical products and therapies. The company's Specialty Brands reporting 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 reporting 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 expectations regarding 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

¹ Fleischmann R, Furst DE, Connolly-Strong E, Liu J, Zhu J, Brasington R. A multicenter study assessing the efficacy and safety of repository corticotropin injection in patients with rheumatoid arthritis: interim data from the open-label treatment period. EULAR 2019.

² Fleischmann R, Furst DE, Brasington R, Connolly-Strong E, Liu J, Barton ME. A multicenter study assessing the efficacy and safety of repository corticotropin injection in patients with rheumatoid arthritis: preliminary interim data from the open-label treatment period. Poster presented at: American College of Rheumatology and Association of Rheumatology Health Professionals (ACR/ARHP) Annual Meeting; October 19-24, 2018; Chicago, IL.

³ Mayo Clinic website. Rheumatoid Arthritis. Overview. Available at: <https://www.mayoclinic.org/diseases-conditions/rheumatoid-arthritis/symptoms-causes/syc-20353648>. Accessed October 11, 2018.

⁴ What is Rheumatoid Arthritis? Arthritis Foundation. Available at: <http://www.arthritis.org/about-arthritis/types/rheumatoid-arthritis/what-is-rheumatoid-arthritis.php>. Accessed September 10, 2018.

⁵ Arthritis Foundation. Rheumatoid Arthritis Treatment. Available at: <http://www.arthritis.org/about-arthritis/types/rheumatoid-arthritis/treatment.php>. Accessed September 10, 2018.

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