CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-432 / N_000
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Indication(s):	Infantile Spasms
Applicant:	Questcor Pharmaceuticals
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Keywords:	Sample size, retrospective

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The sponsor obtained source efficacy data from three published, randomized, controlled studies. Among three studies, Study 222017-01 showed that Acthar Gel was significantly better than prednisone in both EEG response and clinical seizure response as well as the overall response ($p<0.01$). Study 222017-05 had 59 patients enrolled in the trial but a number of patients did not complete the study protocol, which had a considerable impact on the results of the trial. Depending on the population used for analyses, the conclusion can vary. Study 222017-04 compared Acthar low-dose with prednisone and showed that the low dose did not differ much from prednisone numerically ($p>0.99$).

Even though Study 222017-01 showed highly significant treatment effect of Acthar Gel, it is somewhat concerning that the conclusion cannot be directly confirmed in the other two trials. The analyses are retrospective and the sample size in each trial is small. With such small sample size, the study sample may not be a good representation of the intended pediatric population. The data to draw a definitive conclusion are limited. The efficacy evidence from three trials needs to be weighted carefully.

1.2 Brief Overview of Clinical Studies

The sponsor presented the efficacy results based on 3 published, randomized controlled trials (RCTs) where Acthar was evaluated for the treatment of patients with infant spasms (Baram 1996, Hrachovy 1994, Hrachovy 1983).

Study 222017-01 (Baram 1996) is a single-blind study compared high dose Acthar (150 U/ m^2/day) administered twice daily and prednisone (2 mg/kg/day) administered twice daily in patients with IS. 15 patients were randomized to Acthar and 14 patients were randomized to prednisone.

Study 222017-05 (Hrachovy 94) is a prospective, controlled, randomized, single-blind study that compared an Acthar high-dose regimen (150 U/m^2/qd) to Acthar low-dose regimen (20 U/qd) in patients with IS. 59 patients were enrolled in the study. 9 patients did not complete the treatment protocol.

Study 222017-04 (Hrachovy 83) is a randomized, controlled, double-blind study that compared low dose Acthar (20 to 30 U/day) administered as a single daily dose to prednisone at a dose of 2 mg/kg/day in patients with IS. 12 patients were randomized to Acthar Gel and 12 were randomized to prednisone.

1.3 Statistical Issues and Findings

Unlike the conventional pivotal trials submitted for drug approvals, the efficacy evidence of Acthar gel in treating infantile spasms is based on three published randomized controlled trials. Although the sponsor obtained the source efficacy data of those three trials and re-analyzed them, there was no prospectively defined statistical analysis plan. The sample size of each trial is small. With such small sample size, the study sample may not be a good representation of the intended pediatric population. Therefore the efficacy data to draw conclusions are limited. Even though the sponsor used one study (222017-04) as the pivotal trial and the other two as supportive trials, this was not determined prospectively. All three studies should be weighted carefully. Furthermore, the so-called primary endpoint may not carry as much weight as the primary endpoint in the conventional clinical trials since it was not defined prospectively.

Study 222017-05 had a number of patients who did not complete the treatment protocol. Depending on the population used for analyses, the conclusion can vary. The analyses of overall response and EEG response showed no statistically significant differences between the 2 treatment groups. The analysis of the spasm control response by IS etiology showed a nominally significant difference between the Acthar high-dose and Acthar low-dose treatment groups in favor of Acthar high-dose. This is based on the sponsor-defined mITT population. The significance disappeared if some other defined population is used (e.g., ITT population, completed patients population). Study 222017-04 showed similar overall response rate in both Acthar low-dose group and prednisone group. It cannot be determined whether it suggests that the low dose Acthar has similar effect in treatment infantile spasms as prednisone, or it is likely due to the small sample size of the trial.

2. INTRODUCTION

2.1 Overview

Out of 5 published, randomized controlled trials (RCTs) where Acthar was evaluated for the treatment of patients with infant spasms, the sponsor was able to obtain source efficacy data from the following 3 studies:

- Questcor obtained source efficacy data from the study conducted by Dr. Baram (Baram 1996). Questcor's analyses of these data are presented as CSR 222017-01. CSR 222017-01 is designated as the pivotal efficacy study.

- Questcor obtained source efficacy data from the 2 additional RCTs conducted and published by Dr. Hrachovy and colleagues (Hrachovy 1994, Hrachovy 1983). Questcor's analyses of these data are presented as CSR 222017-05 and CSR 222017-04, respectively. CSR 222017-05 is presented as the supportive efficacy study. Additional efficacy data supporting the use of Acthar for the treatment of IS patients is presented in CSR 222017-04.

Pivotal study 222017-01 is a single-blind comparison of response to treatment. It compared Acthar 150 U/ m^2/day administered as 75 U/ m^2/bid IM for 2 weeks with a taper to zero for an additional 2 weeks and prednisone 2 mg/kg/day administered as 1 mg/kg/bid orally (PO) for 2 weeks with a taper to zero over 2 weeks in patients with IS. 15 patients were randomized to Acthar and 14 patients were randomized to prednisone.

The supportive efficacy study 222017-05 is a prospective, controlled, randomized, single-blind study that compared an Acthar high-dose regimen (150 U/ m^2/qd) to Acthar low-dose regimen (20 U/qd) in patients with IS. The study enrolled 59 patients (30 in high-dose, 29 in low-dose). Nine patients (4 in the high-dose group, 5 in the low-dose group) did not complete the treatment protocol.

Study 222017-04 is a randomized, controlled, double-blind study that compared Acthar at a dose of 20 to 30 U/day administered as a single daily (20 to 30 U/qd) IM dose (Acthar low-dose) to prednisone at a dose of 2 mg/kg/day PO in patients with IS. 12 patients were randomly assigned to Acthar Gel and 12 were randomly assigned to prednisone.

2.2 Data Sources

The sponsor's electronic submission is stored under the directory of
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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 STUDY 222017-01

3.1.1.1 Study Objectives

The objective of this study was to compare the efficacy of H.P.Acthar Gel (repository Corticotropin injection or ACTH) 150 U/m^2/day and prednisone (2 mg/kg/day), administered for 2 weeks, in suppressing clinical spasms and hypsarrhythmic electroencephalogram (EEG) in patients with infantile spasms (IS).

3.1.1.2 Study Design

The study was initially designed as a single-blind comparison of response to treatment, evaluating a single dose of ACTH 20 U/day compared to ACTH 150 U/m^2/day and to prednisone (2g/kg/day) in the treatment of infants with IS. Acthar 150 U/m2/day was administered as 75 U/m2/bid IM for 2 weeks and then tapered to zero for an additional 2 weeks. Prednisone 2 mg/kg/day was administered as 1 mg/kg/bid PO for 2 weeks, and then tapered to zero over 2 weeks. The study was amended to eliminate the 20 U/day ACTH dose. As a result of the amendment, the study was a single-blind comparison of response to treatment, evaluating 150 U/m2/day ACTH and 2mg/kg/day prednisone in the treatment of infants with IS. The investigators were unblinded to the treatment assignment but the interpreter of the video -EEG was blinded. Patients with persistent spasms or hypsarrhythmia after initial treatment were offered the alternative treatment.

Patients eligible for enrollment into this study were diagnosed with clinical IS. An infant previously treated with any steroid or Acthar treatment was not eligible for the study. All patients had a 24-hour video-EEG to ascertain the presence of hypsarrhythmia before initiation of treatment. Seizure frequency was monitored throughout the 2-week treatment period by parents who maintained seizure diaries. After 2 weeks of treatment, a repeat video-EEG was performed, and both clinical and EEG responses were assessed. Video-EEG monitoring was performed for a minimum of 4 hours and optimally, for 24 hours and included a minimum of 1 full sleep-wake cycle.

3.1.1.3 Efficacy Measures

(1) Primary Efficacy Endpoint

Since this is re-analysis of a published study, the sponsor did not specify primary or secondary endpoints. The endpoints were referred as efficacy endpoints. The efficacy measure of the study was a combined clinical (seizure) and video-EEG response, which was used to establish response to treatment. In addition, the sponsor also provided analysis of response adjusted for age as well as the analysis of response to crossover treatment.

(2) Secondary Efficacy Endpoints

Not applicable.

3.1.1.4 Patient Disposition, Demographic and Baseline Characteristics

Fifteen (15) patients were randomized to Acthar and 14 patients were randomized to prednisone.

Table 1 Summary of Demographic and Baseline Characteristics

	Prednisone N[a]=14	Acthar Gel N=15	All Patients N=29	*P*-value
Age, months[b]				0.0616
Mean	7.5	5.1	6.3	
SD	4.51	2.21	3.66	
Median	7.0	5.0	6.0	
Min, Max	3, 21	2, 11	2, 21	
Gender, n[a] (%)[c]				0.0959
Female	6 (42.9)	11 (73.3)	17 (58.6)	
Male	8 (57.1)	4 (26.7)	12 (41.4)	
Etiology Category, n (%)[c]				0.9408
Symptomatic	12 (85.7)	13 (86.7)	25 (86.2)	
Cryptogenic	2 (14.3)	2 (13.3)	4 (13.8)	

a. N/n is the number of patients.
b. The comparison of age distributions between treatment groups was performed with a Mann-Whitney test.
c. The comparisons of gender and etiology category frequencies by treatment were performed with a Pearson chi-square test.

[Source: Sponsor's clinical study report 222017-01 Table 11.1, confirmed by the reviewer]

3.1.1.5 Sponsor's Primary Efficacy Results

As mentioned previously in Section 3.1.1.3, the sponsor did not specify primary or secondary endpoints. So the reviewer also referred the analyses as efficacy analyses. For a patient to be considered a responder to treatment, both video-EEG and clinical (seizure) responses were necessary. The sponsor reported that the overall response (ie, EEG plus clinical response) indicated greater efficacy of Acthar Gel (13/15, 86.7%) compared to prednisone (4/14, 28.6%), *P*=0.0015.

Table 2 Analysis of Response to Treatment

	Prednisone N=14	**Acthar Gel N=15**	***P*-value**
Overall Response (EEG + Clinical), n (%)			0.0015
Yes	4 (28.6)	13 (86.7)	
No	10 (71.4)	2 (13.3)	
EEG Response, n (%)			0.0015
Yes	4 (28.6)	13 (86.7)	
No	10 (71.4)	2 (13.3)	
Clinical Response, n (%)			0.0003
Yes	4 (28.6)	14 (93.3)	
No	10 (71.4)	1 (6.7)	

* p-value is based on Pearson Chi-square test
[Source: Sponsor's clinical study report 222017-01 Table 11.2, confirmed by the reviewer]

The sponsor performed analyses of response to treatment adjusted for age group for the overall, EEG, and clinical response. Each analysis to evaluate the relative response rate (risk) for ACTH compared to prednisone was stratified by age at 2 levels. The analysis was performed for age groups defined by thresholds at 5, 6, 7, 8, 9, or 10 months. The sponsor reported that the differences between ACTH and prednisone for EEG and clinical responses remained statistically significant favoring the ACTH treatment group after adjusting for age group ($P<0.01$, for all comparisons).

Table 3 Analyses of Overall Response to Treatment Adjusted for Age

Age Groups (Months)	N	Response	Treatment: Prednisone (N=15)	Treatment: ACTH (N=14)	Weighted Relative Risk (95% CI)	P-value (d)
< 5	9	Yes	0 (0.0%)	5 (83.3%)	3.37 (1.32, 8.58)	0.0015
		No	3 (100%)	1 (16.7%)		
>=5	20	Yes	4 (36.4%)	8 (88.9%)		
		No	7 (63.6%)	1 (11.1%)		
< 6	14	Yes	0 (0.0%)	7 (77.8%)	3.81 (1.44, 10.09)	0.0006
		No	5 (100%)	2 (22.2%)		
>=6	15	Yes	4 (44.4%)	6 (100%)		
		No	5 (55.6%)	0 (0.0%)		
< 7	19	Yes	1 (16.7%)	11 (84.6%)	3.95 (1.26, 12.38)	0.0017
		No	5 (83.3%)	2 (15.4%)		
>=7	10	Yes	3 (37.5%)	2 (100%)		
		No	5 (62.5%)	0 (0.0%)		
< 8	21	Yes	2 (25.0%)	11 (84.6%)	3.27 (1.28, 8.37)	0.0021
		No	6 (75.0%)	2 (15.4%)		
>=8	8	Yes	2 (33.3%)	2 (100%)		
		No	4 (66.7%)	0 (0.0%)		

[Source: Sponsor's clinical study report 222017-01 Section 14.2 Table 3, confirmed by the reviewer]

The p-values in the tables were calculated based on Mantel-Haenszel test by controlling the age factor. The weighted relative risk is obtained from the Estimate of the Common Relative Risk (Row1/Row2) in SAS.

Assuming that the true prednisone response rate is 28.6%, as observed in the current study, the sponsor suggested that a future study, with 15 subjects randomized to Acthar Gel and 14 to prednisone would have at least 80% power to detect a treatment difference if the true Acthar Gel response rate is at least 84.4%. The study had only 10% power to detect a 20% difference in response rates compared between treatments.

Patients were also followed up for an average of 15 months (minimum of 1 month and maximum of 48 months).

3.1.1.6 Sponsor's Secondary Efficacy Results

Not applicable.

3.1.1.7 Reviewer's Results

The reviewer confirmed sponsor's analyses of response to treatment. Due to the small numbers in each cell, it would be more appropriate to use Fisher's Exact test instead of Chi-square test to compare the response rates between Acthar Gel group and prednisone group. The results based on Fisher's Exact test are shown in the following table (Table 4). The results do not differ much from the sponsor's results.

Table 4 Analysis of Response to Treatment using Fisher's Exact Test

	Prednisone	Acthar Gel	p-value
Overall response			0.0025
Yes	4	13	
No	10	2	
EEG response			0.0025
Yes	4	13	
No	10	2	
Clinical Response			0.0005
Yes	4	14	
No	10	1	

The median follow up time in this study is 11 months and mean follow up time is 15.3 months. The minimum and maximum follow up time for the 29 patients are 1 month and 48 months, respectively. 1 patient was recorded to have relapse in the sponsor's dataset.

3.1.1.8 Conclusions

Pivotal study 222017-01 appears to show that Acthar was superior to prednisone in infant spasms using twice-daily administration and 2-week high-dose regimen with a 2-week taper.

3.1.2 STUDY 222017-05

3.1.2.1 Study Objectives

The primary objectives of this study analysis were to compare the efficacy and safety of Acthar high-dose with that of Acthar low-dose in the treatment of patients with infantile spasms (IS). The secondary objective of this study analysis was to assess efficacy based on spasm cessation alone (Spasm Control Response) and by resolution of the hypsarrhythmic EEG pattern (Hypsarrhythmia EEG Pattern Response) alone between the 2 treatment groups.

3.1.2.2 Study Design

This is a randomized, controlled, single-blind study of Acthar high-dose (150 U/m2/once-daily [qd]), long-duration (3 weeks treatment plus 9 weeks taper) versus Acthar low-dose (20 U/qd), short-duration (2 to 6 weeks treatment plus 1 to 2 weeks taper) in patients with IS. Before initiation of treatment, each patient was monitored for up to 24 hours to confirm the presence of clinical spasms and to characterize the EEG pattern. At the end of the 12-week treatment period, patients returned for an EEG monitoring session to evaluate response to therapy. Developmental testing was repeated at this time. Nonresponders were treated with prednisone, 2 mg/kg/day for 4 to 6 weeks, and then followed in a routine clinical manner. Reviewers of the monitoring studies were unaware of the dosage of ACTH administered.

3.1.2.3 Efficacy Measures

(1) Primary Efficacy Endpoint

The primary efficacy endpoint was the Overall Response. An Overall Response was defined as both cessation of spasms and resolution of the hypsarrhythmic EEG pattern at any time during the study.

(2) Secondary Efficacy Endpoints

The secondary efficacy endpoints were the assessment of efficacy based on spasm cessation alone (Spasm Control Response) and by resolution of the hypsarrhythmic EEG pattern (Hypsarrhythmia EEG Pattern Response) alone between the 2 treatment groups.

Note that the original publication (Hrachovy 1994) did not use primary and secondary endpoints.

3.1.2.4 Patient Disposition, Demographic and Baseline Characteristics

Fifty-nine (59) patients were enrolled in the study. In the original publication (Hrachovy 94), only 50 out of the 59 patients were included in the analysis. Nine patients (4 in the high-dose group, 5 in the low-dose group) were excluded because they did not complete the treatment protocol due to various reasons. Among the nine patients, information from eight patients was recovered. The sponsor subsequently included all patients in the analyses as requested by the Division.

Among the fifty-nine patients, thirty (30) patients were randomly assigned to the Acthar high-dose group and 29 were randomly assigned to the Acthar low-dose group. Twelve (12) patients were withdrawn from the study prior to completion of the protocol: 4 patients were withdrawn due to AEs, 1 patient was withdrawn due to death, and 7 patients were withdrawn due to another reason. The chart for 1 patient (90-999) could not be located; based on information provided by the investigator, this patient was randomly assigned to the Acthar low-dose group Two patients (90-005, 90-006) were randomized and assigned to treatment but did not receive any Acthar doses.

Table 5 Summary of Patient Disposition by Treatment Group (ITT Population)

Parameter	Acthar High Dose n=30	Acthar Low Dose n=29	Acthar All Patients N=59
Number of patients enrolled, n (%)	30 (100)	29 (100)	59 (100)
Number of patients completed, n (%)	25 (83.3)	21 (72.4)	46 (78.0)
Number of patients with no documentation, n (%)	0	1 (3.4)	1 (1.7)
Number of patients prematurely withdrew, n (%)	5 (16.7)	7 (24.1)	12 (20.3)
Number of patients withdrew due to AEs	1 (3.3)	3 (10.3)	4 (6.8)
Number of patients withdrew due to death	0 (0.0)	1 (3.4)	1 (1.7)
Number of patients withdrawn due to other reason	4 (13.3)	3 (10.3)	7 (11.9)

[Source: Sponsor's clinical study report 222017-05 Table 10.1, confirmed by the reviewer]

There are 4 efficacy analysis populations for this study. These were defined as follows:

The mITT Population (n=51) includes all patients who were randomized, received ≥ 1 dose of Acthar study medication, and had sufficient data to evaluate the Overall Response. This was sponsor's primary efficacy analysis population.

The ITT Population (n=59) includes all patients randomized to treatment. This population included the 1 patient who was randomized to Acthar low-dose whose chart was not able to be located by Dr. Hrachovy; this is the only population that includes this patient. The ITT Population was used to perform a sensitivity analysis of the treatment efficacy response. All patients with unknown Spasm Control Response or Hypsarrhythmic EEG Pattern Response were classified as responders if in the Acthar low-dose group, and as nonresponders if in the Acthar high-dose group.

The Spasms Population (n=55) includes all patients with sufficient data to evaluate the Spasm Control Response.

The Completed Patients Population (n=50) includes the 50 patients identified by the investigators as having completed the study protocol. The Completed Patients Population was analyzed for this report so that Questcor could perform an independent analysis of the same population of patients analyzed by the investigators. This population is identical to the one used in Hrachovy 94 publication. Note that the sponsor reported 46 patients who completed study in Table 5. The sponsor stated that it was unknown what criteria were used by Dr. Hrachovy in identifying the 50 patients in his analysis. No analysis was done on the 46 "completed patients" selected by the sponsor.

The Safety Population (n=57) includes all patients known to have been dosed with ≥ 1 dose of Acthar. Patients were classified by treatment. Safety summaries were based on the Safety Population.

Table 6 and Table 7 provide summary on analysis populations, as well as demographic and baseline statistics.

Table 6 Analysis Populations by Treatment Group

	Acthar High Dose n=30	**Acthar Low Dose n=29**	**Acthar All Patients N=59**
Populations for Analysis, n (%)			
ITT Population	30 (100.0)	29 (100.0)	59 (100.0)
mITT Population	24 (80.0)	27 (93.1)	51 (86.4)
Spasms Population	28 (93.3)	27 (93.1)	55 (93.2)
Completed Patients Population	26 (86.7)	24 (82.8)	50 (84.7)
Safety Population	28 (93.3)	29 (100)	57 (96.6)

[Source: Sponsor's clinical study report 222017-05 Table 10.2, confirmed by the reviewer]

Table 7 Summary of Demographic and Baseline Characteristics

Variable	Treatment Group: Acthar High Dose n=24	Acthar Low Dose n=27	Acthar All Patients N=51
Age at onset of spasms (months)			
n	24	26	50
Mean (SD)	8.05 (5.149)	9.07 (6.31)	8.58 (5.746)
Median	6.77	6.39	6.62
Min, max	1.9, 25.2	2.6, 28.2	1.9, 28.2
Age at start of treatment (months)			
n	24	26	50
Mean (SD)	8.25 (5.159)	9.31 (6.457)	8.8 (5.836)
Median	6.98	6.41	6.72
Min, max	1.9, 25.2	2.6, 28.2	1.9, 28.2
Sex, n (%)			
Male	12 (50.0)	19 (70.4)	31 (60.8)
Female	12 (50.0)	8 (29.6)	20 (39.2)
Race, n (%)			
White	9 (37.5)	11 (40.7)	20 (39.2)
Black or African-American	5 (20.8)	6 (22.2)	11 (21.6)
Unknown	9 (37.5)	7 (25.9)	16 (31.4)
Other	1 (4.2)	0 (0.0)	1 (2.0)
Etiology Category, n (%)			
Symptomatic	17 (70.8)	18 (66.7)	35 (68.6)
Cryptogenic	7 (29.2)	9 (33.3)	16 (31.4)

* one patient did not have data for age
[Source: Sponsor's clinical study report 222017-05 Table 10.3, confirmed by the reviewer]

3.1.2.5 Sponsor's Primary Efficacy Results

The Overall Response rate in the mITT Population (N=51) was 15/24 (62.5%) in the Acthar high-dose group and 13/27 (48.1%) in the Acthar low-dose group. The risk ratio was 1.318. However, the Overall Response rates between the 2 groups were not significantly different. The treatment comparison was *P*=0.2768.

The Overall Response rate in the ITT Population sensitivity analysis (N=59) was 15/30 (50.0%) in the Acthar high-dose group and 15/29 (51.7%) in the Acthar low-dose group. The risk ratio was 0.982. The Overall Response rates in the sensitivity analysis were not significantly different. The treatment comparison was *P*=0.9443.

The sponsor attributed the non-significant results of the trial to the once-daily administration of Acthar in this trial. In this study, Acthar was administered as a once-daily dose of 150 U/m^2. Although this daily dose was equivalent to the total daily dose in CSR 222017-01, the Acthar in the CSR 222017-01 was administered as 2 divided daily doses (ie, 75 U/m^2 per dose). The sponsor argued that this once-daily dosing could yield a lower ACTH accumulation when compared to the ACTH accumulation from twice-daily dosing.

3.1.2.6 Sponsor's Secondary Efficacy Results

The Spasm Control Response rate in the mITT Population (N=51) was greater in the Acthar high-dose group (19/24, 79.2%) than in the Acthar low-dose group (14/27, 51.9%). The risk ratio was 1.553 and the treatment comparison was *P*=0.0329.

The Hypsarrhythmic EEG Pattern Response rate in the mITT Population (N=51) was 16/24 (66.7%) in the Acthar high-dose and 14/27 (51.9%) in the Acthar low-dose groups. The risk ratio was 1.299 and the treatment comparison was *P*=0.2686.

The sponsor also performed a number of sensitivity analyses based on different populations as shown in Table 8, Table 9, and Table 10 (ITT population, spasm population, and completed patients population). The p-values were calculated based on Mantel-Haenszel test comparing response rates between treatments, stratified on etiology. The risk ratio is the common relative risk calculated by PROC FREQ procedure.

Table 8 Sensitivity Analyses in ITT Population (N=59)

Outcome	Acthar Treatment	n	Responders n (%)	Nonresponders n (%)	Risk Ratio	*P*-value
Overall Response	High Dose	30	15 (50.0)	15 (50.0)	0.982	0.9443
	Low Dose	29	15 (51.7)	14 (48.3)		
Spasm Control Response	High Dose	30	23 (76.7)	7 (23.5)	1.410	0.0691
	Low Dose	29	16 (55.2)	13 (44.8)		
Hypsarrhythmic EEG Pattern Response	High Dose	30	16 (53.3)	14 (46.7)	0.865	0.5209
	Low Dose	29	18 (62.1)	11 (37.9)		

[Source: Sponsor's clinical study report 222017-05 Table 11.4, confirmed by the reviewer]

There were 4 patients in the low dose group who did not have complete EEG data and were therefore assigned as EEG responders in the ITT analysis (Patients 90-007, 90-008, 90-999, and 97-068).

Table 9 Sensitivity Analyses in Spasms Populations (N=55)

Outcome	Acthar Treatment	n	Responders n (%)	Nonresponders n (%)	Risk Ratio	*P*-value
Overall Response	High Dose	28	15 (53.6)	13 (46.4)	1.133	0.6363
	Low Dose	27	13 (48.1)	14 (51.9)		
Spasm Control Response	High Dose	28	23 (82.1)	5 (17.9)	1.612	0.0126
	Low Dose	27	14 (51.9)	13 (48.1)		
Hypsarrhythmic EEG Pattern Response	High Dose	28	16 (57.1)	12 (42.9)	1.116	0.6580
	Low Dose	27	14 (51.9)	13 (48.1)		

[Source: Sponsor's clinical study report 222017-05 Table 11.5, confirmed by the reviewer]

Table 10 Sensitivity Analyses in Completed Patients Populations (N=50)

Outcome	Acthar Treatment	n	Responders n (%)	Nonresponders n (%)	Risk Ratio	*P*-value
Overall Response	High Dose	26	15 (57.7)	11 (42.3)	1.058	0.8225
	Low Dose	24	13 (54.2)	11 (45.8)		
Spasm Control Response	High Dose	26	21 (80.8)	5 (19.2)	1.374	0.0782
	Low Dose	24	14 (58.3)	10 (41.7)		
Hypsarrhythmic EEG Pattern Response	High Dose	26	16 (61.5)	10 (38.5)	1.050	0.8349
	Low Dose	24	14 (58.3)	10 (41.7)		

[Source: Sponsor's clinical study report 222017-05 Table 11.6, confirmed by the reviewer]

3.1.2.7 Reviewer's Results

The reviewer is able to confirm the results reported by the sponsor. The reviewer compared response rates across all three trials (Table 11). While the response rates in prednisone group and in ACTH low dose group vary in different trials, the response rates in ACTH high dose group differ the most across trials. The response rate in ACTH high dose group is much lower in Study 222017-05 than in Study 222017-01. One possible explanation of the rate difference could be due to the once-daily dosing versus the twice-daily dosing and this would be agreeable to the sponsor's argument.

3.1.2.8 Conclusions

The efficacy results in Study 222071-01 cannot be confirmed in this trial. The analysis of Overall Response (spasms cessation and resolution of the hypsarrhythmic pattern on EEG) showed no statistically significant differences between the 2 treatment groups in any of the 4 defined populations. The analysis of the Spasm Control Response by IS etiology, however, showed a nominal statistical significance between the Acthar high-dose and Acthar low-dose treatment groups in favor of Acthar high-dose (P=0.0329) based on the sponsor-defined mITT population.

Even though this is the largest study among three studies included in this application, the sample size is still small. The study can be underpowered. The different administration of ACTH (twice-daily in Study 222017-01 versus once-daily in Study 222017-05) may have effect on the outcome; however, it cannot be proven definitively. The efficacy results of this study remain inconclusive.

Table 11 Comparison of Response Rates across All Three Studies

	Acthar Gel						prednisone		
	High dose			Low dose					
Study	overall response rate (%)	EEG response rate (%)	clinical response rate (%)	overall response rate (%)	EEG response rate (%)	clinical response rate (%)	overall response rate (%)	EEG response rate (%)	clinical response rate (%)
222017-01	86.7	86.7	93.3	NA	NA	NA	28.6	28.6	28.6
222017-05*	62.5	66.7	79.2	48.1	51.9	51.9	NA	NA	NA
222017-04**	NA	NA	NA	41.7	75.0	41.7	33.3	41.7	33.3

* Based on mITT population defined by the sponsor

** The response rates are calculated using initial stage only

3.1.3 STUDY 222017-04

3.1.3.1 Study Objectives

The primary objective of this study was to compare the efficacy of H.P. Acthar Gel (repository corticotropin injection) (20 to 30 U/day) with prednisone (2 mg/kg/day) in treating infantile spasms (IS).

3.1.3.2 Study Design

This is a double-blind crossover study of Acthar Gel or prednisone therapy in patients with IS. After completion of a baseline 24 to 48-hour monitoring period to confirm the presence of IS and to establish a baseline seizure frequency, patients were randomly assigned to receive Acthar Gel 20 U/day intramuscularly (IM) and a prednisone placebo orally (PO) or prednisone 2 mg/kg/day PO and an Acthar Gel placebo IM, for 2 weeks. Acthar Gel and matching placebo were administered as a single dose/day. Prednisone and matching placebo were administered as 2/mg/kg/day.

If the patient responded to therapy within the first 2 weeks, the dosage of the drug was tapered to zero over a 1 to 2-week period. Then, the patient was monitored at 2 weeks and 6 weeks after discontinuation of therapy to substantiate a continued response.

If a patient did not respond after the first 2 weeks, therapy was continued (Acthar Gel 30 U/day or prednisone 2 mg/kg/day) for an additional 4 weeks, after which study drug was tapered to zero over a 2-week period.

Nonresponders to the initial 2 weeks of therapy or the additional 4 weeks of therapy were then crossed over to the other drug after a 1-week washout period, and the protocol was repeated. Patients who failed to respond to either Acthar Gel or prednisone were treated with clonazepam (0.03 to 0.18 mg/kg/day) over an 8-week period. Note that the so-called cross-over is not a typical cross-over design in the clinical trial. In this trial, the sponsor simply re-assigned the non-responders to the other treatment group. It did not involve all subjects in the trial.

The response to therapy was evaluated at specific times throughout the study by 24-hour video and polygraphic monitoring, developmental testing, and determination of serum cortisol concentrations.

3.1.3.3 Efficacy Measures

(1) Primary Efficacy Endpoint

The primary response to therapy in this study was defined as total cessation of spasms and disappearance of the hypsarrhythmic EEG pattern. Spasms and hypsarrhythmic EEG pattern were assessed by serial 24-hour video and polygraphic monitoring.

(2) Secondary Efficacy Endpoints

Secondary endpoints included EEG changes in nonresponders and changes in mental and developmental status.

Note that again the original publication (Hrachovy 1983) did not use primary and secondary endpoints.

3.1.3.4 Patient Disposition, Demographic and Baseline Characteristics

Twenty-four infants with IS and hypsarrhythmic EEG patterns were enrolled in the study; 12 were randomly assigned to Acthar Gel plus prednisone placebo and 12 were randomly assigned to prednisone and an Acthar Gel placebo.

Table 12 Summary of Patient Disposition by Treatment Group

	Acthar Gel N=12 n (%)	Prednisone N=12 n (%)	All Patients N=24 n (%)
Number of patients enrolled	12 (100.0)	12 (100.0)	24 (100.0)
Number of patients completed initial phase[a]	9 (75.0)	12 (100.0)	21 (87.5)
Number of patients in the crossover phase	4 (33.3)	8 (66.7)	12 (50.0)
Number of patients prematurely withdrew	3 (25.0)	0 (0.0)	3 (12.5)
Number of patients withdrew due to AEs	2 (16.7)	0 (0.0)	2 (8.3)
Number of patients withdrew due to death	0 (0.0)	0 (0.0)	0 (0.0)
Number of patients withdrew due to other reason	1 (8.3)	0 (0.0)	1 (4.2)

[Source: Sponsor's clinical study report 222017-04 Table 10.1, confirmed by the reviewer]

The median age of all patients is 8.20 months (range: 3.5 to 24.4 months) at start of treatment. More patients are female (14/24, 58.3%) than male (10/24, 41.7%). Most patients are White (15/24, 62.5%). The majority of patients had symptomatic etiology of IS (19/24, 79.2%); 8 patients (8/24, 66.7%) were symptomatic in the Acthar Gel group and 11 patients (11/24, 91.7%) were symptomatic in the prednisone group.

3.1.3.5 Sponsor's Primary Efficacy Results

There is no difference in overall response rate between Acthar Gel and prednisone in patients who were non-responders in the initial phase of the study and who received these treatments as alternative therapy in the crossover phase of the study.

Table 13 Analysis of Response to Treatment

Treatment Phase	Treatment	N	Treatment Response			*P*-value[a]
			EEG Responder	Clinical Spasms Responder	Overall Responder	
Initial	Acthar Gel	12	9 (75.0%)	5 (41.7)	5 (41.7)	>0.9999
	Prednisone	12	5 (41.7)	4 (33.3)	4 (33.3)	
Crossover[b]	Acthar Gel	8	3 (37.5)	4 (50.0)	3 (37.5)	>0.9999
	Prednisone	7	4 (57.1)	3 (42.9)	3 (42.9)	
Final[c]	Acthar Gel	13	8 (61.5)	9 (69.2)	8 (61.5)	ND[d]
	Prednisone	11	8 (72.7)	7 (63.6)	7 (63.6)	

a. *P*-value based on the 2-sided Fisher's exact test for treatment effect on overall response rate.
b. Crossover was conditional, including only patients did not respond to initial treatment.
c. Count based on each patient's last treatment. If patient did not crossover to another treatment then final treatment was the initial treatment, if a patient did crossover then crossover treatment was the final treatment
d. Not done because final treatment was not randomly assigned but a mix of initial treatment randomization and crossover conditional on initial treatment response.

[Source: Sponsor's clinical study report 222017-04 Table 11.1]

3.1.3.6 Sponsor's Secondary Efficacy Results

There does not appear to be a relationship between treatment or treatment response and change in mental and developmental status. Complete disappearance of the hypsarrhythmic EEG pattern was reported in 1 nonresponder (1/9, 11.1%).

The sponsor argued that the trial was under powered to show a meaningful treatment difference.

3.1.3.7 Reviewer's Results

The reviewer is able to confirm the results reported by the sponsor.

Note that the so-called cross-over is not a typical cross-over design in the clinical trial. In this trial, the sponsor simply re-assigned the non-responders to the other treatment group. It did not involve all subjects in the trial. The reviewer would focus only on the initial stage as the result is much easier to interpret.

3.1.3.8 Conclusions

The sponsor argued that this study evaluated a dose that is below that being recommended by Questco. The overall response rates seen in these analyses to both Acthar low-dose and prednisone are similar between the 2 treatments. Again, the sample size is small and the efficacy data are limited. The results can be due to the small sample size or due to ineffectiveness of the low dose ACTH. Conclusion on efficacy of ACTH cannot be drawn based on this trial.

3.2 Evaluation of Safety

Please refer to the clinical review for safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Ethnic group

Due to small number of patients enrolled in each of the trial, it is hard to reach any conclusion based on subgroup analyses. The reviewer provided summary statistics for each study.

Please refer to Table 3 for subgroup analysis by age in Study 222017-01. Table 14 shows the number of overall responses in each gender. Ethnicity information is not available in Study 222017-01.

Table 14 Summary of Overall Responses by Gender in Study 222017-01

	Acthar Gel		Prednisone	
Gender	N	responses	N	Responses
female	11	9	6	1
male	4	4	8	3

Table 15 Summary of Overall Responses by Subgroups in Study 222017-05

	Acthar High Dose		Acthar Low Dose	
	N*	Responses	N	Responses
White	10	6	11	4
Other	17	9	13	8
Female	14	5	8	4
Male	14	10	19	9
Age>7 month	16	9	13	7
Age<=7 month	12	6	14	6

* Total number of patients may not add up across subgroups due to some missing information

Subgroup analyses in study 222017-04 are based on initial stage before non-responders were crossed over to the other treatment group.

Table 16 Summary of Responses by Subgroups in Study 222017-04

	Acthar		Prednisone	
	N	Responses	N	Responses
White	7	3	8	2
Other	5	2	4	2
Female	7	3	7	3
Male	5	2	5	1
Age>7 month	7	3	9	3
Age<=7 month	5	2	3	1

4.2 Other Subgroup Populations

Other subgroup analyses are not performed in this review.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Unlike the conventional pivotal trials submitted for drug approvals, the efficacy evidence of Acthar gel in treating infantile spasms is based on three published randomized controlled trials. Although the sponsor obtained the source efficacy data of those three trials and re-analyzed them, there was no prospectively defined statistical analysis plan. The sample size of each trial is small. With such small sample size, the study sample may not be a good representation of the intended pediatric population. Therefore the efficacy data to draw conclusions are limited. Even though the sponsor used one study (222017-04) as the pivotal trial and the other two as supportive trials, this was not determined prospectively. All three studies should be weighted carefully. Furthermore, the so-called primary endpoint may not carry as much weight as the primary endpoint in the conventional clinical trials since it was not defined prospectively.

Study 222017-05 had a number of patients who did not complete the treatment protocol. Depending on the population used for analyses, the conclusion can vary. The analyses of overall response and EEG response showed no statistically significant differences between the 2 treatment groups. The analysis of the spasm control response by IS etiology showed a nominally significant difference between the Acthar high-dose and Acthar low-dose treatment groups in

favor of Acthar high-dose. This is based on the sponsor-defined mITT population. The significance disappeared if some other defined population is used (e.g., ITT population, completed patients population). Study 222017-04 showed similar overall response rate in both Acthar low-dose group and prednisone group. It cannot be determined whether it suggests that the low dose Acthar has similar effect in treatment infantile spasms as prednisone, or it is likely due to the small sample size of the trial.

The reviewer compared response rates across all three trials for consistency (Table 11). While the response rates in prednisone group and in ACTH low dose group vary in different trials, the response rates in ACTH high dose group differ the most across trials. The response rate in ACTH high dose group is much lower in Study 222017-05 than in Study 222017-01.

5.2 Conclusions and Recommendations

The sponsor obtained source efficacy data from three published, randomized, controlled studies. Among three studies, Study 222017-01 showed that Acthar Gel was significantly better than prednisone in both EEG response and clinical seizure response as well as the overall response ($p<0.01$). Study 222017-05 had 59 patients enrolled in the trial but a number of patients did not complete the study protocol, which had a considerable impact on the results of the trial. Depending on the population used for analyses, the conclusion can vary. Study 222017-04 compared Acthar low-dose with prednisone and showed that the low dose did not differ much from prednisone numerically ($p>0.99$).

Even though Study 222017-01 showed highly significant treatment effect of Acthar Gel, it is somewhat concerning that the conclusion cannot be directly confirmed in the other two trials. The analyses are retrospective and the sample size in each trial is small. With such small sample size, the study sample may not be a good representation of the intended pediatric population. The data to draw a definitive conclusion are limited. The efficacy evidence from three trials needs to be weighted carefully.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICALS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)

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/s/

JIALU ZHANG
04/02/2010

KUN JIN
04/02/2010
I concur with this review.

KOOROS MAHJOOB
04/05/2010
I read this review and I discussed my views with the reviewer. My views are incorporated in this final version and I concur with that.