Mallinckrodt Announces New Clinical Data Evaluating Acthar® Gel (Repository Corticotropin Injection) in Rheumatoid Arthritis (RA) at the 2019 American College of Rheumatology/Association of Rheumatology Professionals (ACR/ARP) Annual Meeting

November 12, 2019

-- New analysis from Phase 4 study in RA showed that statistically significant improvement from baseline in patient-reported outcomes for pain, fatigue, physical functioning and work-related impairment was associated with Acthar Gel treatment -

-- Results from an exploratory analysis showed bone and cartilage biomarker levels in patients treated with Acthar Gel were largely stable and markers of bone degeneration remained stable --

STAINES-UPON-THAMES, United Kingdom, Nov. 12, 2019 /PRNewswire/ -- Mallinckrodt plc (NYSE: MNK), a global biopharmaceutical company, today announced data on patient-reported outcomes (PROs) showing Acthar® Gel (repository corticotropin injection) improved disease measures that impact rheumatoid arthritis (RA) patients with persistently active disease, as well as new data from an exploratory analysis. The data originate from new analyses from Mallinckrodt's Phase 4 study of Acthar Gel in RA patients with persistently active disease and was recently presented at the 2019 American College of Rheumatology/Association of Rheumatology Professionals (ACR/ARP) Annual Meeting, held Nov. 8-13 in Atlanta.

The study posters can be accessed here on the company's website.

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). Please see Important Safety Information for Acthar Gel below.

"Patient-reported outcomes, like fatigue, pain, and physical functioning, are an important part of any trial assessing clinical treatment outcomes. These additional data shed light on managing this challenging patient population whose symptoms persist after use of first-line therapies and suggest Acthar Gel treatment improved PROs in patients with persistently active RA," said Dr. Nancy E. Lane, Distinguished Professor of Medicine, Rheumatology and Aging, and Director of the UC Davis Center for Musculoskeletal Health. "The data exploring the effect of Acthar Gel treatment on patient-reported outcomes may help clinicians better understand Acthar Gel's use for patients with difficult-to-manage RA, those who have continued symptoms following standard therapies. The need for additional treatment options in this patient population is critical."

Patient-Reported Outcomes and Impact of Treatment (Abstract #439)

New data from the company's two-part Phase 4 multicenter, placebo-controlled study assessing the efficacy and safety of Acthar Gel in patients with persistently active RA who were previously treated with disease-modifying anti-rheumatic drugs (DMARDs) and corticosteroids showed that Acthar Gel treatment significantly improved patient-reported pain, fatigue, physical functioning and work-related impairment as early as Week 4, and resulted in clinically meaningful improvements in PROs.

The analysis examined PRO measures as a secondary endpoint from Part 1 of the study, the 12-week open-label period, and assessed mean changes at baseline and at Weeks 4, 8 and 12.

Patient-Reported Outcomes From the 12-Week Open-label RCI Treatment Perioda,2

<table>
<thead>
<tr>
<th>PRO Assessment</th>
<th>Baseline, Mean (SD)</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACIT-F</td>
<td>22.8 (8.4)</td>
<td>−5.0 (8.2) *</td>
<td>−6.5 (8.4) *</td>
<td>−8.7 (8.4) *</td>
</tr>
<tr>
<td>HAQ-DI</td>
<td>1.7 (0.6)</td>
<td>−0.5 (0.5) *</td>
<td>−0.6 (0.6) *</td>
<td>−0.84 (0.6) *</td>
</tr>
<tr>
<td>Patient global assessment of disease activityb,3</td>
<td>63.4 (20.0)</td>
<td>−17.8 (23.6) *</td>
<td>−25.7 (25.2) *</td>
<td>−35.0 (27.3) *</td>
</tr>
<tr>
<td>WPAI-RA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent work time missed due to RA 5</td>
<td>24.9 (27.6)</td>
<td>−7.0 (26.6)</td>
<td>−5.2 (28.0)</td>
<td>−10.8 (26.5) **</td>
</tr>
<tr>
<td>Percent impairment while working due to RA 5</td>
<td>50.3 (27.1)</td>
<td>−18.7 (24.4) *</td>
<td>−18.0 (23.9) *</td>
<td>−25.2 (25.3) *</td>
</tr>
<tr>
<td>Percent overall work impairment due to RA 5</td>
<td>58.1 (28.6)</td>
<td>−17.6 (27.0) *</td>
<td>−17.6 (27.5) *</td>
<td>−25.5 (29.2) *</td>
</tr>
<tr>
<td>Percent activity impairment due to RA 5</td>
<td>63.2 (24.2)</td>
<td>−18.1 (24.3) *</td>
<td>−22.5 (25.3) *</td>
<td>−32.8 (27.4) *</td>
</tr>
<tr>
<td>Patient global assessment of paind</td>
<td>64.9 (20.4)3</td>
<td>−20.8 (23.3) *</td>
<td>−27.8 (25.3) *</td>
<td>−37.4 (27.4) *</td>
</tr>
</tbody>
</table>

*a p<0.001 vs baseline. **p=0.003 vs baseline.

b mITT population (all patients who received study drug and had any post-treatment efficacy assessment).

c MCID = 15% absolute/20% relative improvement.
MCID = 7% absolute change.

Abbreviations and MCID references: FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue (MCID = 3.4); HAQ-DI, Health Assessment Questionnaire – Disability Index (MCID = 0.2); MCID, minimum clinically important difference; mITT, modified intent-to-treat; PRO, patient-reported outcome; RCI, repository corticotropin injection; SD, standard deviation; WPAI-RA, Work Productivity and Activity Impairment Questionnaire – Rheumatoid Arthritis.

AEs observed in the Phase 4 study were consistent with those in previous trials of Acthar Gel.

**Study Limitations**

- Sample bias may exist for the open-label phase of the ongoing study, and patients were aware that they were receiving Acthar Gel.
- Examiner bias may also exist as the patient had to reach low disease activity in order to enter the second phase of the study.
- 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.

“Mallinckrodt remains committed to the rheumatology community and to improving the lives of patients with autoimmune-mediated diseases like RA who continue to have debilitating symptoms and disease exacerbations despite standard treatments,” said Steven Romano, M.D., Chief Scientific Officer and Executive Vice President at Mallinckrodt. “We are pleased to be at this year’s ACR Annual Meeting to present new data on Acthar Gel that will broaden our understanding of its utility in rheumatology clinical practice for patients with difficult-to-manage RA and areas of high unmet need.”

**Assessment of Bone and Cartilage Turnover Markers (Abstract #528)**

A new exploratory analysis from the Phase 4 RA study assessed bone markers associated with bone loss to evaluate the impact of Acthar Gel treatment on bone turnover in patients with persistently active RA. Bone and cartilage biomarker levels were evaluated throughout the study, at baseline and Weeks 12 and 24 and included: C-terminal cross-linking telopeptide (CTX), C-terminal cross-linking telopeptide of type I collagen (CTX-I), osteoprotegrin (OPG), N-terminal propeptide of type I collagen (PINP), and soluble receptor activator of nuclear factor kappa-β ligand (sRANKL) and cartilage degradation biomarkers (C-terminal cross-linking telopeptide of type II collagen (CTX-II) and CTX-II creatinine (CRT)).

At Week 12, the open-label period, significant decreases in mean levels of the bone turnover biomarker PINP (P < 0.01) and mean levels of cartilage degradation biomarkers CTX-II (P < 0.01) and CTX-II CRT (P < 0.001) were observed. At Week 24, the end of the study's double-blind period, there was a significant increase from baseline in mean sRANKL levels at both Week 12 and Week 24 (P < 0.05) compared to placebo, suggesting a potential increase in osteoclast differentiation. Mean levels of all other bone and cartilage biomarkers remained stable at all time points and markers of bone degeneration remained stable.

Results from the full RA study were presented earlier this year at the Annual European League Against Rheumatism (EULAR 2019) in Madrid in June. More information on the Phase 4 RA study can be found here on ClinicalTrials.gov.

**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. An estimated 1.5 million U.S. adults are living with RA. Treatment is aimed at stopping inflammation to put the disease in remission and relieve symptoms. 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)
- 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 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. Acthar® Gel (repository corticotropin injection) [prescribing information]. Mallinckrodt ARD LLC.

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