A multicenter study assessing the efficacy and safety of Acthar® Gel (repository corticotropin injection) in patients with persistently active rheumatoid arthritis

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Presented at the European League Against Rheumatism (EULAR) 2019
Madrid, Spain • June 12–15, 2019

INDICATION

Acthar® Gel (repository corticotropin injection) is indicated for adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in rheumatoid arthritis (selected cases may require low-dose maintenance therapy).

SELECT 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

DISCLOSURE STATEMENT

Funding to support the preparation of this content was provided by Mallinckrodt Pharmaceuticals.
ACTHAR WAS ASSESSED IN A TWO-PART, MULTICENTER RANDOMIZED WITHDRAWAL STUDY OF 259 PATIENTS*1

OBJECTIVE

- To evaluate the efficacy and safety of Acthar in patients with persistently active rheumatoid arthritis (RA) despite the use of a corticosteroid and 1 or 2 DMARDs

STUDY DESIGN

Multicenter, Two-Part Study

<table>
<thead>
<tr>
<th>Study Period</th>
<th>Treatment</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Open-Label Treatment Period</strong></td>
<td>12-week open-label treatment period</td>
<td>4 weeks</td>
</tr>
<tr>
<td><strong>Part 1</strong></td>
<td>Acthar 80 U SC twice a week</td>
<td></td>
</tr>
<tr>
<td><strong>Part 2</strong></td>
<td>Acthar 80 U SC twice a week or placebo (1 mL) twice a week</td>
<td>4 weeks</td>
</tr>
<tr>
<td><strong>Double-Blind Withdrawal Period</strong></td>
<td>Randomization (Acthar:Placebo=1:1)</td>
<td>4 weeks</td>
</tr>
<tr>
<td><strong>Week 12</strong></td>
<td>LDA</td>
<td></td>
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<tr>
<td><strong>Screening (4 weeks)</strong></td>
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</tbody>
</table>

**Part 1: 12-week open-label treatment period**

- Participating patients were required to have persistently active RA despite treatment with 1 to 2 biologic/nonbiologic DMARDs and corticosteroids, and must be on stable background medication throughout the study
  - Patients received Acthar 80 U SC twice a week for the entire 12-week period

**Part 2: 12-week, randomized, double-blind withdrawal period**

- Patients who achieved low disease activity (LDA) as defined as DAS28-ESR Score <3.2 at Week 12 were entered into the second portion of the study
  - Patients received either Acthar 80 U SC twice a week or placebo (1 mL) SC twice a week
  - Patients who did not achieve LDA at Week 12 or who experienced an RA flare were discontinued from the study

- RA flare is defined as an increase of >0.6 DAS28-ESR from Week 0 sustained over 2 consecutive visits or an increase of >1 DAS28-ESR from Week 0 at a single visit

SELECT IMPORTANT SAFETY INFORMATION

**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

**STUDY ASSESSMENTS**

- **Primary endpoint:** Proportion of patients who achieved LDA (DAS28-ESR <3.2) at Week 12
- **Secondary and exploratory endpoints:**
  - Disease activity flare rate at Week 24, defined as fulfillment of any of the following criteria:
    - DAS28-ESR <3.2 and increase of 1.2 from Week 12
    - DAS28-ESR ≥3.2 and an increase of >0.6 from Week 12, sustained for 2 consecutive study visits
    - DAS28-ESR ≥3.2 and an increase of >1 from Week 12 at a single visit
  - Proportion of patients who maintained LDA (defined by DAS28-ESR <3.2) from Weeks 12 to 24
  - Proportion of patients with CDAI score ≤10 at Week 12, and who maintained CDAI score ≤10 from Weeks 12 to 24
  - Proportion of patients who met ACR20, ACR50, and ACR70 criteria

**STUDY LIMITATIONS**

- Data reported here are results from the open-label period and top-line results from the double-blind withdrawal period. Full results from double-blind period may vary from top-line analysis†
- Sample bias may exist in the open-label period as patients were aware that they were receiving Acthar†
- Examiner bias may also exist as the patient had to reach low disease activity in order to enter the double-blind withdrawal period†
- The results cannot be solely attributed to Acthar since patients were on different medications at the start of the trial and no washout periods were undertaken. Acthar has not been formally studied in combination with other treatments†

ACR=American College of Rheumatology; AEs=adverse events; CDAI=Clinical Disease Activity Index; DAS28-ESR= Disease Activity Score with 28 joint count and Erythrocyte Sedimentation Rate; DMARD=disease-modifying antirheumatic drug; SC=subcutaneously.

†In a randomized withdrawal study, patients who have an apparent response to treatment in an open-label period or in the treatment arm of a randomized trial are randomized to continued drug treatment or to placebo treatment.2

2The proportion of patients who achieved LDA (DAS28-ESR ≤3.2) at Week 12.
PATIENT OVERVIEW

Key Inclusion Criteria
- Age ≥18 years
- Meet criteria for RA as defined by the 2010 ACR/EULAR classification at screening
- Persistently active RA defined as a DAS28-ESR >3.2 despite prior biologic/nonbiologic DMARD(s) and a corticosteroid at screening and baseline
- Use of a corticosteroid in 12 weeks prior to screening and on a stable dose of 5-10 mg of prednisone (or equivalent) for 4 weeks before screening
- Use of 1 of the following for ≥12 weeks prior to screening (and must remain on same doses throughout study):
  - Methotrexate ≤20 mg per week and 1 biologic/nonbiologic DMARD
  - 1 allowed biologic DMARD
- Known contraindications to Acthar

Key Exclusion Criteria
- Use of any investigational treatment for RA or any biologic investigational agent during the 24 weeks before the first dose of study drug or any nonbiologic investigational agent within 6 weeks before the first dose of study drug
- History of sensitivity to Acthar or use of Acthar preparations for RA
- Current rheumatoid autoimmune disease or inflammatory joint disease other than RA
- Use of intra-articular corticosteroids in the 14 days before screening
- Use of B-cell–mediated therapies (eg, rituximab) in the 24 weeks before screening
- Known contraindications to Acthar

DMARDs Permitted During the Study

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<tr>
<th>Nonbiologic DMARDs</th>
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<td>Infliximab</td>
</tr>
<tr>
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<td>Adalimumab</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Etanercept</td>
</tr>
<tr>
<td>Tofacitinib*</td>
<td>Abatacept</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>—</td>
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SELECT IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont’d)
- 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 (eg, 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

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Patient Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Open-Label Period</th>
<th>Double-Blind Withdrawal Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acthar (N=259)</td>
<td>Acthar (n=77)</td>
<td>Placebo (n=76)</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>51.0 (12.2)</td>
<td>50.1 (12.2)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>231 (89)</td>
<td>67 (87)</td>
</tr>
<tr>
<td>Weight, kg, mean (SD)</td>
<td>72.9 (17.0)</td>
<td>70.8 (15.7)</td>
</tr>
<tr>
<td>DAS28-ESR score at baseline, mean (SD)</td>
<td>6.3 (1.0)</td>
<td>6.2 (0.9)</td>
</tr>
<tr>
<td>ESR at baseline, mean (SD)</td>
<td>43.6 (24.8)</td>
<td>40.3 (21.5)</td>
</tr>
<tr>
<td>DAS28-ESR at Week 12, mean (SD)</td>
<td>3.6 (1.4)</td>
<td>2.8 (0.4)</td>
</tr>
<tr>
<td>ESR at Week 12, mean (SD)</td>
<td>24.0 (21.5)</td>
<td>15.8 (12.2)</td>
</tr>
</tbody>
</table>

SD=standard deviation.
*Targeted synthetic DMARD (tsDMARD).

Please see additional Important Safety Information throughout and on back cover.
Please see accompanying full Prescribing Information.
**PRIMARY ENDPOINT**

- Efficacy results are presented for the modified intent-to-treat (mITT) population, which include all patients who received ≥1 dose of study drug and contributed any efficacy data to the study.

**Open-Label Treatment Period (Part 1)**

63% of Patients Treated With Acthar Achieved LDA (DAS28-ESR Score <3.2) at Week 12 During the Open-Label Period, mITT Population

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Change From Baseline, Mean (SD)</th>
<th>MID/MCID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>−1.4 (1.1)†</td>
<td>1.2†</td>
</tr>
<tr>
<td>Week 8</td>
<td>−2.0 (1.2)†</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>−2.8 (1.4)†</td>
<td></td>
</tr>
</tbody>
</table>

**KEY SECONDARY ENDPOINTS**

65% of Patients Treated With Acthar Achieved LDA Defined by CDAI Scores ≤10 at Week 12 During the Open-Label Period, mITT Population

**SELECT IMPORTANT SAFETY INFORMATION**

Warnings and Precautions (cont’d)

- 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.

Please see additional Important Safety Information throughout and on back cover.

Please see accompanying full Prescribing Information.

**KEY SECONDARY ENDPOINTS**

**Open-Label Treatment Period (Part 1)**

ACR 20/50/70 Response Was Achieved by 83%, 63%, and 30% of Patients, Respectively, Assessed at Week 12 During the Open-Label Period, mITT Population

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Change From Baseline, Mean (SD)</th>
<th>MID/MCID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>51†</td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>72‡</td>
<td>3.4‡</td>
</tr>
<tr>
<td>Week 12</td>
<td>83§</td>
<td></td>
</tr>
</tbody>
</table>

Acthar Therapy Was Associated With Significant Improvements in Swollen and Tender Joint Counts and Measures of Fatigue (FACIT-F) and Physical Function (HAQ-DI) During the Open-Label Period, mITT Population (N=259)

**Outcome**

- DAS28-ESR
- Swollen joint count
- Tender joint count
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)
- Health Assessment Questionnaire-Disability Index (HAQ-DI)

**Please see additional Important Safety Information throughout and on back cover.**

**Please see accompanying full Prescribing Information.**

MID=minimally important difference; MCID=minimally important clinical difference; ND=not determined.

*P<.001 from 1-sample binomial test (open-label period) or Pearson’s chi-square test (double-blind withdrawal period). P values denote differences from baseline for the open-label period and from placebo for the double-blind withdrawal period.

†Percentages above bars are rounded to the nearest whole number.

‡P≤.05.

§P<.001 from 1-sample t test.
KEY SECONDARY ENDPOINTS

Double-Blind Withdrawal Period (Part 2)

62% of Patients Treated With Acthar Sustained LDA (DAS28-ESR <3.2) at Week 24 During the Double-Blind Withdrawal Period, mITT Population

<table>
<thead>
<tr>
<th></th>
<th>Acthar Gel (n=77)</th>
<th>Placebo (n=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 12</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>Week 16</td>
<td>75</td>
<td>70</td>
</tr>
<tr>
<td>Week 20</td>
<td>81</td>
<td>65</td>
</tr>
<tr>
<td>Week 24</td>
<td>62*</td>
<td>43</td>
</tr>
</tbody>
</table>

More Patients Treated With Acthar Met ACR 20/50/70 Criteria at Week 24 Than Placebo During the Double-Blind Withdrawal Period, mITT Population

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Week 12</td>
<td>99</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>Week 16</td>
<td>97</td>
<td>87</td>
<td>83</td>
</tr>
<tr>
<td>Week 20</td>
<td>96</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Week 24</td>
<td>97</td>
<td>86</td>
<td>86*</td>
</tr>
</tbody>
</table>

SAFETY ENDPOINTS

AEs of Interest

<table>
<thead>
<tr>
<th>AE</th>
<th>Open-Label Period</th>
<th>Double-Blind Withdrawal Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acthar (N=259)</td>
<td>Acthar (n=77)</td>
</tr>
<tr>
<td>Any AE (%)</td>
<td>98 (38)</td>
<td>25 (33)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>1 (0.4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Glycosylated hemoglobin increased (%)</td>
<td>4 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Liver function test increased (%)</td>
<td>1 (0.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hyperglycemia (%)</td>
<td>3 (1)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>4 (2)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Weight increased (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

• AEs observed were consistent with those of previous trials of Acthar
• Most common AEs observed were: urinary tract infection (n=10), headache (n=9), and pharyngitis (n=7)
• Three patients reported serious AEs (chest pain, pneumonia, and cranio-cerebral injury)

*P<.05 vs placebo from Pearson’s chi-square test.
†P≤.05.

SELECT IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont’d)

• 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

Please see additional Important Safety Information throughout and on back cover.
Please see accompanying full Prescribing Information.
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**DATA SUMMARY**

- By Week 24 of the double-blind, placebo-controlled, randomized withdrawal period, there was a sustained effect of Acthar on the disease activity.
- During the open-label period, Acthar therapy was associated with significant improvements in:
  - Disease activity scores (DAS28-ESR and CDAI)
  - Swollen and tender joint counts
  - Measures of fatigue (FACIT-F) and physical function (HAQ-DI)
- The proportions of patients who met the ACR 20/50/70 criteria had significantly increased at Week 12.
- Top-line data suggest that, at the end of the double-blind withdrawal period (Week 24):
  - Significantly more patients treated with Acthar than with placebo had maintained LDA, as assessed by the DAS28-ESR.
  - Significantly more patients treated with Acthar than with placebo had maintained CDAI ≤10, as another evidence of low disease activity.
  - There was sustained effect of Acthar on DAS28-ESR <3.2, CDAI ≤10, and ACR 20/50/70.
  - Cumulative disease activity flare rate was significantly lower in patients treated with Acthar than with placebo.
- Most common AEs observed were: urinary tract infection (n=10), headache (n=9), and pharyngitis (n=7). Three patients reported serious AEs (chest pain, pneumonia, and cranioencephalic injury).
- These results showed that Acthar has the potential for sustained effectiveness in patients with rheumatoid arthritis who were treated previously with multiple standard therapies but continued to have active disease.

**SELECT IMPORTANT SAFETY INFORMATION**

**Warnings and Precautions (cont’d)**

- 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.

**STUDY LIMITATIONS**

- Data reported here are results from the open-label period and top-line results from the double-blind withdrawal period. Full results from double-blind period may vary from top-line analysis.
- Sample bias may exist in the open-label period as patients were aware that they were receiving Acthar.
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**REFERENCES**

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ADVERSE REACTIONS

- 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.
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Other adverse events reported are included in the full Prescribing Information.

Please see accompanying full Prescribing Information.