Acthar® Gel (repository corticotropin injection) for active rheumatoid arthritis despite aggressive treatment: A randomized controlled withdrawal trial

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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, including juvenile 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 origin

DISCLOSURE STATEMENT

Funding to support the preparation of this content was provided by Mallinckrodt Pharmaceuticals.

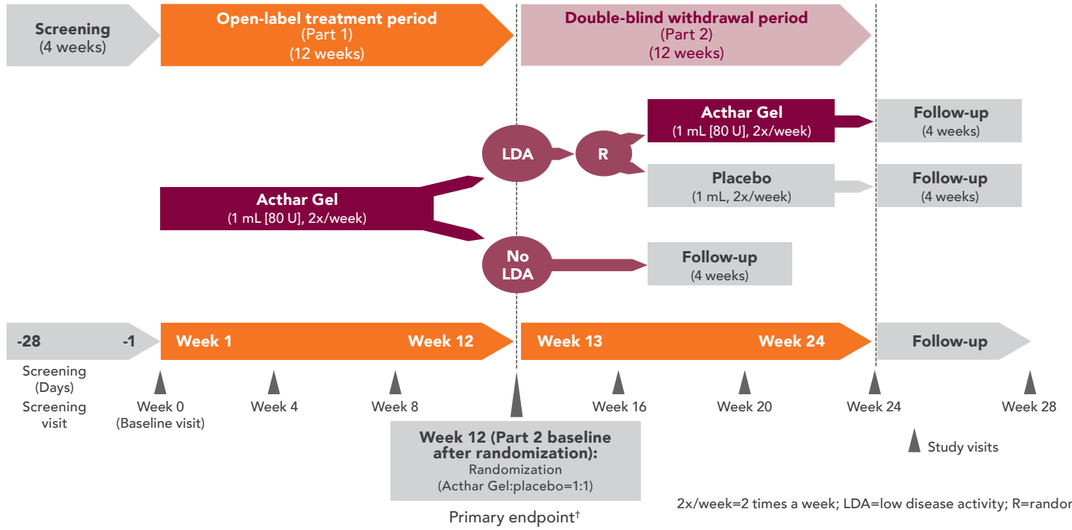
ACTHAR GEL WAS ASSESSED IN A PHASE 4, TWO-PART, MULTICENTER, RANDOMIZED WITHDRAWAL STUDY OF 259 PATIENTS[1]*

OBJECTIVE

- To evaluate the efficacy, safety, and tolerability of Acthar Gel in patients with persistently active rheumatoid arthritis (RA) despite treatment with a glucocorticoid and 1 or 2 DMARD(s)

STUDY DESIGN

Multicenter, two-part study



2x/week=2 times a week; LDA=low disease activity; R=randomization.

- **Part 1: 12-week, open-label treatment period**
  - Patients were required to have persistently active RA defined as DAS28-ESR >3.2 despite treatment with a stable low-dose glucocorticoid and required biologic/nonbiologic DMARD(s)
    - Patients were on stable background medication throughout the study
    - Patients received Acthar Gel 80 U SC twice a week for 12 weeks, a dosage that previous studies suggest is effective
    - Patients who did not achieve LDA at Week 12 were discontinued from the study
- **Part 2: 12-week, randomized, double-blind withdrawal period**
  - Patients who achieved low disease activity (LDA) defined as DAS28-ESR <3.2 at Week 12 were entered into the second portion of the study
    - Patients were randomly assigned to receive either Acthar Gel 80 U SC twice a week or placebo (1 mL) SC twice a week

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

Please see additional Important Safety Information throughout and on page 13 and full Prescribing Information.

STUDY ASSESSMENTS

- **Primary endpoint:** Proportion of patients who achieved LDA (DAS28-ESR <3.2) at Week 12
- **Selected secondary and exploratory endpoints:**
  - Proportion of patients who maintained LDA (DAS28-ESR <3.2) from Weeks 12 to 24
  - Proportion of patients who achieved remission (DAS28-ESR <2.6) at Weeks 12 and 24
  - Time to disease activity flare from Weeks 12 to 24, defined as fulfillment of any of the following criteria:
    - DAS28-ESR <3.2 and an 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 with CDAI score ≤10 at Weeks 12 and 24
  - Proportion of patients who met ACR20, ACR50, and ACR70 criteria at Weeks 12 and 24‡
  - Changes in HAQ-DI, FACIT-F, and WPAI scores from baseline to Weeks 12 and 24
  - Changes in key markers of bone turnover from baseline to Weeks 12 and 24
- **Safety endpoints evaluated by study period and throughout study:**
  - AEs
  - Vital signs
  - Laboratory test results

STUDY LIMITATIONS

- 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% 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

ACR20=American College of Rheumatology, 20% improvement; ACR50=American College of Rheumatology, 50% improvement; ACR70=American College of Rheumatology, 70% improvement; 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; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI=Health Assessment Questionnaire-Disability Index; SC=subcutaneously; WPAI=Work Productivity and Activity Impairment.

*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 placebo.[2]

†The proportion of patients who achieved LDA (DAS28-ESR <3.2) at Week 12.

‡ACR50 and ACR70 responses at Week 24 were evaluated post hoc.

PATIENT OVERVIEW[1]

Key inclusion criteria

Men and nonpregnant, nonlactating women aged ≥18 years

Met the 2010 ACR/EULAR criteria for having RA that was active, defined as DAS28-ESR >3.2

Use of a glucocorticoid in the 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

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

Use of intra-articular glucocorticoids in the 14 days before screening or use of B-cell–mediated therapies in the 24 weeks before screening

Known contraindications to Acthar Gel, history of sensitivity to Acthar Gel, or use of Acthar Gel preparations for RA

Current rheumatic autoimmune disease or inflammatory joint disease other than RA, current type 1 or type 2 diabetes mellitus, a history of chronic active hepatitis or tuberculosis, a solid tumor or hematologic malignancy, drug/alcohol abuse, or a clinically significant infection

DMARDs permitted during the study

Nonbiologic DMARDs			Biologic DMARDs		
Sulfasalazine	Hydroxychloroquine	Methotrexate	Infliximab	Etanercept	Golimumab
Leflunomide	Tofacitinib*	—	Adalimumab	Certolizumab	Abatacept

Most common (≥3% of patients) DMARDs included:

- Biologic DMARDs: adalimumab,†‡ etanercept,†‡ abatacept,†‡ certolizumab pegol,†‡ tocilizumab,† and infliximab†
- Nonbiologic DMARDs: hydroxychloroquine,†‡ sulfasalazine,†‡ leflunomide,†‡ chloroquine,†‡ and tofacitinib†

*Targeted synthetic DMARD (tsDMARD).
†Prior DMARDs.
‡Concomitant DMARDs.

SELECT IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont'd)

- 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

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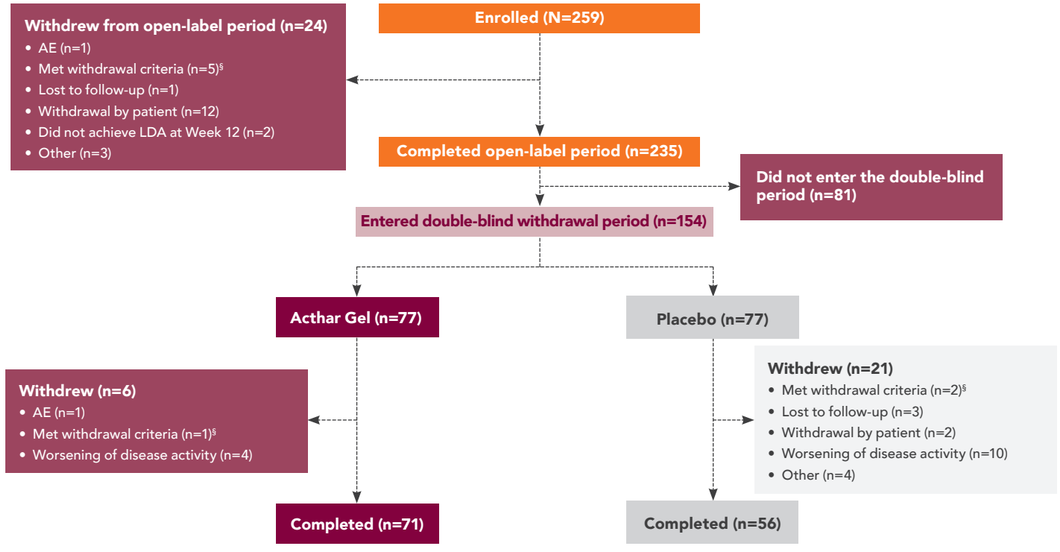
Patient disposition



Patient demographics and baseline characteristics, safety population

Characteristic	Open-label period	Double-blind withdrawal period	
	Acthar Gel (N=259)	Acthar Gel (n=77)	Placebo (n=77)
Age, y, mean (SD)	51.0 (12.2)	50.1 (12.2)	50.9 (11.3)
Female, n (%)	231 (89.2)	67 (87.0)	69 (89.6)
Weight, kg, mean (SD)	72.9 (17.0)	70.8 (15.7)	72.4 (14.5)
Disease duration, y, mean (SD)	10.3 (8.0)	10.1 (6.8)	9.4 (8.8)
Prednisone (or equivalent) dose, mg/day, mean (SD)	6.3 (5.0)	5.9 (1.7)	6.9 (8.7)
DAS28-ESR, mean (SD)	6.3 (1.0)	6.2 (0.9)	6.2 (1.0)
ESR, mean (SD)	43.6 (24.8)	40.3 (21.5)	42.0 (22.9)
DAS28-ESR at Week 12, mean (SD)	3.6 (1.4)	2.8 (0.4)	2.7 (0.5)
ESR at Week 12, mean (SD)	24.0 (21.5)	15.8 (12.2)	15.2 (12.6)

ACR=American College of Rheumatology; ESR=erythrocyte sedimentation rate; EULAR=European League Against Rheumatism; SD=standard deviation.

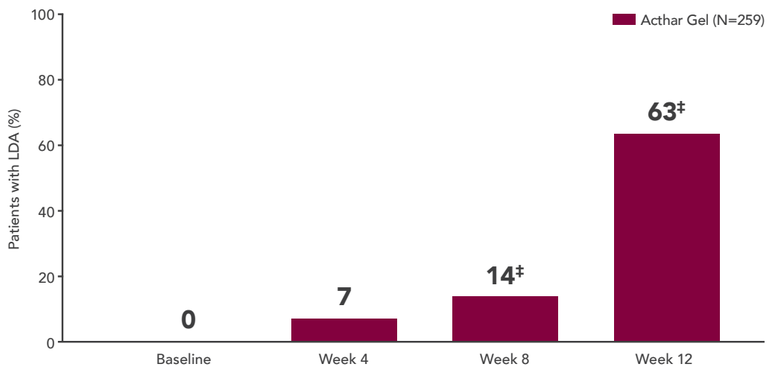
§Patients met withdrawal criteria if they developed a condition that met any of the study exclusion criteria or failed to meet any inclusion criteria during the study that was not considered an AE, or if they were noncompliant.

PRIMARY ENDPOINT[1]

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

Open-label treatment period (Part 1)

63% (n=163) of patients treated with Acthar Gel achieved LDA (DAS28-ESR <3.2) at Week 12 during the open-label period, mITT population*†



- 19% (n=49) of patients treated with Acthar Gel achieved remission (DAS28-ESR <2.6) at Week 12

SELECT IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont'd)

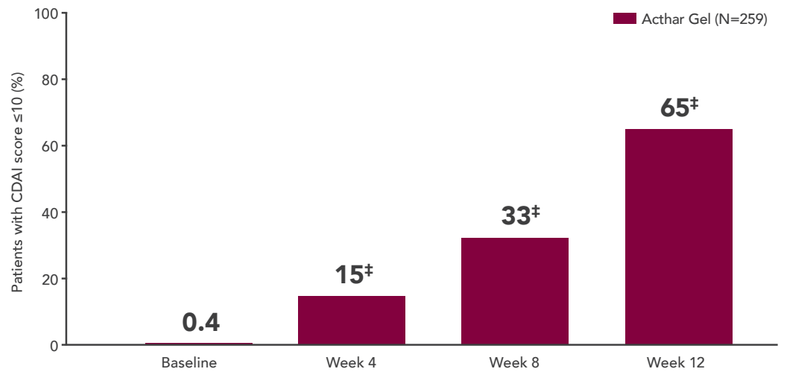
- Acthar often acts by masking symptoms of other diseases/disorders. Monitor patients carefully during and for a period following discontinuation of therapy
- Acthar can cause GI bleeding and gastric ulcer. There is also an increased risk for perforation in patients with certain gastrointestinal disorders. Monitor for signs of bleeding
- 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

Please see additional Important Safety Information throughout and on page 13 and full Prescribing Information.

KEY SECONDARY ENDPOINTS[1]

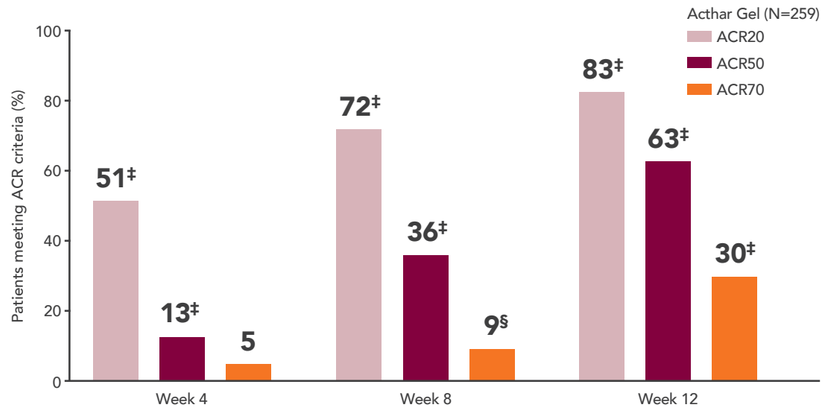
Open-label treatment period (Part 1)

65% (n=169) of patients treated with Acthar Gel achieved LDA defined by CDAI scores ≤10 at Week 12 during the open-label period, mITT population*†



Open-label treatment period (Part 1)

ACR20/50/70 response was achieved by 83% (n=215), 63% (n=162), and 30% (n=78) of patients, respectively, assessed at Week 12 during the open-label period, mITT population*†



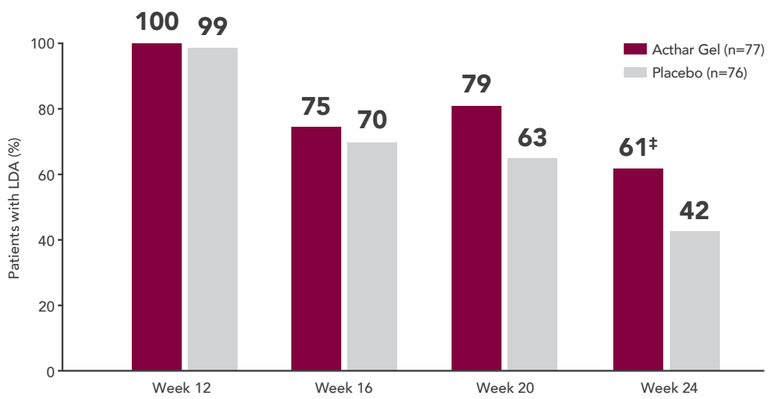
*Percentages above bars are rounded to the nearest whole number.
†*P* values from 1-sample binomial test (open-label period). *P* values denote differences from baseline for the open-label period.
‡*P*<.0001.
§*P*≤.05.

Acthar® GEL
(repository corticotropin injection) 80 U/mL

KEY SECONDARY ENDPOINTS[1,3]

Double-blind withdrawal period (Part 2)

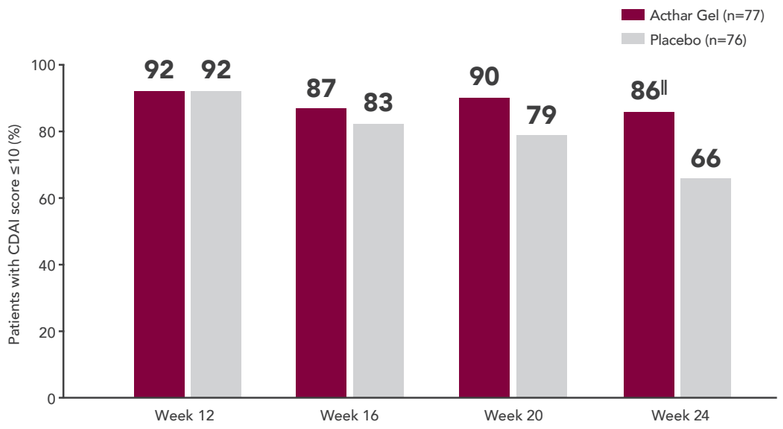
61% (n=47) of patients treated with Acthar Gel sustained LDA (DAS28-ESR <3.2) at Week 24 during the double-blind withdrawal period, mITT population*†



- 30% (n=23) of patients treated with Acthar Gel and 30% (n=23) of patients who received placebo achieved remission (DAS28-ESR <2.6) at Week 24[§]

Double-blind withdrawal period (Part 2)

At Week 24, a significantly greater proportion of patients treated with Acthar Gel maintained LDA (CDAI score ≤10) compared with patients who received placebo during the double-blind withdrawal period, mITT population*†



SELECT IMPORTANT SAFETY INFORMATION

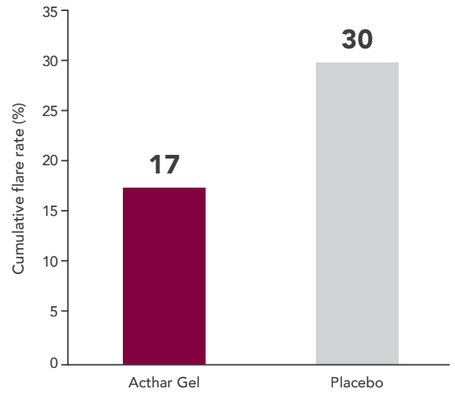
Warnings and Precautions (cont'd)

- 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

Please see additional Important Safety Information throughout and on page 13 and full Prescribing Information.

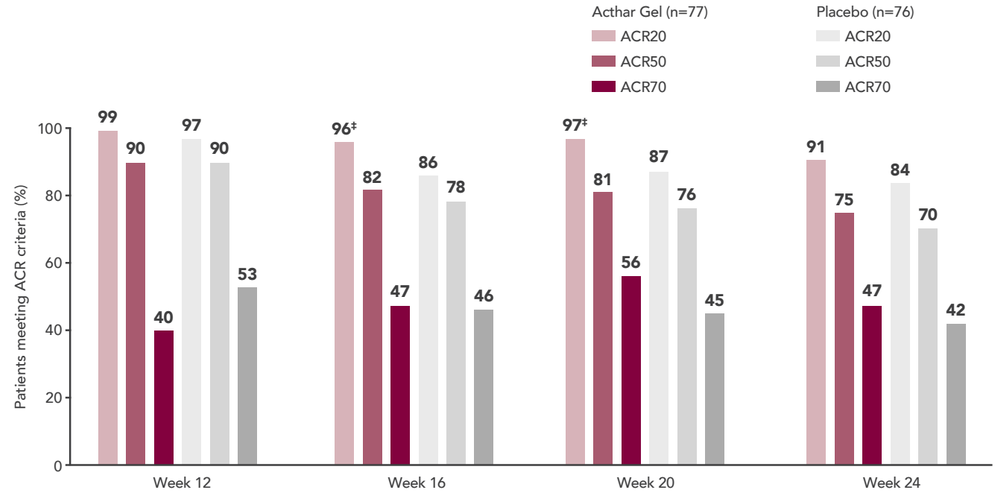
Double-blind withdrawal period (Part 2)

At Week 24, the cumulative disease activity flare rate was significantly lower for patients treated with Acthar Gel (17%) than with placebo (30%; *P*=.049) during the double-blind withdrawal period, mITT population*¶



Double-blind withdrawal period (Part 2)

More patients treated with Acthar Gel maintained ACR20/50/70 criteria at Week 24 than placebo during the double-blind withdrawal period, mITT population*†#



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

†*P* values from Pearson's chi-square test (double-blind period). *P* values denote differences from placebo for the double-blind period.

‡*P*≤.05.

§*P*=.828.

‖*P*≤.01.

¶Cumulative disease activity flare rate data from 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 persistently active rheumatoid arthritis. Poster presented at: European Congress of Rheumatology; June 12-15, 2019; Madrid, Spain.

#ACR50 and ACR70 responses at Week 24 were evaluated post hoc.

Acthar® GEL
(repository corticotropin injection) 80 U/mL

KEY EXPLORATORY ENDPOINTS[1]

Open-label treatment period (Part 1)

Acthar Gel 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	Baseline, mean	Change from baseline, mean			MID/MCID
		Week 4	Week 8	Week 12	
DAS28-ESR	6.3	-1.4†	-2.0†	-2.8†	1.2[4]
C-Reactive protein (µg/mL)	19.7	—	—	-2.3	ND
Swollen joint count	10.9	-5.3‡	-6.9‡	-8.1‡	ND
Tender joint count	14.7	-7.0‡	-8.9‡	-10.7‡	ND
FACIT-F	22.8	-5.0‡	-6.6‡	-8.9‡	3–4[5]
HAQ-DI	1.7	-0.5‡	-0.6‡	-0.8‡	0.22–0.25[5]

Open-label treatment period (Part 1)

Most bone turnover markers were stable during the open-label period, mITT population§‖

Time point	Marker, mean (SD)						
	CTX, µg/L	CTX-I, µg/L	CTX-II, µg/L	CTX-II CRT, ng/mmol	OPG, pmol/L	PINP, µg/L	sRANKL, pmol/L
Baseline	4.79 (2.09)	0.39 (0.21)	3.46 (2.31)	452.4 (325.4)	4.71 (1.80)	52.23 (28.21)	2057.70 (3592.90)
Week 12	4.76 (1.93)	0.39 (0.21)	2.99¶ (2.17)	362.5‡ (273.1)	4.68 (1.98)	47.37¶ (26.21)	2107.55 (3794.56)

- During Week 12 of the open-label period, levels of cartilage degeneration markers, CTX-II and CTX-II CRT, and bone formation marker, PINP, significantly decreased

CTX=C-terminal crosslinking telopeptide; CTX-I=C-terminal crosslinking telopeptide of type I collagen; CTX-II=C-terminal crosslinking telopeptide of type II collagen; CTX-II CRT=creatinine-adjusted CTX-II; MCID=minimal clinically important difference; MID=minimal important difference; ND=not determined; OPG=osteoprotegerin; PINP=N-terminal peptide of type I collagen; sRANKL=soluble receptor activator of nuclear kappa B ligand.

SELECT IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont'd)

- 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

Please see additional Important Safety Information throughout and on page 13 and full Prescribing Information.

Double-blind withdrawal period (Part 2)

Acthar Gel therapy was associated with improvements in swollen and tender joint counts and measures of fatigue (FACIT-F) and physical function (HAQ-DI) during the double-blind withdrawal period, mITT population Acthar Gel (n=77), Placebo (n=76)#

Outcome	Baseline, mean		Change from baseline, mean								MID/MCID
			Week 12		Week 16		Week 20		Week 24		
	Acthar Gel	Placebo	Acthar Gel	Placebo	Acthar Gel	Placebo	Acthar Gel	Placebo	Acthar Gel	Placebo	
DAS28-ESR	6.2	6.2	-3.5	-3.5	-3.4	-3.1	-3.4**	-3.1	-3.0	-2.8	1.2[4]
C-Reactive protein (µg/mL)	12.1	21.8	2.2	-4.9	—	—	—	—	4.3	-1.8	ND
Swollen joint count	9.7	10.1	-8.8	-9.2	-8.6	-8.3	-8.7	-8.1	-8.1	-7.8	ND
Tender joint count	13.5	13.5	-12.0	-12.1	-11.9	-10.9	-12.0	-10.8	-11.1	-10.4	ND
FACIT-F	22.7	22.6	-10.0	-10.3	-8.7	-8.7	-10.1	-10.0	-9.2	-10.2	3–4[5]
HAQ-DI	1.7	1.7	-1.0	-1.0	-0.9	-0.9	-0.9	-0.9	-0.8	-0.9	0.22–0.25[5]

Double-blind withdrawal period (Part 2)

Most bone turnover markers were stable during the double-blind withdrawal period, mITT population§††

Time point	Marker, mean (SD)						
	CTX, µg/L	CTX-I, µg/L	CTX-II, µg/L	CTX-II CRT, ng/mmol	OPG, pmol/L	PINP, µg/L	sRANKL, pmol/L
Baseline							
Acthar Gel	4.77 (1.89)	0.44 (0.22)	3.69 (2.47)	463.7 (316.9)	4.86 (1.83)	54.76 (28.79)	1519.42 (2378.26)
Placebo	4.58 (1.98)	0.38 (0.18)	3.61 (2.42)	460.5 (368.3)	4.65 (1.78)	52.46 (26.38)	2416.34 (3825.88)
Week 12							
Acthar Gel	4.58 (1.40)	0.45 (0.23)	2.93 (2.19)	368.0 (228.6)	4.79 (2.23)	51.19 (29.06)	2451.77‡‡ (4417.55)
Placebo	4.61 (1.63)	0.40 (0.21)	3.21 (2.36)	382.5 (257.5)	4.73 (1.89)	48.69 (25.07)	2358.63 (4401.72)
Week 24							
Acthar Gel	4.79 (2.76)	0.44 (0.20)	3.13 (1.87)	339.4 (189.7)	4.93 (2.04)	54.34 (40.08)	2938.96¶ (5006.25)
Placebo	4.47 (1.68)	0.41 (0.20)	3.27 (2.05)	391.6 (236.0)	5.12 (2.12)	53.10 (26.16)	2105.64 (4116.93)

- During the double-blind period, levels of osteoclast differentiation marker, sRANKL, significantly increased from baseline to Weeks 12 and 24 in the Acthar Gel group, but not the placebo group

*P values from 1-sample binomial test (open-label period). P values denote differences from baseline for the open-label period.

†$P \leq .001$.

‡$P < .001$.

§Data do not include bone density imaging and should not be used to conclude that Acthar Gel is safe for the bone in RA.

‖P values from 1-sample t test for Week 12 versus baseline.

¶$P < .01$.

#P values from Pearson's chi-square test (double-blind period). P values denote differences from placebo for the double-blind period.

**$P \leq .05$.

††P values from 2-sample t test for Acthar Gel time point versus baseline.

‡‡$P < .05$.

Acthar® GEL
(repository corticotropin injection) 80 U/mL

SAFETY ENDPOINTS[1]

Summary of AEs, safety population

Part 1 (Open-label period)	
AE	**Acthar Gel (N=259)**
Any AE,* n (%)	98 (37.8)
Anemia, n (%)	5 (1.9)
Glycosylated hemoglobin increased, n (%)	4 (1.5)
Headache, n (%)	9 (3.5)
Hypertension, n (%)	4 (1.5)
Nasopharyngitis, n (%)	4 (1.5)
Nausea, n (%)	5 (1.9)
Pharyngitis, n (%)	7 (2.7)
Upper respiratory tract infection, n (%)	4 (1.5)
Urinary tract infection, n (%)	10 (3.9)
AE resulting in study drug withdrawal, n (%)	3 (1.2)
Serious AE, n (%)	3 (1.2)
Serious infectious event, n (%)	1 (0.4)
Opportunistic infections, herpes zoster, n (%)	1 (0.4)

Part 2 (Double-blind period)		
AE	**Acthar Gel (n=77)**	**Placebo (n=77)**
Any AE,* n (%)	25 (32.5)	31 (40.3)
Anemia, n (%)	2 (2.6)	2 (2.6)
Back pain, n (%)	2 (2.6)	0
Diarrhea, n (%)	1 (1.3)	3 (3.9)
Dizziness, n (%)	1 (1.3)	1 (1.3)
Gastritis, n (%)	1 (1.3)	2 (2.6)
Glycosylated hemoglobin increased,† n (%)	1 (1.3)	2 (2.6)
Headache, n (%)	5 (6.5)	5 (6.5)
Hyperglycemia, n (%)	3 (3.9)	2 (2.6)
Hypertension, n (%)	3 (3.9)	0
Influenza, n (%)	1 (1.3)	1 (1.3)
Nasopharyngitis, n (%)	2 (2.6)	2 (2.6)
Rhinitis, n (%)	0	2 (2.6)
Upper respiratory tract infection, n (%)	0	3 (3.9)
Urinary tract infection, n (%)	2 (2.6)	3 (3.9)
AE resulting in study drug withdrawal, n (%)	0	1 (1.3)

*AEs reported in ≥1.5% of patients in part 1 or in either group in part 2.
†Refers to glycosylated hemoglobin values >6.5%.

- AEs that are typically associated with glucocorticoid use (eg, hypertension, hyperglycemia, weight gain, and edema) occurred at less than 5%
  - A greater incidence of common AEs associated with glucocorticoid use may occur if Acthar Gel therapy is continued indefinitely. Further studies are needed to evaluate the safety of long-term Acthar Gel therapy
- Three patients reported serious AEs (chest pain, pneumonia, and craniocerebral injury) during the open-label period. No serious AEs were reported during the double-blind period
- No deaths were reported in the overall study

Please see additional Important Safety Information throughout and on page 13 and full Prescribing Information.

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.

NOTES

NOTES

REFERENCES

1. Fleischmann R, Furst DE, Connolly-Strong E, Liu J, Zhu J, Brasington R. Repository corticotropin injection for active rheumatoid arthritis despite aggressive treatment: A randomized controlled withdrawal trial. *Rheumatol Ther.* Published online March 17, 2020. doi: 10.1007/s40744-020-00199-3. **2.** US Department of Health and Human Services. Enrichment strategies for clinical trials to support determination of effectiveness of human drugs and biological products. Guidance for industry. March 2019. https://www.fda.gov/media/121320/download. Accessed June 11, 2019. **3.** 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 persistently active rheumatoid arthritis. Poster presented at: European Congress of Rheumatology; June 12-15, 2019; Madrid, Spain. **4.** Curtis JR, Yang S, Chen L, et al. Determining the minimally important difference in the clinical disease activity index for improvement and worsening in early rheumatoid arthritis patients. *Arthritis Care Res (Hoboken).* 2015;*67*(10):1345-1353. **5.** Orbai AM, Bingham CO III. Patient reported outcomes in rheumatoid arthritis clinical trials. *Curr Rheumatol Rep.* 2015;17(4):28.

Please see additional Important Safety Information throughout and on page 13 and full Prescribing Information.

DATA SUMMARY[1,3]

- At Week 24 of the double-blind, placebo-controlled, randomized withdrawal period, there was a sustained effect of Acthar Gel on disease activity
- During the open-label period, Acthar Gel 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 ACR20/50/70 criteria at Week 12
- By Week 24 of the double-blind withdrawal period:
  - Significantly more patients treated with Acthar Gel than with placebo had maintained LDA, as assessed by the DAS28-ESR
  - Significantly more patients treated with Acthar Gel than with placebo had maintained CDAI ≤10, as an additional data point for low disease activity
  - There was sustained effect of Acthar Gel on ACR20/50/70 for both Acthar Gel and placebo groups
  - Cumulative disease activity flare rate was significantly lower in patients treated with Acthar Gel than with placebo*
- Three patients reported serious AEs (chest pain, pneumonia, and craniocerebral injury) during the open-label period. No serious AEs were reported during the double-blind period
- No deaths were reported in the overall study
- These results showed that Acthar Gel has the potential for sustained effectiveness in patients with rheumatoid arthritis who were treated previously with multiple standard therapies, but continued to have highly active disease

STUDY LIMITATIONS

- 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% 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

*Cumulative disease activity flare rate data from 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 persistently active rheumatoid arthritis. Poster presented at: European Congress of Rheumatology; June 12-15, 2019; Madrid, Spain.

SELECT IMPORTANT SAFETY INFORMATION

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Mallinckrodt Pharmaceuticals

Acthar® GEL
(repository corticotropin injection) 80 U/mL